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for malaria

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Summary of recommendations

1. ABBREVIATIONS

2. EXECUTIVE SUMMARY

2.1 Guideline Translations

3. INTRODUCTION

4. PREVENTION

4.1 Vector control

4.1.1 Interventions recommended for large-scale deployment

Strong recommendation for , High certainty evidence

Pyrethroid-only nets (2019)

Pyrethroid-only long-lasting insecticidal nets (LLINs) should be deployed for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

Remark:

- WHO recommends ITNs that have been prequalified by WHO for deployment in protecting populations at risk of malaria.
- ITNs are most effective where the principal malaria vector(s) bite predominantly at night after people have retired under their nets.
- ITNs can be used both indoors and outdoors, wherever they can be suitably hung (though hanging nets in direct sunlight should be avoided, as sunlight can affect insecticidal activity).

Conditional recommendation for , Moderate certainty evidence

Pyrethroid-PBO ITNs (2022)

Pyrethroid-PBO ITNs instead of pyrethroid-only LLINs can be deployed for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission where the principal malaria vector(s) exhibit pyrethroid resistance.

Remark:
The conditionality of this recommendation is largely driven by the current higher unit cost of pyrethroid-PBO ITNs compared to pyrethroid-only LLINs and therefore the uncertainty of their cost-effectiveness. Furthermore, as PBO is less wash-resistant than pyrethroids, its bioavailability declines faster over the three-year estimated life of an ITN; therefore, the added impact of pyrethroid-PBO ITNs over that of pyrethroid-only LLINs may decline over time. The evidence comes from two sites in eastern Africa with pyrethroid resistance and not from other geographies where transmission levels and vector characteristics may vary. PBO acts by inhibiting certain metabolic enzymes, primarily oxidases, and so are likely to provide greater protection than pyrethroid-only LLINs where mosquitoes display mono-oxygenase-based insecticide resistance mechanisms.

In deciding whether pyrethroid-PBO ITNs may be appropriate in their context, malaria programmes should:

- consider the deployment of pyrethroid-PBO ITNs in areas where resistance to pyrethroids in local vectors has been detected;
- determine whether resources are adequate to cover the extra cost of pyrethroid-PBO ITNs, while ensuring that coverage of populations at risk of malaria is not affected;
- note that WHO recommends that ITNs prequalified by WHO be selected for deployment.

Strong recommendation for , Moderate certainty evidence New

Pyrethroid-chlorfenapyr ITNs vs pyrethroid-only LLINs (2023)

Pyrethroid-chlorfenapyr ITNs should be deployed instead of pyrethroid-only LLINs for prevention of malaria in adults and children in areas with pyrethroid resistance.

Remark:
Note: Recommendations on deployment of pyrethroid-chlorfenapyr nets were separated into two distinct recommendations for better clarity, but share the same evidence to decision, justification, practical info and research needs. Please refer to the following section.

Conditional recommendation for , Moderate certainty evidence New

Pyrethroid-chlorfenapyr ITNs vs pyrethroid-PBO ITNs (2023)

Pyrethroid-chlorfenapyr ITNs can be deployed instead of pyrethroid-PBO ITNs for prevention of malaria in adults and children in areas with pyrethroid resistance.

Remark:
The conditionality of the recommendation to deploy pyrethroid-chlorfenapyr ITNs instead of pyrethroid-PBO ITNs is based on the GDG's judgement that the balance of desirable and undesirable effects probably favours pyrethroid-chlorfenapyr ITNs over pyrethroid-PBO ITNs. However, the evidence for this recommendation is from only one trial in Africa.

In deciding whether to deploy pyrethroid-chlorfenapyr ITNs instead of pyrethroid-only LLINs or pyrethroid-PBO ITNs, malaria programmes should:

- determine whether resources are adequate to cover the extra costs compared to pyrethroid-only LLINs or pyrethroid-PBO ITNs, while ensuring optimal coverage of populations at risk of malaria;
- generate additional information or conduct analyses with the aim of maximizing impact through targeted deployment (e.g. stratification of malaria risk, assessment of the characteristics of local vectors, such as pyrethroid resistance mechanisms). ITNs for prevention of malaria in adults and children in areas with pyrethroid resistance; and
- note that WHO recommends that ITNs prequalified by WHO be selected for deployment.

Conditional recommendation for , Moderate certainty evidence New

Pyrethroid-pyriproxyfen ITNs vs pyrethroid-only LLINs (2023)

Pyrethroid-pyriproxyfen ITNs can be deployed instead of pyrethroid-only LLINs for prevention of malaria in adults and children in areas with pyrethroid resistance.

Remark:
The conditionality of the recommendation to deploy pyrethroid-pyriproxyfen ITNs instead of pyrethroid-only LLINs is based on the GDG's concerns that the available evidence indicates poor cost-effectiveness of pyrethroid-pyriproxyfen ITNs compared to pyrethroid-only LLINs and that the extra resources currently required to purchase these ITNs may negatively impact on coverage and equity.

In deciding whether pyrethroid-pyriproxyfen ITNs should be deployed instead of pyrethroid-only LLINs, malaria programmes should:

- determine whether resources are adequate to cover the extra cost compared to pyrethroid-only LLINs, while ensuring optimal coverage of populations at risk of malaria;
- generate additional information or conduct analyses with the aim of maximizing impact through targeted deployment (e.g. stratification of malaria risk, assessment of the characteristics of local vectors, such as pyrethroid resistance mechanisms); and
- note that WHO recommends that ITNs prequalified by WHO be selected for deployment.

Note: Recommendations on deployment of pyrethroid-pyriproxifen nets were separated into two distinct recommendations for better clarity, but share the same evidence to decision, justification, practical info and research needs. Please refer to the following section.

Conditional recommendation against , Moderate certainty evidence New

Pyrethroid-pyriproxyfen ITNs vs pyrethroid-PBO ITNs (2023)

Pyrethroid-pyriproxyfen ITNs are not recommended for deployment over pyrethroid-PBO ITNs for prevention of malaria in adults and children in areas with pyrethroid resistance.

Remark:
The conditionality of the recommendation against the deployment of pyrethroid-pyriproxyfen ITNs instead of pyrethroid-PBO ITNs is based on the GDG's judgement that the balance of effects favours pyrethroid-PBO ITNs over pyrethroid-pyriproxyfen ITNs and that, based on current cost and efficacy data, pyrethroid-PBO ITNs are more cost-effective. The GDG acknowledged that evidence to support this recommendation is derived from only a single trial in Africa.

Strong recommendation for , High certainty evidence

Insecticide-treated nets: Humanitarian emergency setting (2022)

Insecticide-treated nets (ITNs) should be deployed for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission affected by a humanitarian emergency.

Remark:
This recommendation is limited to classes of ITNs currently recommended by WHO. As with ITNs deployed in more stable settings, WHO recommends that ITNs that are prequalified by WHO be selected for use in humanitarian emergencies.

When considering deployment of ITNs in humanitarian emergencies, the infrastructure, access, logistical capacity and resources available must be taken into account, as these may influence the feasibility and cost of procuring and deploying nets.

Good practice statement

Achieving and maintaining optimal coverage with ITNs for malaria prevention and control (2019)

To achieve and maintain optimal ITN coverage, countries should apply mass free net distribution through campaigns, combined with other locally appropriate delivery mechanisms such as continuous distribution using antenatal care (ANC) clinics and the Expanded Programme on Immunization (EPI).

Recipients of ITNs should be advised (through appropriate communication strategies) to continue using their nets beyond the three-year expected lifespan, irrespective of the condition and age of the net, until a replacement net is available.

Good practice statement

Management of old ITNs (2019)

Old ITNs should only be collected where there is assurance that: i) communities are not left without nets, i.e. new ITNs are distributed to replace old ones; and ii) there is a suitable and sustainable plan in place for safe disposal of the collected material.

If ITNs and their packaging (bags and baling materials) are collected, the best option for disposal is high-temperature incineration. They should not be burned in the open air. In the absence of appropriate facilities, they should be buried away from water sources and preferably in non-permeable soil.

Recipients of ITNs should be advised (through appropriate communication strategies) not to dispose of their nets in any water body, as the residual insecticide on the net can be toxic to aquatic organisms (especially fish).

Strong recommendation for , Low certainty evidence

Indoor residual spraying (2019)

IRS should be deployed for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

Remark:
WHO recommends that WHO-prequalified insecticidal products be selected for IRS use and that these be selected based on the insecticide susceptibility of the local malaria vector(s). IRS is considered an appropriate intervention where:

- the majority of the vector population feeds and rests indoors;
- people mainly sleep indoors at night;
- the malaria transmission pattern is such that the population can be protected by one or two rounds of IRS per year; and
- the majority of structures are suitable for spraying.

Conditional recommendation for , Very low certainty evidence

Indoor residual spraying: Humanitarian emergency setting (2022)

IRS can be deployed for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission affected by a humanitarian emergency.

Remark:
The conditionality of this recommendation is largely driven by the very low certainty of the evidence that IRS reduces malaria in such settings and due to concerns around feasibility and cost.

When deciding whether IRS may be appropriate for prevention and control of malaria in humanitarian emergency settings, programmes should consider:

- whether the structures are suitable for spraying. Some shelters provided in emergency settings may not be suitable for application of insecticides, such as open-sided structures and those built from materials that affect the residual nature of the insecticides;
- whether the target coverage of IRS can be feasibly achieved in the setting;
- whether there are sufficient resources to cover the relatively high costs associated with an IRS programme. In such settings, transport of commodities to hard-to-reach areas, coupled with the need to quickly procure items and establish human capacity to deliver the intervention, is likely to incur higher costs than when deploying IRS in more stable settings.

As with the deployment of IRS in more stable settings, WHO recommends that WHO-prequalified insecticides be selected for IRS use in humanitarian emergencies. It is important to ensure that the vector population is susceptible to the insecticide selected for spraying.

4.1.2 Co-deploying ITNs and IRS

Conditional recommendation against , Moderate certainty evidence

Prioritize optimal coverage with either ITNs or IRS over combination (2019)

The co-deployment of ITNs and IRS is not recommended for prevention and control of malaria in children and adults in areas with ongoing malaria transmission. Priority should be given to delivering either ITNs or IRS at optimal coverage and to a high standard, rather than introducing the second intervention as a means to compensate for deficiencies in the implementation of the first intervention.

Remark:
In settings where optimal ITN coverage, as specified in the strategic plan, has been achieved and where ITNs remain effective, additionally implementing IRS may have limited utility in reducing malaria morbidity and mortality. Given the resource constraints across malaria-endemic countries, it is recommended that effort be focused on good-quality implementation of either ITNs or IRS, rather than deploying both in the same area. However, the combination of these interventions may be considered for resistance prevention, mitigation or management should sufficient resources be available.

Good practice statement

Access to ITNs or IRS at optimal coverage levels (2019)

Access to effective vector control using ITNs or IRS at optimal coverage levels should be ensured for all populations at risk of malaria in most epidemiological and ecological settings.

Good practice statement

No scale-back in areas with ongoing local malaria transmission (2019)

In areas with ongoing local malaria transmission (irrespective of both the pre-intervention and current level of transmission), vector control interventions should not be scaled back. Ensuring access to effective malaria vector control at optimal levels for all inhabitants of such areas should be pursued and maintained.

4.1.3 Supplementary interventions

Conditional recommendation for , Low certainty evidence

Larviciding (2019)

Insecticides can be regularly applied to water bodies (larviciding) for the prevention and control of malaria in children and adults as a supplementary intervention to ITNs or IRS in areas with ongoing malaria transmission where aquatic habitats are few, fixed and findable.

Remark:
The conditionality of this recommendation is due to the low certainty of evidence, the impact being limited to non-extensive habitats, and concerns about feasibility.

When considering larviciding, programmes should note the following:

- Larviciding only reduces vector density and so does not have the same potential for health impact as ITNs and IRS; ITNs provide protection from biting vectors and both ITNs and IRS reduce adult longevity.
- Larviciding should not be seen as a substitute for ITNs or IRS or a means to fill a coverage gap in areas with significant malaria risk; rather, larviciding represents a potential supplementary strategy for malaria control.
- Feasibility and cost-effectiveness should be taken into account; larviciding will generally be most cost-effective in areas where larval habitats are few, fixed and findable, and likely less feasible in areas where the aquatic habitats are abundant, scattered and variable.

The following settings are potentially the most suitable for larviciding as a supplementary measure implemented alongside ITNs or IRS:

- urban areas: where breeding sites are relatively few, fixed and findable in relation to houses (which are targeted for ITNs or IRS);
- arid regions: where larval habitats may be few and fixed throughout much of the year.

Larval habitat modification and/or larval habitat manipulation (2021)

No recommendation can be made because the evidence on the effectiveness of a specific larval habitat modification and/or larval habitat manipulation intervention for the prevention and control of malaria was deemed to be insufficient.

Larvivorous fish (2019)

No recommendation can be made because no evidence on the effectiveness of larvivorous fish for the prevention and control of malaria was identified.

Conditional recommendation against , Low certainty evidence

Topical repellents (2019)

The deployment of topical repellents in areas with ongoing malaria transmission is not recommended if the aim is to prevent and control malaria at the community level.

Remark:
The panel recommended against the implementation of topical repellents with the aim of controlling malaria at the community level, given the lack of evidence of a significant impact. To achieve community-level impact, it is likely that a high level of individual compliance would be needed. Further work is required to separate out the potential protective effects at the individual and/or community level and therefore fully assess the potential public health value of topical repellents.

Conditional recommendation against , Low certainty evidence

Insecticide-treated clothing (2019)

Deployment of insecticide-treated clothing is not recommended for the prevention and control of malaria at the community level in areas with ongoing malaria transmission; however, insecticide-treated clothing may be beneficial as an intervention to provide personal protection against malaria in specific population groups.

Remark:
The GDG recommended against the deployment of insecticide-treated clothing due to the lack of evidence of an impact in the general population. In the absence of ITNs, there is some evidence that insecticide-treated clothing may reduce the risk of malaria infection in specific populations such as refugees and military personnel.

Spatial/Airborne repellents (2019)

No recommendation can be made because the evidence on the effectiveness of spatial/airborne repellents for the prevention and control of malaria was deemed to be insufficient.

Conditional recommendation against , Very low certainty evidence

Space spraying (2019)

Space spraying is not recommended for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission; IRS or ITNs should be prioritized instead.

Remark:
The panel recommended against the deployment of space spraying to control malaria, given the lack of evidence of impact against malaria. Due to the short-lived nature of the insecticides used, space spraying is generally costly and wasteful of resources.

Conditional recommendation for , Low certainty evidence

House screening (2021)

Screening of residential houses can be used for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission.

Remark:

The GDG determined that a conditional recommendation should be given for house screening because of the low- to moderate-certainty evidence of an impact against malaria. Furthermore, programmes would need to consider a number of local contextual factors when considering screening of residential houses as a public health strategy, such as:

- how the intervention will be delivered and maintained;
- whether the structure and condition of the residential houses in the community allow for the installation of screening;
- the feasibility and resources needed for implementation, especially if deployed on a large scale.

Programmes should note that this recommendation addresses the use of screening of windows, ceilings, doors and/or eave spaces, and does not cover other ways of blocking entry points into houses.

4.1.4 Research needs

4.2 Preventive chemotherapies

4.2.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

Strong recommendation for , Moderate certainty evidence

Intermittent preventive treatment of malaria in pregnancy (2022)

In malaria-endemic areas, pregnant women of all gravidities should be given antimalarial medicine at predetermined intervals to reduce disease burden in pregnancy and adverse pregnancy and birth outcomes.

Remark:

- Sulfadoxine-pyrimethamine (SP) has been widely used for malaria chemoprevention during pregnancy and remains effective in improving key pregnancy outcomes.
- IPTp-SP should start as early as possible in the second trimester and not before week 13 of pregnancy.
- Doses should be given at least one month apart, with the objective of ensuring that at least three doses are received.
- Antenatal care (ANC) contacts remain an important platform for delivering IPTp. Where inequities in ANC service and reach exist, other delivery methods (such as the use of community health workers) may be explored, ensuring that ANC attendance is maintained and underlying inequities in ANC delivery are addressed.
- IPTp is generally highly cost-effective, widely accepted, feasible for delivery and justified by a large body of evidence generated over several decades.

4.2.2 Perennial malaria chemoprevention (PMC) - formerly intermittent preventive treatment of malaria in infants (IPTi)

Conditional recommendation for , Moderate certainty evidence

Perennial malaria chemoprevention (2022)

In areas of moderate to high perennial malaria transmission, children belonging to age groups at high risk of severe malaria can be given antimalarial medicines at predefined intervals to reduce disease burden.

Remark:

- Perennial malaria chemoprevention (PMC) schedules should be informed by the age pattern of severe malaria admissions, the duration of protection of the selected drug, and the feasibility and affordability of delivering each additional PMC course (see “Practical info”).
- Sulfadoxine-pyrimethamine (SP) has been widely used for chemoprevention in Africa, including for PMC. Artemisinin-based combination therapies (ACTs) have been effective when used for PMC, but evidence is limited on their safety, efficacy, adherence to multi-day regimens, and cost-effectiveness in the context of PMC.
- Previously, PMC was recommended in infants (<12 months of age) as intermittent preventive treatment in infants (IPTi). Since the initial recommendation, new data have documented the value of malaria chemoprevention in children aged 12 to 24 months.
- The Expanded Programme on Immunization (EPI) platform remains important for delivering PMC. Other methods of delivery can be explored to optimize access to PMC and integration with other health interventions.
- Moderate to high perennial malaria transmission settings are defined as areas with *P. falciparum* parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000 *[30]*. These thresholds are indicative and should not be regarded as absolutes for determining applicability of the PMC recommendation.

4.2.3 Seasonal malaria chemoprevention (SMC)

Strong recommendation for , Moderate certainty evidence

Seasonal malaria chemoprevention (2022)

In areas of seasonal malaria transmission, children belonging to age groups at high risk of severe malaria should be given antimalarial medicines during peak malaria transmission seasons to reduce disease burden.

Remark:

- Eligibility for seasonal malaria chemoprevention (SMC) is defined by the seasonality of malaria transmission and age groups at risk of severe malaria. Thresholds for assessing these criteria change over time and location. Malaria programmes should assess the suitability of SMC based on the local malaria epidemiology and available funding (see “Practical info”). The added value of a seasonally targeted intervention is likely to be greatest where transmission is intensely seasonal.
- Monthly cycles of sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) have been widely used for SMC in African children under 5 years old and have been shown to be efficacious, safe, well tolerated, available and inexpensive (Thwing *et al* *unpublished evidence*).

4.2.4 Intermittent preventive treatment of malaria in school-aged children (IPTsc)

Conditional recommendation for , Low certainty evidence

Intermittent preventive treatment of malaria in school-aged children (2022)

School-aged children living in malaria-endemic settings with moderate to high perennial or seasonal transmission can be given a full therapeutic course of antimalarial medicine at predetermined times as chemoprevention to reduce disease burden.

Remark:

- Intermittent preventive treatment in school-aged children (IPTsc) has been evaluated in children aged 5–15 years. The burden of malaria and benefits of IPTsc may vary across this age range, but evidence is limited.
- National malaria programmes can consider IPTsc if resources allow for its introduction among school-aged children without compromising chemoprevention interventions for those carrying the highest burden of severe disease, such as children < 5 years old.
- Schools may provide a low-cost means to deliver chemoprevention to school-aged children. However seasonal variation in malaria transmission and the timing of school terms, as well as equity concerns, may mean alternative delivery channels are needed to maximize impact.
- First- and second-line malaria treatments should not be used for IPTsc if safe and effective alternatives are available (see “Practical info”).
- The dosing schedule for IPTsc should be informed by the local malaria epidemiology and timed to give protection during the period of greatest malaria risk (see “Practical info”).
- Moderate to high malaria transmission settings are defined as areas with *P. falciparum* parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000 *[30]*. These thresholds are indicative and should not be regarded as absolutes for determining applicability of the IPTsc recommendation.

4.2.5 Post-discharge malaria chemoprevention (PDMC)

Conditional recommendation for , Moderate certainty evidence

Post-discharge malaria chemoprevention (2022)

Children admitted to hospital with severe anaemia living in settings with moderate to high malaria transmission can be given a full therapeutic course of an antimalarial medicine at predetermined times following discharge from hospital to reduce re-admission and death.

Remark:

- Post-discharge malaria chemoprevention (PDMC) should be given to children following admission with severe anaemia *[133]* that is not due to blood loss following trauma, surgery, malignancy or a bleeding disorder.
- PDMC implementation should be tailored to admissions of children with severe anaemia and consider the duration of protection of the selected antimalarial, and the feasibility and affordability of delivering each additional PDMC course (see “Practical info”).
- Moderate to high perennial malaria transmission settings are defined as areas with a *P. falciparum* parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000 *[30]*. These thresholds are indicative and should not be regarded as absolute for determining applicability of the PDMC recommendation.

4.2.6 Mass drug administration (MDA)

4.2.6.1 MDA for burden reduction

Conditional recommendation for , Low certainty evidence

MDA for burden reduction (2022)

Antimalarial medicine can be given as chemoprevention through mass drug administration (MDA) in areas of moderate to high transmission of *P. falciparum* to provide short-term reductions in disease burden.

Remark:

- MDA may quickly reduce clinical malaria incidence in settings with moderate to high *P. falciparum* transmission, but the effect wanes within 1–3 months. Therefore, if MDA is implemented, it should be one of several components of a robust malaria control programme (including good coverage of effective case management and appropriate prevention tools and strategies).
- Malaria programmes should judge the suitability of using MDA in their context based on the desired impact, level of endemicity, and resources required. MDA for burden reduction should be targeted at moderate to high transmission settings, regardless of seasonality (see “Practical info”).
- Moderate to high malaria transmission settings are defined as areas with *P. falciparum* parasite prevalence greater than 10%, or incidence greater than 250 *P. falciparum* cases per 1000 population per year *[30]*. These thresholds should not be regarded as absolutes for determining applicability of MDA implementation. It is biologically plausible that MDA in intermediate transmission settings may reduce both disease burden and transmission intensity.

4.2.6.2 MDA for burden reduction in emergency settings

Conditional recommendation for , Low certainty evidence

MDA for burden reduction in emergency settings (2022)

During emergencies or periods of health service disruption, antimalarial medicine can be used for mass drug administration (MDA) in defined geographical areas to provide short-term reductions in the burden of disease caused by *P. falciparum*.

Remark:

- MDA may quickly reduce clinical malaria incidence in settings with moderate to high *P. falciparum* transmission, but the effect wanes within 1–3 months. As far as possible, MDA should be implemented as part of a package of malaria control measures (including effective case management and appropriate prevention tools and strategies).
- Malaria programmes should judge the suitability of using MDA in their context based on the desired impact, level of endemicity, and resources required (see “Practical info”).
- There is very limited evidence on the impact of MDA on disease in emergency settings. However, the biological effects of MDA on disease in non-emergency settings are likely to translate to MDA recipients in emergency settings. The size of effect will vary according to the type of emergency and level of disruption to health services, as well as underlying transmission intensity, choice of drug, delivery method and other factors.

4.2.6.3 MDA to reduce transmission of *P. falciparum* in very low to low transmission settings

Conditional recommendation for , Low certainty evidence

MDA to reduce transmission of *P. falciparum* in very low to low transmission settings (2022)

In areas with very low to low levels of *P. falciparum* transmission, antimalarial medicine can be given as chemoprevention through mass drug administration (MDA) to reduce transmission.

Remark:

- MDA may quickly reduce transmission of *P. falciparum* in very low to low transmission areas, but the effect wanes within 1–3 months. Therefore, if MDA is implemented, it should be one of several components of a robust malaria elimination programme (including, at minimum, good coverage of case-based surveillance with parasitological diagnosis, effective antimalarial treatment, and appropriate prevention tools and strategies) in order to reduce the risk of resurgence after the MDA programme has ended.
- MDA should be considered only for geographical areas where there is limited risk of importation of malaria either from adjacent communities or through travel of the population to endemic areas.
- Malaria programmes should consider whether sufficient resources are available to implement MDA without affecting other components of a robust malaria elimination programme.
- Very low to low transmission settings are defined as areas with *P. falciparum* parasite prevalence less than 10%, or *P. falciparum* incidence less than 250 cases per 1000 population per year *[30]*. These thresholds should not be regarded as absolutes for determining applicability of MDA implementation for transmission reduction. MDA implemented in areas with levels of transmission near these cut-offs may reduce both disease burden and transmission intensity.

4.2.6.4 MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings

Conditional recommendation against , Very low certainty evidence

MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings (2022)

In areas with moderate to high levels of *P. falciparum* transmission, providing antimalarial medicine through mass drug administration (MDA) to reduce transmission is not recommended.

Remark:

- The studies included in the systematic review did not demonstrate evidence that MDA has either a short- or long-term effect on *P. falciparum* transmission in moderate to high transmission settings.
- Recommendations on MDA to reduce the burden of malaria in moderate to high transmission settings can be found in section *4.2.4.1 MDA for burden reduction*. Moderate to high transmission settings are defined as areas with *P. falciparum* parasite prevalence greater than 10%, or *P. falciparum* incidence above 250 cases per 1000 population per year *[30]*. These thresholds should not be regarded as absolutes for determining applicability of MDA.

4.2.6.5 MDA to reduce transmission of *P. vivax*

Conditional recommendation for , Very low certainty evidence

MDA to reduce transmission of *P. vivax* (2022)

In areas with *P. vivax* transmission, antimalarial medicine can be given as chemoprevention through mass drug administration (MDA) to reduce transmission.

Remark:

- MDA may quickly reduce transmission of *P. vivax*, but the effect wanes within 1–3 months. Therefore, if MDA is implemented, it should be one of several components of a robust malaria elimination programme (including, at minimum, good coverage of case-based surveillance with parasitological diagnosis, effective antimalarial treatment including treatment for hypnozoites, and appropriate prevention tools and strategies) in order to reduce the risk of resurgence after the MDA programme has ended.
- MDA should be considered only for geographical areas where there is limited risk of importation of malaria either from adjacent communities or through travel of the population to endemic areas.
- Malaria programmes should consider whether sufficient resources are available to implement MDA without affecting other components of a robust malaria elimination programme.
- Programmes considering implementing MDA for *P. vivax* should carefully reflect on how to safely and feasibly administer treatment to prevent relapses.

4.2.6.6 Mass relapse prevention (MRP) to reduce transmission of *P. vivax*

Conditional recommendation against , Very low certainty evidence

Mass relapse prevention (MRP) to reduce transmission of *P. vivax* (2022)

Mass treatment with an 8-aminoquinoline medicine alone to reduce the transmission of *P. vivax* is not recommended.

Remark:

- Without testing for G6PD deficiency, the GDG noted the potential for severe harm from the use of a therapeutic dose of an 8-aminoquinoline for radical cure of *P. vivax* hypnozoites. However, conducting G6PD testing for a large population would significantly add to the complexity and cost of the intervention.
- The GDG noted that there may be highly exceptional circumstances under which mass relapse prevention (MRP) may be appropriate, such as during a small focal outbreak of *P. vivax* in a temperate area. However, under such circumstances the GDG considered that an MDA programme providing a schizonticide in addition to an 8-aminoquinoline would likely be a better strategy.

4.3 Vaccine

Strong recommendation for , High certainty evidence

Malaria vaccine (2021)

The RTS,S/AS01 malaria vaccine should be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO.

Remark:

- The RTS,S/AS01 malaria vaccine should be provided in a four-dose schedule in children from 5 months of age.
- Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy, in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks.
- Countries that choose to introduce the vaccine in a five-dose seasonal strategy are encouraged to document their experiences, including adverse events following immunization.
- RTS,S/AS01 malaria vaccine should be provided as part of a comprehensive malaria control strategy.

5. CASE MANAGEMENT

5.1 Diagnosing malaria

Good practice statement

Diagnosing malaria (2015)

All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.

5.2 Treating malaria

5.2.1 Treating uncomplicated malaria

5.2.1.1 Artemisinin-based combination therapy

Strong recommendation for , High certainty evidence

Artemisinin-based combination therapy (2015)

Children and adults with uncomplicated *P. falciparum* malaria should be treated with one of the following ACTs*:

- artemether-lumefantrine (AL)
- artesunate-amodiaquine (AS+AQ)
- artesunate-mefloquine (ASMQ)
- dihydroartemisinin-piperaquine (DHAP)
- artesunate + sulfadoxine-pyrimethamine (AS+SP)
- artesunate-pyronaridine (ASPY) (2022)

*Artesunate + sulfadoxine-pyrimethamine and artesunate-pyronaridine are not recommended for use in the first trimester of pregnancy. For details of treatment using ACTs in the first trimester of pregnancy, see 5.2.1.4.1 below.

Remark:
Artesunate-pyronaridine is now included in the list of options for the treatment of uncomplicated malaria (2022). See the full recommendation and supporting evidence below.

Strong recommendation for , Low certainty evidence

Artesunate-pyronaridine for uncomplicated malaria (2022)

Artesunate-pyronaridine (ASPY) is recommended as an artemisinin-based combination therapy option for the treatment of uncomplicated *P. falciparum* malaria.

Remark:

- ASPY should be avoided by individuals with known liver disease (clinically apparent liver disease) because ASPY is associated with liver transaminitis.
- Pharmacovigilance should be strengthened where ASPY is used for the treatment of malaria.

5.2.1.1.1 Duration of treatment

Strong recommendation for , High certainty evidence

Duration of ACT treatment (2015)

ACT regimens should provide 3 days' treatment with an artemisinin derivative.

5.2.1.1.2 Dosing of ACTs

Strong recommendation for

Revised dose recommendation for dihydroartemisinin + piperaquine in young children (2015)

Children weighing <25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg bw per day of dihydroartemisinin and 20 mg/ kg bw per day of piperaquine daily for 3 days.

*Not evaluated using the GRADE framework

5.2.1.2 Recurrent falciparum malaria

5.2.1.3 Reducing the transmissibility of treated P. falciparum infections in areas of low-intensity transmission

Strong recommendation for , Low certainty evidence

Reducing the transmissibility of treated *P. falciparum* infections (2015)

In low-transmission areas, a single dose of 0.25 mg/kg bw primaquine should be given with an ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.

5.2.1.4 Special risk groups

5.2.1.4.1 Pregnant and lactating women

Strong recommendation for , Low certainty evidence

Treatment in the first trimester of pregnancy (2022)

Pregnant women with uncomplicated *P. falciparum* malaria should be treated with artemether-lumefantrine during the first trimester.

Remark:

- Limited exposures to other ACTs (artesunate-amodiaquine, artesunate-mefloquine and dihydroartemisinin-piperaquine) suggest that the current evidence is insufficient to make a recommendation for routine use of these other ACTs in the first trimester of pregnancy. However, consistent with the previous WHO recommendation that provided for limited use of ACTs if the first-line recommended medicine was not available, these other ACTs may be considered for use where artemether-lumefantrine is not a recommended ACT for uncomplicated malaria or is not available, given the demonstrated poorer outcomes of quinine treatment, along with the challenges of adherence to a seven-day course of treatment.
- Antifolates are contraindicated in the first trimester of pregnancy. Therefore, ACTs containing sulfadoxine-pyrimethamine are contraindicated during the first trimester of pregnancy.
- There is currently no documented record of the use of artesunate-pyronaridine during the first trimester of pregnancy.
- Continued pharmacovigilance and clinical research, including prospective controlled trials on the efficacy and safety of antimalarial medicines for the treatment of malaria in pregnancy, should be supported and funded.

5.2.1.4.2 Young children and infants

Strong recommendation for

Young children and infants (2015)

Infants weighing < 5 kg with uncomplicated *P. falciparum* malaria should be treated with an ACT at the same mg/kg bw target dose as for children weighing 5 kg.

*Not evaluated using the GRADE framework

5.2.1.4.3 Patients co-infected with HIV

Good practice statement

Patients co-infected with HIV (2015)

In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, artesunate + SP is not recommended if they are being treated with co-trimoxazole, and artesunate + amodiaquine is not recommended if they are being treated with efavirenz or zidovudine.

5.2.1.4.4 Non-immune travellers

Strong recommendation for , High certainty evidence

Non-immune travellers (2015)

Travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings should be treated with an ACT.

5.2.1.4.5 Uncomplicated hyperparasitaemia

Good practice statement

Hyperparasitaemia (2015)

People with *P. falciparum* hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving an ACT.

5.2.1.5 Uncomplicated malaria caused by P. vivax, P. ovale, P. malariae or P. knowlesi

Good practice statement

Blood stage infection (2015)

If the malaria species is not known with certainty, adults and children should be treated as for uncomplicated *P. falciparum* malaria.

Strong recommendation for , High certainty evidence

Blood stage infection (2015)

In areas with chloroquine-susceptible infections, adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria should be treated with either an ACT or chloroquine.

In areas with chloroquine-resistant infections, adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria should be treated with an ACT.

* For details of treatment using ACTs in the first trimester of pregnancy, see section 5.2.1.4.1.

Good practice statement

Blood stage infection (2015)

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.

Strong recommendation for , High certainty evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

To prevent relapse, children and adults (except pregnant women, infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) should be treated with a 14-day course of primaquine in all transmission settings.

Strong recommendation for , Very low certainty evidence

Short-course standard dose primaquine treatment (2022)

To prevent relapse, an additional treatment option of using primaquine 0.5 mg/kg/day for seven days is recommended to treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency).

Remark:

- As recommended previously, the G6PD status of patients should be used to guide administration of primaquine for preventing relapse.
- A shorter regimen can lead to better adherence compared to the standard 14-day regimen and thus to fewer relapses.

Conditional recommendation against , Very low certainty evidence

Short-course standard high-dose primaquine treatment (2022)

To prevent relapse, an additional treatment option of using primaquine 1.0 mg/kg/day for seven days to treat *P. vivax* or *P. ovale* malaria is not recommended.

Remark:

- There is a significantly increased risk of serious adverse events (moderate to large undesirable effect) at this daily dosing of the standard high dose.

Conditional recommendation for , Very low certainty evidence

Preventing relapse in people with G6PD deficiency (2015)

In people with G6PD deficiency, primaquine base at 0.75 mg/kg bw once a week for 8 weeks can be given to prevent relapse, with close medical supervision for potential primaquine-induced haemolysis.

Good practice statement

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine should be based on an assessment of the risks and benefits of adding primaquine.

Conditional recommendation for , Moderate certainty evidence

Pregnant and breastfeeding women (2015)

In women who are pregnant or breastfeeding, weekly chemoprophylaxis with chloroquine can be given until delivery and breastfeeding are completed, then, on the basis of G6PD status, primaquine can be given to prevent future relapse.

5.2.2 Treating severe malaria

5.2.2.1 Artesunate

Strong recommendation for , High certainty evidence

Treating severe malaria (2015)

Adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) should be treated with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, treatment should be completed with 3 days of an ACT.

Strong recommendation for

Treating severe malaria in children (2015)

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.

*Not evaluated using the GRADE framework; recommendation based on pharmacokinetic modelling

5.2.2.2 Parenteral alternatives when artesunate is not available

Conditional recommendation for , Low certainty evidence

Parental alternatives when artesunate is not available (2015)

If artesunate is not available, artemether should be used in preference to quinine for treating children and adults with severe malaria.

5.2.2.3 Pre-referral treatment options

Strong recommendation for , Moderate certainty evidence

Pre-referral treatment options (2015)

Where complete treatment of severe malaria is not possible, but injections are available, adults and children should be given a single intramuscular dose of artesunate, and referred to an appropriate facility for further care. Where intramuscular artesunate is not available, intramuscular artemether or, if that is not available, intramuscular quinine should be used.

Where intramuscular injection of artesunate is not available, children < 6 years should be treated with a single rectal dose (10mg/kg bw) of artesunate, and referred immediately to an appropriate facility for further care. Rectal artesunate should not be used in older children and adults.

5.2.3 Other considerations in treating malaria

5.2.3.1 Management of malaria cases in special situations

5.2.3.2 Quality of antimalarial drugs

Good practice statement

Antimalarial drug quality (2015)

National drug and regulatory authorities should ensure that the antimalarial medicines provided in both the public and the private sectors are of acceptable quality, through regulation, inspection and law enforcement.

5.2.3.3 Monitoring efficacy and safety of antimalarial drugs and resistance

Good practice statement

Monitoring efficacy and safety of antimalarial drugs and resistance (2015)

All malaria programmes should regularly monitor the therapeutic efficacy of antimalarial drugs using the standard WHO protocols.

5.3 National adaptation and implementation

Good practice statement

National adaptation and implementation (2015)

The choice of ACTs in a country or region should be based on optimal efficacy, safety and adherence.

Good practice statement

National adaptation and implementation (2022)

Drugs used as first line treatment should not be used in IPTp, PMC, SMC, IPTsc or MDA.

Good practice statement

National adaptation and implementation (2015)

When possible:

fixed-dose combinations should be used rather than co-blistered or loose, single-agent formulations; andfor young children and infants, paediatric formulations, with a preference for solid formulations (e.g. dispersible tablets) should be used rather than liquid formulations.

6. INTERVENTIONS IN THE FINAL PHASE OF ELIMINATION AND PREVENTION OF RE-ESTABLISHMENT

6.1 Interventions recommended for mass implementation in delimited geographical areas

6.1.1 Mass testing and treatment (MTaT)

Conditional recommendation against , Moderate certainty evidence

Mass testing and treatment to reduce transmission of malaria (2022)

Mass testing and treatment (MTaT) to reduce the transmission of malaria is not recommended.

Remark:
The GDG noted that there may be exceptional circumstances under which MTaT might be appropriate, such as a transmission focus in a very low transmission or post-elimination setting where MDA is not an acceptable or feasible strategy.

6.2 Interventions targeting infections in people at higher-risk

6.2.1 Targeted drug administration (TDA)

Conditional recommendation for , Very low certainty evidence

Targeted drug administration to reduce transmission of malaria (2022)

In areas with very low to low transmission or post-elimination settings preventing re-establishment of transmission, antimalarial medicine can be given as chemoprevention to people with increased risk of infection relative to the general population to reduce transmission.

Remark:

- Persons given antimalarials should be those with increased risk of infection compared to the general population and their infections should constitute a large proportion of the parasite reservoir in the area.
- The factors identifying individuals or groups at increased risk of infection should be easy to recognise, thereby improving the acceptability and feasibility of the intervention.
- Programmes considering implementing targeted drug administration for *P. vivax* should carefully consider how to safely and feasibly administer treatment to prevent relapses.
- Care should be taken to avoid stigmatizing groups at increased risk of infection.
- Additional complementary strategies to eliminate or prevent re-establishment of malaria transmission should be in place.

6.2.2 Targeted testing and treatment (TTaT)

Conditional recommendation against , Very low certainty evidence

Targeted testing and treatment to reduce transmission of malaria (2022)

Testing and treatment of people with an increased risk of infection relative to the general population to reduce the transmission of malaria is not recommended.

Remark:
The GDG noted that there may be limited circumstances under which targeted testing and treatment (TTaT) could be beneficial. For example, TTaT could be used when people at a higher risk of infection can be easily identified and chemoprevention is not acceptable to the population. Additionally, TTaT could be used if safe and effective implementation of radical cure to prevent *P. vivax* relapses is only feasible for those with confirmed infections.

6.2.3 Testing and treatment at points of entry to reduce importation of malaria

Conditional recommendation against , Very low certainty evidence

Routine malaria testing and treatment at points of entry (2022)

Routine malaria testing and treatment of people arriving at points of entry (land, sea or air) to reduce importation is not recommended.

Remark:
No studies of the impact of testing and treatment at points of entry on the rate of malaria importation were found by the systematic review. Routine testing and treatment for malaria at points of entry is unlikely to be acceptable or feasible to implement.

Conditional recommendation for , Very low certainty evidence

Malaria testing and treatment of organized or identifiable groups arriving or returning from malaria-endemic areas (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, organized or identifiable groups arriving or returning from malaria-endemic areas can be tested and treated soon after entry to reduce importation of malaria.

Relatively easy access to these groups within a short time after entry is required for this strategy to be feasible and acceptable. This strategy may be particularly critical to areas in post-elimination that are working to prevent re-establishment of transmission.

6.3 Interventions in response to detection of confirmed malaria cases

6.3.1 Reactive drug administration (RDA)

Conditional recommendation for , Low certainty evidence

Reactive drug administration for reducing malaria transmission (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, antimalarial medicine can be given as chemoprevention to all people residing with or near a confirmed malaria case and all people who share the same risk of infection (e.g. co-travellers and co-workers) to prevent or reduce malaria transmission.

Remark:

- Programmes implementing reactive drug administration (RDA) should have the capacity to conduct case investigations at the residence to determine the likely location of infection and to identify those individuals co-exposed with the index case.
- Programmes implementing RDA should have the capacity to enumerate and provide antimalarials to the people residing with or near a confirmed malaria case and others that share the same risk of infection.
- The people given antimalarial medicine in an RDA intervention should share the same risk of having acquired infection as the index case or be at risk of acquiring infection from the index case. This includes residents in the same household or neighborhood, co-travellers and co-workers. However, if the infection was imported and the residence is not located in a receptive area, there may be no benefit from RDA.
- Programmes contemplating implementation of RDA for *P. vivax* should carefully consider how to safely and feasibly administer treatment to prevent relapses.

6.3.2 Reactive case detection and treatment (RACDT)

Conditional recommendation for , Very low certainty evidence

Reactive case detection and treatment to reduce transmission of malaria (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, all people residing with or near a confirmed malaria case and all people who share the same risk of infection (e.g. co-travellers and co-workers) can be tested for malaria and treated if positive.

Remark:
Until an area is nearing elimination or is post-elimination, it is unlikely that reactive case detection and treatment (RACDT) will have any effect on malaria transmission. However, RACDT becomes an essential component of surveillance when countries are nearing interruption of transmission to monitor progress towards elimination. When countries are post-elimination and working towards certification, RACDT can strengthen a country's claim that it has reached and maintained zero indigenous cases. RACDT is an essential part of surveillance and response to prevent re-establishment of malaria.

6.3.3 Reactive indoor residual spraying

Conditional recommendation for , Moderate certainty evidence

Reactive indoor residual spraying (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, indoor residual spraying of insecticide can be conducted in in the houses of confirmed cases and neighbours to prevent or reduce transmission of malaria.

Remark:

- In areas approaching elimination or post-elimination settings where proactive indoor residual spraying (IRS) is occurring, programmes can consider switching to reactive IRS only, depending on the receptivity of the area.
- Programmes considering adding reactive IRS on top of proactive IRS should balance the potential added benefit with increasing cost and the risk of insecticide resistance.
- In areas approaching elimination or post-elimination settings where no IRS is occurring, initiating reactive IRS may be beneficial, depending on whether IRS is a suitable vector control strategy. IRS is most effective where the vector population is susceptible to the insecticide(s) being applied, the majority of mosquitoes feed and rest indoors and where most structures are suitable for spraying.
- If the index infection was imported and the residence is not located in a receptive area, there may be no benefit from reactive IRS.

7. SURVEILLANCE

8. METHODS

9. GLOSSARY

10. CONTRIBUTORS AND INTERESTS

10.1 Recommendations for vector control

10.2 Recommendations for chemoprevention

10.3 Malaria vaccine recommendation

10.4 Recommendations for treatment

10.5 Recommendations for interventions in the final phase of elimination and prevention of re-establishment

1. ABBREVIATIONS

ABT	artemisinin-based treatment
Anti-CS	anti circumsporozoite antibody
ACT	artemisinin-based combination therapy
AE	adverse event
AEFI	adverse event following immunization
AESI	adverse event of special interest
AL	artemether-lumefantrine
ANC	antenatal care
AS + AQ	artesunate + amodiaquine
ASPY	artesunate-pyronaridine
AVPU	alert, voice, pain, unresponsive
BCC	behaviour change communication
bw	body weight
CHW	community health worker
CI	confidence interval
CIDG	Cochrane Infectious Diseases Group
CPES	chemoprevention efficacy study
cRCT	community-randomized controlled trial

CS4ME	Civil Society for Malaria Elimination
DALY	disability adjusted life year
DHAP	diydroartemisinin-piperaquine
DHIS2	District Health Information Software 2
DOT	directly observed therapy
DP	dihydroartemisinin-piperaquine
DTP	diphtheria, tetanus and pertussis (vaccine)
EIR	entomological inoculation rate
EPI	Expanded Programme on Immunization
EtD	evidence-to-decision framework
GDG	Guideline Development Group
GMP	Global Malaria Programme
GPIRM	*Global plan for insecticide resistance management*
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRC	Guidelines Review Committee
GTS	*Global technical strategy for malaria 2016 - 2030*
GVCR	Global Vector Control Response

G6PD	glucose-6-phosphate dehydrogenase
HBHI	High burden to high impact approach
HFCA	health-facility catchment area
HRP2	histidine-rich protein 2
ICER	incremental cost-effectiveness ratio
IHR	International Health Regulation
IPTi	intermittent preventive treatment in infants, now referred to as perennial malaria chemoprevention (PMC)
IPTp	intermittent preventive treatment in pregnancy
IPTsc	intermittent preventive treatment in school-aged children
IQR	interquartile range
IRM	insecticide resistance management
IRS	indoor residual spraying
IOS	International Organization for Standardization
ITN	insecticide-treated net
ITPS	insecticide-treated plastic sheeting
IVB	WHO Department for Immunization, Vaccines and Biologicals
IVM	integrated vector management
LLIN	long-lasting insecticidal net
LSM	larval source management
M&E	monitoring and evaluation
MDA	mass drug administration
MPAG	Malaria Policy Advisory Group *(previously Malaria Policy Advisory Committee)*
MRP	mass relapse prevention
MVIP	WHO Malaria Vaccine Implementation Programme
NAAT	nucleic acid amplification test
NMP	national malaria programme
NRS	non-randomised study
NSP	national (malaria) strategic plan
PBO	piperonyl butoxide
PCR	polymerase chain reaction
*Pf*HRP2	*Plasmodium falciparum* histidine-rich protein-2
Pfkelch13	*Plasmodium falciparum kelch13* gene
Pfplasmepsin2/3	*Plasmodium falciparum plasmepsin2/3 gene*
*Pf*PR$_{2-10}$	*Plasmodium falciparum* prevalence in children aged 2-10 years
PDMC	post-discharge malaria chemoprevention
PICO	population, participants or patients; intervention or indicator; comparator or control; outcome
PMC	perennial malaria chemoprevention
POE	points of entry
PPC	preferred product characteristic
PQ	prequalification (WHO)
*p*LDH	*parasite*-lactate dehydrogenase
Pvdhfr	*Plasmodium vivax* dihydrofolate reductase gene
PYAr	person-years at risk
QC	quality control
RACDT	reactive case detection and treatment
RCT	randomized controlled trial
RD	risk difference
RDA	reactive drug administration
RDT	rapid diagnostic test
RR	relative risk, or risk ratio
SAE	serious adverse event
SP	sulfadoxine pyrimethamine
SP + AQ	sulfadoxine-pyrimethamine + amodiaquine
SP + AS	sulfadoxine-pyrimethamine + artesunate
SMC	seasonal malaria chemoprevention
TDA	targeted drug administration
TES	therapeutic efficacy study
TTaT	targeted testing and treatment
UHC	universal health coverage
UN	United Nations
VCAG	Vector Control Advisory Group
VCTEG	Vector Control Technical Expert Group
WHO	World Health Organization

2. EXECUTIVE SUMMARY

The consolidated *WHO Guidelines for malaria* present all of the current WHO recommendations for malaria. These are the product of careful evaluation following standardized methods as part of the WHO process for developing guidelines *[1]*. WHO uses strictly defined processes to assess the quality, consistency and completeness of evidence to determine the strength of each recommendation.

WHO malaria recommendations tend to be short, evidence-based statements. They are usually accompanied by supplementary statements which draw attention to contextual and implementation considerations that may influence the appropriateness and impact of a recommendation in different settings. Clearly distinguishing recommendations from their associated contextual considerations provides a degree of flexibility for national policy-makers to adopt and adapt the strategies that are most appropriate in their settings.

This online platform and the associated PDF help to distinguish the formal recommendations from the supplementary statements. The Global Malaria Programme will use this platform to produce "living guidelines", which can be updated more rapidly than printed documents as new evidence becomes available. The tabs below each recommendation enable users to access the research evidence and evidence-to-decision (EtD) frameworks that informed the recommendation. There is also a feedback tab where users are encouraged to provide input directly related to each intervention.

Scope

The consolidated *WHO Guidelines for malaria* bring together all recommendations for malaria, including prevention using vector control, preventive chemotherapy and the vaccine; diagnosis, treatment and elimination strategies. The Guidelines also provide links to other resources including unpublished evidence reviewed at the time of formulating recommendations, guidance and information on: strategic use of information to drive impact; surveillance, monitoring and evaluation; operational manuals, handbooks and frameworks; and a glossary of terms and definitions.

The Guidelines provide:

- evidence-based recommendations pertaining to vector control tools, technologies and approaches that are currently available for malaria prevention and control, and for which sufficient evidence on their efficacy is available to support systematic reviews. The Guidelines are intended to provide an underlying framework for the design of effective, evidence-based national vector control strategies and their adaptation to local disease epidemiology and vector bionomics;
- evidence-based recommendations on the use of antimalarial medicines as preventive chemotherapy in people living in malaria-endemic areas who are at risk of malaria morbidity and mortality. These approaches include intermittent preventive treatment (IPT) in pregnancy (IPTp), perennial malaria chemoprevention (PMC), seasonal malaria chemoprevention (SMC), intermittent preventive treatment in school aged children (IPTsc), post-discharge malaria chemoprevention (PDMC) and mass drug administration (MDA);
- evidence-based recommendation on the use of the malaria vaccine;
- evidence-based recommendations on the treatment of uncomplicated and severe malaria in all age groups and situations, including in young children and pregnant women; and
- guidance on interventions in the final phase of elimination and prevention of re-establishment.

No guidance is given on the use of antimalarial agents to prevent malaria in people travelling from non-endemic settings to areas of malaria transmission. This is available in the WHO International travel and health guidance *[2]*.

WHO guidelines, recommendations and good practice statements

A WHO guideline is any document developed by WHO containing recommendations for clinical practice, or public health practice or health policy. A recommendation informs the intended end-user what he or she can or should do in specific situations to achieve the best possible health outcomes, individually and/or collectively. It guides the choice among different interventions or measures to ensure a positive impact on health and implications for the use of resources.

In certain situations, good practice statements may be provided. These statements reflect the consensus of the Guidelines Development Group (GDG) that the benefits of adhering to the intervention or course of action are large and unequivocal, and do not need to be supported by a systematic evidence review or could be based on indirect evidence.

The primary purpose of these WHO Guidelines is to support policy-makers in ministries of health and the managers of national malaria control programmes in endemic countries to establish national policies and plans tailored to their local context.

Link to WHO prequalification

When a recommendation is linked to the introduction of a new tool or product, there is a parallel process managed by the WHO Prequalification Team to ensure that diagnostics, medicines, vaccines and vector control products meet global standards of quality, safety and efficacy, in order to optimize use of health resources and improve health outcomes. The prequalification process consists of a transparent, scientifically sound assessment, including dossier review, consistency testing or performance evaluation, and site visits to manufacturers. This information, in conjunction with other procurement criteria, is used by the United Nations (UN) and other procurement agencies to make purchasing decisions regarding these health products. This parallel process aims to ensure that recommendations are linked to prequalified products and that prequalified products are linked to a recommendation for use.

Expert input is important for the interpretation of the evidence,

and the development of guidance may rely on expert opinion, particularly in areas where the evidence is currently weak, scarce or absent. For example, the vector control recommendations presented in the Guidelines are based on a consideration of the evidence gained from randomized controlled trials (RCTs) and other types of trials and studies, as well as the technical knowledge and experience of the GDG and External Review Group involved in the standard guideline development process.

Updating evidence-based guidance
The first edition of these consolidated Guidelines was released in early 2021 as a compilation of the existing recommendations for malaria vector control and treatment.

This version of the Guidelines includes new WHO recommendations on two classes of insecticide-treated nets that were established following the generation of evidence on the epidemiological impact of pyrethroid-chlorfenapyr and pyrethroid-pyriproxyfen ITNs. Given the increasing complexity in prioritization of limited resources across different ITN products, WHO and partners also developed separate guidance on ITN prioritization *[3]* under resource constrained conditions.

Future updates for treatment include recommendations that are already in the Guidelines but for which the evidence was not previously subjected to the GRADE process, and new molecules under development that will be included once the evidence base becomes available.

Readers should note the dates of individual recommendations. Revisions to these Guidelines will be communicated via the Global Malaria Programme website and through WHO's standard dissemination channels. From this point forward, these consolidated Guidelines represent the latest and definitive reference for all WHO guidance on malaria.

Dissemination
These consolidated *WHO Guidelines for malaria* are available on the MAGICapp online platform, linked to the WHO malaria website. The original English version has been translated into French, Spanish and Arabic. All research evidence and references are available on the web platform and will be available to download, and relevant implementation guidance will be linked to the recommendations. When recommendations are updated, they will be labelled as such and will always display the date of the most recent update. Each time there is an update, an updated PDF version of the Guidelines will be downloadable on the WHO Global Malaria Programme website to facilitate access where the Internet is not reliably available. Users should note that older downloaded PDFs of the Guidelines may be outdated and may not contain the latest recommendations.

WHO Headquarters will work closely with its regional and country offices to ensure the wide dissemination of the Guidelines to all malaria-endemic countries. There will also be dissemination through regional, sub-regional and country meetings. Member States will be supported to adapt and implement these Guidelines.

Feedback
The Global Malaria Programme welcomes feedback, either via the tab associated with each recommendation or by e-mail to gmpfeedback@who.int, to help identify recommendations in need of update or development.

2.1 Guideline Translations

The *WHO Guidelines for malaria* have been translated into French, Spanish and Arabic and are linked below:

- Lignes directrices de l'OMS sur le paludisme
- Directrices de la OMS sobre la malaria
- لمباديء التوجيهية لمنظمة الصحة العالمية بشأن الملاريا

3. INTRODUCTION

Background
Malaria continues to cause unacceptably high levels of disease and death, as documented in successive editions of the *World malaria report [4]*. According to the latest report, there were an estimated 247 million cases and 619 000 deaths globally in 2021. Malaria is preventable and treatable, and the global priority is to reduce the burden of disease and death while retaining the long-term vision of malaria eradication. Here, we present the *WHO Guidelines for malaria* developed by the WHO Global Malaria Programme as a comprehensive and inclusive resource for advice on malaria.

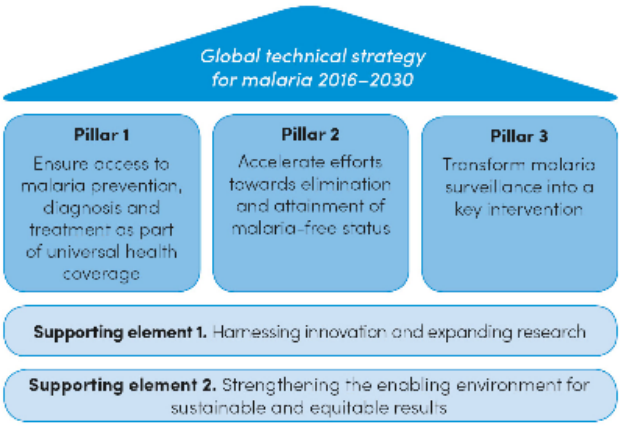
The *Global technical strategy for malaria 2016–2030 [5]* (GTS) provides an overarching framework to guide malaria control and elimination efforts. Adopted by the World Health Assembly in May 2015 and update adopted in May 2021, the Strategy defines goals, milestones and targets on the path to a world free of malaria (Table 1). The goals focus attention on the need to both reduce morbidity and mortality, and to progressively eliminate malaria from countries that had malaria transmission in 2015. The GTS presents a framework through which the goals can be achieved (Figure 1).

Table 1. Goals, milestones and targets for the *Global technical strategy for malaria 2016–2030*

GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

The GTS *[5]* states that it is essential for malaria programmes to '"ensure access to malaria prevention, diagnosis and treatment as part of universal health coverage"' (Fig.1, - Pillar 1). Universal health coverage (UHC) means that all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation and palliative care. For malaria, WHO has recommended a range of interventions - namely, vector control, chemoprevention, diagnostic testing and treatment - to reduce transmission and prevent morbidity and mortality. A UHC approach means ensuring that individuals and communities are covered by the appropriate mix of these interventions, based on local context, to control and ultimately eliminate malaria.

Fig. 1. Global technical strategy for malaria 2016-2030: framework, pillars and supporting elements



The second pillar of the GTS urges all countries to accelerate efforts towards elimination and attainment of a malaria-free status. Progress towards elimination is a continuous process and not a set of independent stages. Countries, subnational areas and communities are situated at different points along the malaria transmission continuum. Malaria transmission intensity varies within a country or area, as does the level of investment, biological determinants, environmental factors, strength of health systems and social, demographic, political and economic factors. Strategies will need to be tailored to the local setting by taking into account the local context and epidemiology of malaria.

The principal objective of national malaria programmes (NMPs) is to combine a selection of these interventions into packages that are tailored to achieve sustainable and equitable impact in a given setting. To decide upon the appropriate intervention package and allocation of resources that will achieve this objective and contribute to UHC, programmes should use a process that combines the analysis of impact and value for money with extensive stakeholder engagement and discussion. The process should be informed by past and current malaria transmission intensity and incidence data; contextual vulnerability related to the human host, parasites, vectors, and past and present intervention coverage; acceptability; and equality of access and use (including analysis of financial barriers and how to address them). When the objective is elimination, a similar process is undertaken, although the types of interventions and value for money analysis will be different than in high-burden settings.

Following progressive reductions in malaria burden between 2000 and 2015, progress stalled. By 2017, the world was off track to achieve the malaria morbidity and mortality reduction targets. In response, a revitalization effort called "High burden to high impact (HBHI)" was launched in 2018 *[6]*. This approach focuses attention on how to get back on track: garnering political will to reduce the toll of malaria; using strategic information to drive impact; developing better guidance, policies and strategies; and improving coordination of support for national malaria responses. Although the impetus for articulating these key activities was the need to get back on track to achieve the GTS morbidity and mortality targets, these activities apply equally well to all malaria-endemic countries and to ensure continued progress towards the GTS elimination goals.

Objectives

These consolidated *WHO Guidelines for malaria* aim to provide the latest evidence-based recommendations in one reference to support countries in their efforts to reduce and ultimately eliminate malaria. The objectives of the Guidelines are:

- to provide evidence-based and context-sensitive recommendations on the appropriate choice(s) for malaria prevention (vector control, preventive chemotherapies and the vaccine), case management (diagnosis and treatment) across all transmission settings and interventions in the final phase of elimination and prevention of re-establishment;
- to support the development by WHO Member States of evidence-based national malaria policies for prevention and case management across all transmission settings;
- to encourage the use of local data to inform subnational stratification to maximize the impact of available resources; and
- to inform the research agenda to enable updates to the Guidelines by identifying gaps in evidence that constrain the development of guidance or weaken current recommendations.

Evidence base

These Guidelines are based on the synthesis of the available evidence on the health effects of interventions, and the grading of

the certainty of that evidence using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach. The synthesized and graded evidence on the health effects of interventions, as well as any evidence on contextual factors, is used to develop an evidence-to-decision (EtD) framework for each recommendation *[7]*. The judgement on the different factors in the EtD framework (including the certainty of evidence) facilitates the determination of the strength and direction of each recommendation.

Expert input is important for the interpretation of the evidence, and the development of guidance may rely on expert opinion, particularly in areas where the evidence is currently weak, scarce or absent. For example, the vector control recommendations presented in the Guidelines are based on a consideration of the evidence gained from randomized controlled trials (RCTs) and other types of trials and studies, as well as the technical knowledge and experience of the GDG and External Review Group involved in the standard guideline development process. Details of how evidence is considered are presented in Section 8: Methods. Details of contributors for specific recommendations are presented in Section 10: Contributors and interests.

Target audience

The primary audience for these Guidelines is policy-makers in ministries of health and the managers of NMPs in endemic countries. The Guidelines may also be of interest to health care practitioners, environmental health service professionals, procurement agencies, the private sector, and civil society groups. The Guidelines are also intended for use by international development partners, donors and funding agencies in order to support decision-making on allocation of resources for interventions and procurement of appropriate malaria control products. In addition, the Guidelines are intended to guide researchers, research funders and those interested in the outcomes of research to address the evidence gaps that are constraining the development of guidance or weakening current recommendations.

Equity, gender and human rights

The right to enjoy the highest attainable standard of physical and mental health (commonly referred to as the right to health) is enshrined in several international human rights treaties, regional agreements, and national constitutions and laws. Member States have minimum "core" obligations that include "the prevention, treatment and control of epidemic, endemic, occupational and other diseases" *[8]*.

Yet, gender-based discrimination, human rights violations, and inequities related to social, economic, environmental, commercial and political determinants of health deprive billions of people around the world of their right to enjoy the highest attainable standard of health and well-being. It is of great concern that, over the past few years, health inequities have been exacerbated by the impacts of the ongoing and interlinked crises of the coronavirus disease (COVID-19), conflict, climate change, food insecurity and the global economy.

Too many people are missing out on the interventions they need to keep them healthy, including interventions to prevent and treat malaria. According to a WHO report *[9]*, malaria, TB and HIV/AIDS are diseases that predominantly impact the chronically disadvantaged. While the magnitude and extent of health inequalities remain poorly understood, it is clear that certain population groups have persistently higher disease mortality and morbidity and more limited access to life-saving interventions. The report documents that the poorest, least educated and rural groups are less likely to seek care for children with fever.

In most countries, Member States have not adequately identified and addressed social and structural barriers to health, or taken action to ensure gender equality, equity and human rights. Communities are often excluded from health decision-making, even though people are entitled to active, free and meaningful participation in decisions that directly affect them, such as the design, implementation and monitoring of health interventions. Participation increases ownership and helps to ensure that policies and programmes are responsive to the needs of the people they are intended to benefit.

The existing inequities are barriers to achieving global and national goals and targets on malaria. Successful implementation of malaria control interventions should, therefore, be viewed through a human rights and health equity lens. This means fully acknowledging the importance of engaging people in the design and delivery of health and care systems to meet their needs, and empowering them to make informed decisions about their health and take action.

As many of the malaria interventions are reliant on broader health care delivery platforms, a rights-based approach is required to ensure that quality health services and programmes are available, accessible and acceptable to all those in need, including nomadic populations, individuals with disabilities, out-of-school youth, and those living in sparsely populated and underserved areas far from health services and schools.

National programmes should address inequity concerns by monitoring the coverage of recommended interventions among individuals in identified risk categories and targeting those most at risk. Health inequities and barriers to health need to be systematically identified and addressed by Member States and other stakeholders through gender-responsive, equitable and human rights-based health systems, with a focus on individuals and groups experiencing intersecting forms of discrimination, marginalization and/or social exclusion.

Etiology

Malaria is a life-threatening disease caused by the infection of red blood cells with protozoan parasites of the genus *Plasmodium* that are transmitted to people through the bites of infected female *Anopheles* mosquitoes. Four species of *Plasmodium* (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*) most commonly infect humans. *P. falciparum* and *P. vivax* are the most prevalent species and *P. falciparum* is the most dangerous. A fifth species, *P. knowlesi* (a species of *Plasmodium* that primarily infects non-human primates) is increasingly being reported in humans inhabiting forested regions of some countries of South-East Asia and the Western Pacific regions, and in particular on the island of Borneo.

Malaria transmission, acquisition of immunity, and clinical manifestations of disease

The intensity of transmission depends on factors related to the parasite, the vector, the human host and the environment. Transmission tends to be more intense in places where the mosquito lifespan is longer and where the females prefer to bite humans rather than other animals. The survival and longevity of female mosquitoes is of critical importance in malaria transmission, as the malaria parasite generally requires a period of 7–10 days to develop inside the mosquito into a form that is infective to humans. Female mosquito longevity is dependent on intrinsic, genetic factors, as well as on environmental factors including temperature and humidity. The strong human-biting habit of the African vector species is one of the reasons why approximately 90% of the world's malaria cases occur in Africa.

Transmission intensity is usually assessed as the incidence of cases or the prevalence of infection. Most countries have information on the annual parasite incidence (number of new parasitologically confirmed malaria cases per 1000 population per year) from routine surveillance and/or on the parasite prevalence from surveys, often conducted during or just after periods of peak transmission *[10]*.

The following categories of transmission intensity are indicative and meant to provide an adaptable framework in which each country can conduct a stratification exercise to classify geographical units according to local malaria transmission.

- Areas of high transmission are characterized by an annual parasite incidence of 450 or more cases per 1000 population and a *P. falciparum* prevalence rate of ≥35%.
- Moderate transmission areas have an annual parasite incidence of 250–450 cases per 1000 population and a prevalence of *P. falciparum/P. vivax* malaria of 10–35%.
- Areas of low transmission have an annual parasite incidence of 100–250 cases per 1000 population and a prevalence of *P. falciparum/P. vivax* of 1–10%. It should be noted that the incidence of cases or infections is a more useful measure in geographical units in which the prevalence is low, given the difficulty of measuring prevalence accurately at low levels *[11]*.
- Very low transmission areas have an annual parasite incidence of < 100 cases per 1000 population and a prevalence of *P. falciparum/P. vivax* malaria that is > 0 but < 1%.

The relation between parasite incidence, parasite prevalence and the number of cases presenting to health facilities per week can be estimated using models *[12]*. Differences in transmission from one area to another may be due to geographical characteristics, such as altitude, temperature, humidity, rainfall patterns, proximity to water bodies, land use, vector species and distribution, socio-demographic characteristics, access to antimalarial treatment, and coverage with vector control. In most endemic areas, seasonal patterns of transmission are observed, with high transmission during part of the year. Both the intensity and timing of transmission are important considerations in designing elimination strategies.

The manifestation of clinical disease depends strongly on the background level of acquired protective immunity, which is a consequence of the pattern and intensity of malaria transmission in the area of residence. In areas of moderate to high transmission, partial immunity to clinical disease and a reduced risk of developing severe malaria are acquired in early childhood. The pattern of acquired immunity is similar across the Sahel subregion, where malaria transmission is intense only during the three- or four-month rainy season and low at other times. In both these situations, clinical disease is confined mainly to young children, who may develop high parasite densities that can progress rapidly to severe malaria. By contrast, in these settings, adolescents and adults are partially immune and suffer clinical disease much less frequently, although they are often infected with low blood-parasite densities. Immunity is modified in pregnancy and gradually lost, at least partially, when individuals move out of the endemic areas for prolonged periods (e.g. a year or more).

In areas of low and very low transmission, as found in much of Asia, Latin America and other malaria-endemic areas, the transmission fluctuates widely by season, year, and over relatively small distances. *P. vivax* is an important cause of malaria in these regions. This generally low transmission delays acquisition of immunity, so that adults and children alike suffer from acute clinical malaria, with a significant risk for progression to severe malaria if left untreated. Epidemics may occur in these low or very low transmission areas when the inoculation rate increases rapidly because of a sudden increase in vectorial capacity. Epidemics may result in a very high incidence across all age groups, which can overwhelm health services.

In moderate and high transmission areas with sustained high coverage of vector control and access to treatment, reduced exposure to malaria infection may change the population structure of acquired immunity to reflect that found in low or very low transmission areas, resulting in a corresponding change in the clinical epidemiology of malaria and an increasing risk of epidemics if control measures are not sustained.

Recommendations and supporting implementation guidance

Evidence-informed recommendations are a critical component to support the development of national malaria strategic plans; they are intended to communicate "what to do". A second critical element is the strategic use of local data. This informs an understanding of the contextual diversity within each malaria-endemic country. Local data provide an understanding of the different types of settings – or strata – within each country. This is an essential prerequisite to identify the optimal mix of interventions and the best means to deliver them in the different subnational strata.

The Global Malaria Programme is working with countries to strengthen the generation and use of local information for stratification, the definition of optimal mixes of interventions, and the rational, safe and ethical prioritization of resources to maximize impact. Local data are also essential to understand the impact of the strategies deployed, providing opportunities to further refine sub-national strategies and inform global knowledge.

WHO also develops implementation guidance such as operational and field manuals to support the "how" aspect of delivering the recommended tools and strategies. Operational manuals and other

guidance hold practical information for increasing the target population's access to interventions. These documents are referenced and linked to these Guidelines. The Global Malaria Programme is working to align this implementation guidance with the recommendations in the *WHO Guidelines for malaria*. However, where there are inconsistencies, the Guidelines should be the default resource for national decisions. Countries may use the implementation guidance to define ways in which a recommendation can be implemented effectively – for example, intermittent preventive treatment for malaria in pregnancy could be implemented through antenatal care and/or community distribution. The intention of the guidance is to enable delivery, not to prescribe exactly how it should be done.

Strategic information to tailor programmatic response and selection of interventions

As malaria control improves, malaria transmission and risk become increasingly heterogeneous, both between and within countries. Thus, a "one-size-fits all" approach to programme decisions on intervention selection becomes inefficient. The situation requires stratification of the country at subnational levels according to past, present and future malaria risk, the structure and function of the health system, and other contextual factors. Stratification provides a rational basis to identify context-specific packages of interventions to target specific populations in the different subnational strata. Local data are essential to complete stratification and to inform the selection of the optimal mixes of interventions to maximize impact. Given that resource constraints usually limit the implementation of all desirable interventions in all areas of malaria risk, a prioritization exercise must also be conducted to ensure that resource allocation also optimizes intervention mixes and resultant impact. Guidance on these activities is available in Section 7: Surveillance.

The choice of interventions in each stratum should be informed by WHO's recommendations. However, given the complexities of malaria, with heterogeneity of risk and the unique contexts that every programme has to consider, global guidance is not intended and should not be used to provide prescriptive guidance on what should be done in every situation. These Guidelines signal a paradigm shift towards a problem-solving approach using local data to identify recommendations that are relevant at a country level and based on local context, defining stratum-specific packages of interventions that optimize impact and are prioritized for resource allocation. This shift moves away from overly prescriptive recommendations and will clearly distinguish evidence-informed recommendations from contextual considerations. The contextual considerations at national and subnational levels will inform how recommendations should be applied and strategies that may increase access for the target population.

Accurate stratification of malaria transmission intensity is essential for effective targeting of interventions. As countries progress towards elimination, finer scale mapping is required, and stratification should be more specific, ideally at the level of localities or health facility catchment areas *[13][14]*. As transmission intensity is progressively reduced, stratification needs to include vulnerability and receptivity to malaria, i.e. the risk for importation of malaria cases and the inherent potential of the vector-human ecosystem to transmit malaria.

Conclusion

These Guidelines provide a framework within which NMPs and their implementing partners may adopt and adapt the recommendations for use. Good quality surveillance data can also feed into this process by providing the granular local information needed to inform and evaluate national programme decisions (see Section 7: Surveillance). Where the boundaries of current knowledge are pushed, it is particularly important to ensure adequate attention to monitoring and evaluation. The information generated can then feed into updated guidance.

4. PREVENTION

Nearly half of the world's population is at risk of malaria. In areas with high malaria transmission, young children and pregnant women are particularly vulnerable to malaria infection and death. Since 2000, expanded access to WHO-recommended malaria prevention tools and strategies – including effective vector control and the use of preventive chemotherapies – has had a major impact in reducing the global burden of this disease.

4.1 Vector control

Background

The consolidated Guidelines incorporate: i) recommendations based on systematic reviews of the available evidence on the effectiveness of vector control interventions conducted since the launch of the Guidelines; and ii) existing WHO recommendations developed previously. The Guidelines commence by providing general recommendations on malaria vector control, followed by more specific recommendations on individual interventions and good practice statements on their deployment. The interventions are divided into categories of those recommended for large-scale deployment and those recommended as supplementary. Interventions that are recommended for large-scale deployment are those that have demonstrated public health value, i.e. have proven protective efficacy to reduce or prevent infection and/or disease in humans at the individual level, community level or both, and that are broadly applicable for populations at risk of malaria in most epidemiological and ecological settings. Malaria vector control interventions recommended for large-scale deployment are: i) ITNs that are prequalified by WHO, which in many settings

continue to be pyrethroid-only long-lasting insecticidal nets (LLINs); and ii) indoor residual spraying (IRS) with a product prequalified by WHO. Specific product choices within these broad intervention types should be informed by insecticide resistance data for the target area(s) and other information compiled during sub-national prioritization exercises. Once optimal coverage with one of these interventions has been achieved, supplementary interventions may be considered for deployment depending on the specifics of the population, situation or setting. These include personal protection measures that have a primary use-pattern of protecting individual users, although they may have some as yet unproven impact when deployed at the community level.

Vectors, their behaviour and distribution

Malaria is transmitted through the bites of infective female *Anopheles* mosquitoes. Of the more than 400 different species of *Anopheles* mosquitoes, only around 40 are malaria vectors of major importance. *Anopheles* mosquitoes lay their eggs in water. The eggs hatch to produce larvae, which undergo several moults before emerging from the pupal stage as adult mosquitoes. Different species of *Anopheles* mosquitoes have their own preferred aquatic habitats; for example, some prefer small, shallow collections of fresh water such as puddles and animal hoof prints, whereas others prefer large, open water bodies including lakes, swamps and rice fields.

Both male and female mosquitoes feed on plant nectar, but it is just the female mosquitoes that feed on blood as they require protein to develop their eggs. Different mosquito species demonstrate preferences for feeding on animals (zoophily) or on humans (anthropophily); however, these preferences are not absolute, and females may take a blood meal from non-preferred hosts when these are present in the area. Different hosts may be more or less attractive to mosquitoes than others. Several factors have been implicated in the attraction of female mosquitoes to a host, including exhaled carbon dioxide, lactic acid, host odours, warmth and moisture. Blood-feeding can take place inside human habitations (endophagy) or outdoors (exophagy), depending on the mosquito species. has implications for the selection and effectiveness of vector control interventions.

Female *Anopheles* mosquitoes blood feed predominantly at night, although some species may bite during the day in heavily shaded conditions, and some exhibit a peak in biting activity in the early evening or early morning. The blood-feeding preferences (zoophily/anthropophily, endophagy/exophagy) as well as the interplay between the peak biting time of *Anopheles* vectors and the activity and sleeping patterns of the human hosts has important consequences for malaria transmission and the choice of appropriate vector control interventions.

After blood-feeding, female mosquitoes rest in order to digest the blood meal and mature their eggs. Female mosquitoes may rest indoors (endophily) or outdoors (exophily), and this depends on innate species preferences as well as the availability of suitable resting sites in the local environment. The mosquitoes' choice of post-feeding resting site also has major implications for the selection of control interventions.

It is important to note that while an individual species of *Anopheles* will characteristically exhibit certain biting and resting behaviours, these are not absolute; subpopulations and individuals may exhibit different behaviours depending on a combination of intrinsic genetic factors, availability of preferred hosts and availability of suitable resting sites. Environmental and climatic factors, including rainfall, moonlight, wind speed, etc., as well as the deployment of vector control interventions can all influence biting and resting behaviours.

Accurate species identification is crucial for all studies and surveillance activities on field populations of vectors. Many of the vectors belong to species complexes and require advanced molecular analyses for species identification, necessitating appropriate laboratory resources. Without accurate species identification, the data collected on behaviour, distribution and infection rates will have limited use for decision-making by control programmes.

Background and rationale for vector control

The role of arthropods in the transmission of diseases to humans was first elucidated in the late 19th and early 20th centuries. Since effective vaccines or drugs were not always available for the prevention or treatment of these diseases, control of transmission often had to rely principally on control of the vector. Early control activities included the screening of houses, the use of mosquito nets, the drainage or filling of swamps and other water bodies used by insects for breeding, and the application of oil or Paris green to breeding places. Following the discovery of the insecticidal properties of dichlorodiphenyltrichloroethane (DDT) in the 1940s and subsequent discovery of other insecticides, the focus of malaria vector control shifted to the deployment of insecticides to target both the larval and adult stages of mosquito vectors.

Nowadays, it is well established that effective vector control programmes can make a major contribution to advancing human and economic development. Aside from direct health benefits, reductions in vector-borne diseases enable greater productivity and growth, reduce household poverty, increase equity and women's empowerment, and strengthen health systems *[15]*. Despite the clear evidence in broad support of vector control efforts, the major vector-borne diseases combined still account for around 17% of the estimated global burden of communicable diseases, claiming more than 700 000 lives every year *[16]*. Recognizing the great potential to enhance efforts in this area, WHO led the development of the *Global vector control response 2017–2030 [16]*, which is outlined in the subsequent section.

Between 2000 and 2015, the infection prevalence of *Plasmodium falciparum* in endemic Africa was halved and the incidence of clinical disease fell by 40% *[17]*. Malaria control interventions averted an estimated 663 million (credible interval (CI) 542–753 million) clinical cases in Africa, with ITNs making the largest contribution (68% of cases averted). Indoor residual spraying (IRS) contributed an estimated 13% (11–16%), with a larger proportional contribution where intervention coverage was high *[17]*.

Global vector control response 2017–2030

The vision of WHO and the broader infectious diseases community is a world free of human suffering from vector-borne diseases. In 2017, the World Health Assembly welcomed the *Global vector control response 2017–2030 [16]* (GVCR) and adopted a resolution to promote an integrated approach to the control of vector-borne diseases. The approach builds on the concept of integrated vector management (IVM), but with renewed focus on improved human capacity, strengthened infrastructure and systems, improved surveillance, and better coordination and integrated action across sectors and diseases. Development programmes, including, for example, irrigated agriculture, hydroelectric dam construction, road building, forest clearance, housing development and industrial expansion, all have the potential to influence vector-borne diseases, offering the opportunity for intersectoral collaboration and the adoption of strategies other than those based on insecticides.

The ultimate aim of the GVCR is to reduce the burden and threat of vector-borne diseases through effective, locally adapted, sustainable vector control in full alignment with Sustainable Development Goal 3.3: to end epidemics of malaria by 2030.

Effective and sustainable vector control is achievable only with sufficient human resources, an enabling infrastructure and a functional health system. As recommended under the GVCR, national programmes should lead a vector control needs assessment across the relevant sectors *[18]* to help appraise current capacity, define the requisite capacity to conduct proposed activities, identify opportunities for improved efficiency in vector control delivery, and guide resource mobilization to implement the national strategic plan.

Prevention, mitigation and management of insecticide resistance

Widespread and increasing insecticide resistance poses a threat to effective malaria vector control. Failure to mitigate and manage insecticide resistance is likely to result in an increased burden of disease, potentially reversing some of the substantial gains made in controlling malaria over the last decade.

WHO maintains a global insecticide resistance database and an online mapping tool that consolidate information on the status of the insecticide susceptibility of *Anopheles* mosquitoes in malaria-endemic countries. The latest data reveal that almost 90% of the malaria-endemic countries reporting insecticide resistance have detected resistance of their vectors to at least one insecticide class. Globally, resistance to pyrethroids is widespread, having been detected in at least one malaria vector in 68% of the sites for which data were available. Resistance to organochlorines was reported in 64% of the sites. Resistance to carbamates and organophosphates was less prevalent, detected in 34% and 28% of the sites that reported monitoring data, respectively *[4]*.

To date, there is no evidence of operational failure of vector control programmes as a direct result of increasing frequency of pyrethroid resistance *[19][20]*. Based on past experience, however, it is likely that operational failure will eventually occur if effective insecticide resistance management (IRM) strategies are not designed and implemented. Ideally, such strategies should be implemented early to prevent the spread and increase in the intensity of resistance. The overarching concepts of such resistance management strategies were outlined in the *Global plan for insecticide resistance management in malaria vectors* (GPIRM) in 2012 *[21]*.

Guidance on monitoring of insecticide resistance, interpretation of test results and implications for decision-making are given in the WHO *Test procedures for monitoring insecticide resistance in malaria vector mosquitoes [22]* and in the *Framework for a national plan for monitoring and the management of insecticide resistance in malaria vectors [23]*. When deciding whether adjustments to the national malaria strategic plan are required in a given area, at least the following must be considered for that locality:

- current and past transmission levels;
- current and past interventions deployed, including the coverage, usage and duration of efficacy;
- the insecticide resistance profile of the main vector species (including resistance intensity and resistance mechanisms); and
- other entomological information including vector species distribution, abundance and other bionomic data.

The susceptibility of mosquitoes to insecticides and determination of the species-specific presence, intensity and mechanisms of resistance in vector populations can be used to guide the selection of the most appropriate insecticidal products to deploy. Generally, if mosquitoes are found to be resistant to an insecticide, insecticides with a different mode of action should be deployed. However, there are reports of mosquitoes having differential susceptibility to insecticides within the same class, and questions have been raised about the level of cross-resistance between pyrethroid products *[21]*. The Global Fund to Fight AIDS, Tuberculosis and Malaria recently commissioned a review of the interpretation of insecticide resistance assays when selecting insecticidal products *[24]*.The review aimed to answer the question: In areas where pyrethroid resistance exists, but mosquitoes of the same population differ in their susceptibility to different pyrethroids, should programmes consider selecting one pyrethroid over another in order to manage insecticide resistance? Based on a review of evidence from molecular, laboratory and field data, the authors concluded that differences between adult mosquito mortalities in pyrethroid insecticide resistance assays are not indicative of a true or operationally relevant difference in the potential performance of pyrethroids currently in common use (deltamethrin, permethrin, α-cypermethrin and λ-cyhalothrin). Consequently, switching between pyrethroid insecticides (to improve intervention efficacy) should not be used as a means of managing insecticide resistance. This finding supports WHO's past and present position. Given that pyrethroid resistance in mosquitoes is widespread, WHO encourages the development and continued evaluation of nets treated with alternative insecticides *[25]*.

Key technical principles for addressing insecticide resistance are as follows:

- Insecticides should be deployed with care and deliberation in order to reduce unnecessary selection pressure and maximize impact on disease. National malaria programmes (NMPs) should consider whether they are using insecticides judiciously, carefully and with discrimination, and if there is a clear epidemiological benefit.
- Vector control programmes should avoid using a single class of insecticide everywhere and over consecutive years. Whenever possible, vector control programmes should diversify from pyrethroids to preserve their effectiveness. Although pyrethroids will continue to be used for ITNs in the near term, they should not generally be deployed for IRS in areas with pyrethroid ITNs, whether alone or combined with insecticides from a different class.
- IRM principles and methods should be incorporated into all vector control programmes, not as an option, but as a core component of programme design.
- NMPs should engage with the agricultural sector to coordinate insecticide use, with the aim of avoiding use of the same classes of insecticide for both crop protection and public health within the same geographical area.
- Routine monitoring of insecticide resistance is essential to inform the selection and deployment of insecticides.
- The additional costs of deploying new vector control tools as part of a comprehensive IRM response should be balanced against the potential long-term public health impact. Where feasible, formal economic evaluation is encouraged to investigate the likely incremental costs and effectiveness of potential IRM approaches, relative to feasible alternatives, for a given context.

Approaches

Historically, the most common way insecticides have been deployed to control malaria vectors has been through "sequential use". In essence, this is when a single insecticide class is used continuously or repeatedly until resistance has rendered it less effective or ineffective, after which a switch is made to an insecticide with a different mode of action to which there is no (or less) resistance. In theory, this may allow for an eventual switch back to the original insecticide class if resistance decreases to the point that it is no longer detectable by means of bioassays.

The agricultural industry has had some success in managing resistance by using different insecticides over space and time. Similar approaches have been proposed with the aim of preventing or delaying the spread and increase of resistance by removing selection pressure or by killing resistant mosquitoes. These strategies include mixtures of insecticides, mosaic spraying, rotations of insecticides and deployment of multiple interventions in combination.

- Mixtures are co-formulations that combine two or more insecticides with different modes of action. Effective deployment of a mixture requires the presence of resistance to all insecticides in the mixture to be rare, so that any individual mosquito that survives exposure to one insecticide is highly likely to be killed by the other insecticide or insecticides. Ideally, all insecticides in a mixture should have a similar residual life and remain bioavailable over time; in practice, this is difficult to achieve, particularly for vector control products that are meant to last for a number of years, such as long-lasting insecticidal nets (LLINs). An ITN product containing a pyrethroid and a pyrrole insecticide and another containing a pyrethroid and a juvenile hormone mimic have been developed and prequalified by WHO. Trials are ongoing to assess the epidemiological impact of these products after which their public health value will be assessed in order to develop any WHO recommendation. A mixture of a pyrethroid and a neonicotinoid insecticide for IRS has been prequalified by WHO.
- Rotations involve switching between insecticides with different modes of action at pre-set time intervals, irrespective of resistance frequencies. The theory is that resistance frequencies will decline (or at least not increase) during the period of non-deployment of insecticides with a specific mode of action.
- Mosaics involve the deployment of insecticides with different modes of action in neighbouring geographical areas. The optimal spatial scale (size of areas) for mosaics has yet to be determined, and rotations are generally considered to be more practical and feasible.
- Combinations expose the vector population to two classes of insecticides with differing modes of action through the co-deployment of different interventions in the same place, such as ITNs co-deployed with non-pyrethroid IRS (where both are at high coverage; see recommendation under section 4.1.2).

For malaria vector control, however, there is still little evidence of the success of these strategies and no consensus on the best IRM approach or approaches to apply in a given situation. Success of a particular approach will likely depend on mosquito genetics, behaviour and population dynamics, and the chemical nature of the insecticides and their formulation. A 2013 review of experimental and modelling studies on insecticide, pesticide and drug resistance concluded that mixtures generally lead to the slowest evolution of resistance *[26]*. However, more recently, an exploration of overlaps between agriculture and public health found that – owing to caveats and case specificity – there is only weak evidence of one IRM approach being better than another, and that the standard practice of using insecticides until resistance emerges before switching to an alternative (i.e. sequential use) may be equally effective under certain circumstances. More data, both from research and programmatic operations, are needed to compare resistance management approaches in the field *[27]* and to improve understanding of the biological mechanisms that are likely to favour different approaches in different situations *[28][29]*.

Evidence-based planning

To achieve optimal impact against malaria, control measures must be suitable for the geographic area (based on vector bionomics) and, well targeted and deployed at sufficient coverage. Without an evidence base or sufficient capacity to deploy interventions appropriately, resources may be used

suboptimally. Given the heavy reliance on insecticidal interventions – primarily ITNs and IRS – the impacts on the environment and insecticide resistance of local vectors are key considerations in vector control planning and implementation. The inappropriate deployment of insecticides both in agriculture and in public health programmes has the potential to result in avoidable insecticide contamination of the environment and/or development of insecticide resistance of local vectors. Ideally, IRM practices should be implemented as part of routine operations, rather than waiting for resistance to spread or increase and for control failure to be suspected or confirmed. A pragmatic approach must be taken that seeks to select appropriate vector control interventions based on the insecticide resistance profile of the major malaria vectors in the target area. To outline how resistance will be monitored and managed, NMPs should develop and implement national plans in accordance with the WHO *Framework for a national plan for monitoring and management of insecticide resistance in malaria vectors [23]*. Detailed information on insecticide resistance monitoring methods and on how to use the data to inform the selection of appropriate interventions will be provided in the revised WHO *Test procedures of monitoring insecticide resistance in malaria vectors*, anticipated to be published in 2022. Further information on insecticide resistance monitoring and, more broadly, on entomological surveillance is included in the WHO *Malaria surveillance, monitoring & evaluation: a reference manual*, which outlines priority data across different transmission settings *[30]*.

IRM plans should be revisited regularly to consider new information, and to integrate new interventions once they have been supported by WHO recommendations and prequalified.

Vector control across different malaria transmission settings
Access to effective vector control interventions will need to be maintained in the majority of countries and locations where malaria control has been effective. This includes settings with ongoing malaria transmission, as well as those in which transmission has been interrupted but in which some level of receptivity and vulnerability remains. Malaria elimination is defined as the interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite species in a defined geographical area as a result of deliberate intervention activities. Following elimination, continued measures to prevent re-establishment of transmission are usually required *[30]*. Interventions are no longer required once eradication has been achieved. Malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by all human malaria parasite species as a result of deliberate activities.

Residual transmission
WHO acknowledges that malaria can persist despite high coverage of antimalarial interventions, including in areas with optimal access to and use of ITNs or with high IRS coverage *[31]*. This persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme is referred to as residual transmission. Residual transmission occurs as a result of a combination of human and vector behaviours, for example, when people reside in or visit forest areas or do not sleep in protected houses, or when local mosquito vector species exhibit one or more behaviours that enable them to avoid vector control interventions, such as biting outside early in the evening before people have retired indoors and/or resting outdoors. The sources and risk of residual transmission may, therefore, vary by location, time and the existing components of the current malaria programme.

In some settings, supplementary interventions may be used in addition to ITNs or IRS to further reduce transmission. Recommendations on larviciding with chemical or biological insecticides and the use of house screening are outlined in a subsequent chapter. Supplementary interventions should be implemented in accordance with the principles outlined in the *Global vector control response 2017–2030 [16]*.

Residual transmission can be difficult to measure, as is the specific impact of supplementary tools on this component of ongoing transmission. Standardized methods for quantifying and characterizing this component of transmission are required in order to evaluate the effectiveness of single or combined interventions in addressing this biological challenge to malaria prevention, control and elimination.

There is an urgent need for greatly improved knowledge of the bionomics of the mosquitoes responsible for maintaining local transmission. New interventions and strategies should be evaluated against these vectors in order to effectively address residual transmission. While this knowledge is being gained and interventions are being developed, NMPs must prioritize the effective implementation of current interventions to reduce transmission to the lowest level possible. At the same time, they should collaborate with academic or research institutions to generate local evidence on the magnitude of the problem of residual transmission of malaria, including information on human and vector behaviours, and the effectiveness of existing and novel interventions.

Acceptability, participation and ethical considerations
Community participation in the implementation of vector control interventions often takes the form of “instruction” or “information”, with decisions about the need for interventions being made at international and national levels. Taking into account communities’ views on the recommended interventions may promote acceptance and adherence to the intervention. Increased levels of participation (e.g. consultation, inclusion and shared decision-making) should be included in the development and deployment of vector control interventions – from inception through to the planning and implementation stages.

WHO acknowledges that appropriate policy-making often requires explicit consideration of ethical matters in addition to scientific evidence. However, the ethical issues relevant to vector-borne disease control and research have not received the analysis necessary to further improve public health programmes. Moreover, WHO Member States lack specific guidance in this area. The Seventieth World Health Assembly *[32]* requested the Director-General “to review and provide technical guidance on the ethical aspects and issues associated with the implementation of new vector control approaches in order to develop mitigating strategies and solutions; and to undertake a

review of the ethical aspects and related issues associated with vector control implementation that include social determinants of health, in order to develop mitigating strategies and solutions to tackle health inequities." A scoping meeting was convened by WHO to identify the ethical issues associated with vector-borne diseases *[33]*. Unique ethical issues associated with vector control that were identified include the ethics of coercive or mandated vector control, the deployment of insecticides (and growing vector resistance to insecticides), and research on and/or deployment of new vector control technologies. Genetically modified mosquitoes are one such innovation that presents potential challenges, including how to prevent their spread beyond the intended geographical target areas and limit potential effects on the local fauna. In 2020 WHO published guidance on vector-borne disease and ethical considerations *[34]*. Work is continuing the develop guidance in this area.

Equity, gender and human rights
WHO advocates for optimal coverage with recommended vector control interventions. As such, malaria vector control should be implemented without discrimination on the basis of age, sex, ethnicity, religion or other characteristics. In some cases, special effort is required to reach populations that are geographically isolated or adopt a nomadic lifestyle.

Resource implications and prioritization
In the Guidelines, resource implications and the cost-effectiveness of vector control interventions have been largely addressed by drawing on a recent systematic review of the cost and cost-effectiveness of vector control interventions *[35]* and expert opinion within the GDG.

The systematic review of the cost and cost-effectiveness of vector control interventions that was used to inform the current vector control guidelines was published in 2021, as part of a broader systematic review on the cost and cost-effectiveness of malaria control interventions, drawing on evidence published between 2005 and 2018 *[35]*. The body of evidence on vector control interventions was based on the use of ITNs/LLINs, IRS and larval source management (LSM) mostly in sub-Saharan African countries. The review reported that, overall, WHO-recommended malaria interventions including vector control represent value for money; however, there was great variation in the costs of intervention delivery, reflecting not only differences in the actual resource use, but also the various types of costing methodologies employed. The available cost and cost-effectiveness data focused largely on individual interventions and less so on packages of interventions, which are recommended for effective malaria control. The authors reported that, due to the heterogeneity of the study contexts and the way data were presented, comparative analysis of the cost-effectiveness of interventions was not possible.

The WHO Global Malaria Programme is working with partners to update the evidence review on the cost and cost-effectiveness of the vector control interventions covered in the Guidelines to support future Guideline development deliberations, for example, by building and updating a database for the cost and cost-effectiveness of vector control and other malaria interventions. It is also planned that systematic reviews commissioned in the future will include a search of the literature on both the cost and cost-effectiveness of interventions under consideration as well as those previously approved.

4.1.1 Interventions recommended for large-scale deployment

Interventions that are recommended for large-scale deployment in terms of malaria vector control are those that have proven protective efficacy to reduce or prevent infection and/or disease in humans and are broadly applicable for populations at risk of malaria in most epidemiological and ecological settings.

Vector control interventions applicable for all populations at risk of malaria in most epidemiological and ecological settings are: i) deployment of ITNs that are prequalified by WHO, and ii) IRS with a product prequalified by WHO. Between 2000 and 2015, 78% of the clinical malaria cases averted was attributed to insecticidal vector control, namely through the widespread scale-up of ITNs and IRS *[17]*.

Programmatic targets against malaria, as detailed within national strategic plans, should be used to guide the decision-making process to assemble context-appropriate intervention packages. Decision-making around the intervention mix to deploy and the coverage level of each intervention needs to consider available local data to guide the stratification of interventions, the available funding, the relative cost-effectiveness of available intervention options, the resources required to provide access within the broader context of universal health coverage (UHC), the feasibility of deploying the intervention(s) at the desired coverage level, and the country's strategic goal. The resulting optimal coverage of the components of an intervention package for a given geographical area will also depend on other site-specific factors such as past and present transmission intensity, past and present intervention coverage, acceptability, and equity of access/use.

For malaria vector control interventions recommended for large-scale deployment namely, ITNs and IRS, optimal coverage refers to providing populations at risk of malaria with access to ITNs coupled with health promotion to maximize use, and ensuring timely replacement; or providing these populations with regular application of IRS. Either intervention should be deployed at a level that provides the best value for money while reflecting programmatic realities. In practice, this often means quantifying commodities to provide full access by the population at risk while realizing that this will not result in 100% coverage or 100% access due to various system inefficiencies. Being cognizant of such constraints, decision-making should then consider other alternatives as part of the intervention package, ranging from chemoprevention to supplementary vector control, instead of pursuing the idealistic

goal of providing full population coverage.

Insecticide-treated nets

For the ITN classes covered by WHO recommendations as interventions for use in protecting populations at risk of malaria, including in areas where malaria has been eliminated but the risk of reintroduction remains, WHO recommends products that have been prequalifed by WHO. WHO Member States and their procurement partners are encouraged to draw on the list of prequalified products to inform their choice of product(s).

An ITN may repel, disable and/or impact the fecundity of mosquitoes that come into contact with the insecticide on the netting material in addition to providing a physical barrier, thereby protecting the individual user. In addition, some studies have indicated that ITNs produce a "community effect", which means that when enough ITNs are being used in a community, the survival of the mosquito population as a whole is affected; this effect increases the protection against malaria for ITN users and extends protection to members of the community who do not sleep under an ITN *[36][37][38][39][40]*. However, such a community effect has not been observed in all settings *[41][42][43]*. The WHO Global Malaria Programme commissioned a review to examine the evidence for a community effect and to investigate the biological mechanisms by which ITNs provide both personal- and community-level protection against malaria. The review also investigated what factors may determine the presence of a community effect and moderate its intensity (Lines *et al unpublished evidence*).

The review concluded that a community effect does occur in the majority of settings, and that its extent is driven by a number of contextual factors. These factors include vector behaviour (particularly the extent of anthropophily, i.e. the propensity to feed on people, and endophagy, i.e. the tendency of mosquitoes to blood-feed indoors); the relative availability of human and non-human hosts in the locality; the level of ITN coverage and use in a community; the insecticide used (its residual insecticidal activity and repellency); and the resistance of the local malaria vectors, both physiological and behavioural, to the insecticide on the net.

The ITN coverage threshold for when the community effect becomes apparent depends on a large number of contextual factors. Regardless of the context-dependent starting threshold, the extent of the community-level protection increases as ITN coverage and net use in a given community increases. Because ITNs kill insecticide-susceptible mosquitoes that come into contact with the insecticide on the netting material, more mosquitoes will be killed as ITN coverage increases. This killing effect reduces both mosquito population density and mosquito longevity, resulting in fewer malaria vectors overall and a lower infectivity rate as fewer mosquitoes will survive the time it takes for the malaria parasite to develop in the mosquito. Consequently, the reduced density, age and proportion of the local mosquito population that is infective offer an additional level of protection to the community as a whole beyond the individual protection provided by ITNs.

Large-scale field trials *[40][44]* and transmission models *[45][46]* originally suggested that community coverage (i.e. the proportion of human population using an ITN with effective insecticide treatments each night) of ≥ 50% is expected to result in some level of community-wide protection. The WHO-commissioned review indicated that this area-wide protection may start to occur at lower coverage levels (Lines *et al unpublished evidence*). The review modelled the short-term effect of increasing ITN coverage on the EIR (infectious bites per person per year) in an area with high malaria transmission and an insecticide-susceptible, anthropophilic vector, assuming fixed human infectiousness. In the coverage range of 15% to 85%, an additional 20% increase in coverage of the human population at risk was shown to result in a reduction in malaria transmission intensity of approximately 50% (these findings are taken from the report submitted to WHO; findings may be revised if indicated by peer review). Additional ITN coverage is always beneficial in terms of providing more protection to individuals – both users and non-users of ITNs – and, conversely, any reduction in coverage may result in increased malaria transmission. However, there may be diminishing marginal returns to increasing coverage at higher levels. In terms of absolute cases of malaria averted, a reduction in malaria transmission when increasing ITN coverage from 80% to 100% may not generate the same impact as a 20% increase in coverage at lower levels of coverage; the marginal costs required to increase coverage at high levels (>80%) will also increase due to growing system inefficiencies. At the country level, these diminishing returns must be balanced against potential investments in other cost-effective malaria prevention and control activities by means of a well-informed prioritization process.

Three main ITN classes are recognized by WHO as given below. With the March 2023 update to the guidelines, these classes are now formally:

- ITNs designed to kill host-seeking insecticide-susceptible mosquito populations that have demonstrated public health value compared to untreated nets and whose entomological effects consist of killing and reducing the blood-feeding of insecticide-susceptible mosquito vectors. This intervention class covers pyrethroid-only nets prequalified by WHO and conventionally treated nets that rely on periodic re-treatment with a WHO prequalified self-treatment kit. Public health value has been demonstrated for products within this class and WHO recommends use of pyrethroid-only LLINs prequalified by WHO for large-scale deployment.
- ITNs designed to kill host-seeking insecticide-resistant mosquitoes and for which a first-in-class product demonstrates public health value compared to the epidemiological impact of pyrethroid-only nets. This class includes nets that are treated with a pyrethroid insecticide and a synergist such as piperonyl butoxide (PBO) and nets

treated with insecticides other than pyrethroid-based formulations. Public health value has been demonstrated for this class and WHO has issued recommendations for deployment of pyrethroid-PBO nets and for pyrethroid-chlorfenapyr nets in areas with pyrethroid-resistant mosquitoes.
- ITNs designed to sterilize and/or reduce the fecundity of host-seeking insecticide-resistant mosquitoes for which a first-in-class product demonstrates public health value compared to the epidemiological impact of pyrethroid-only nets. Nets treated with pyrethroid + pyriproxyfen (an insect growth regulator), which fall into this class, are now conditionally recommended for deployment instead of pyrethroid-only LLINs.

ITNs are most effective where the principal malaria vector(s) mosquitoes bite predominantly at night after people have retired under their nets. ITNs can be used both indoors and outdoors, wherever they can be suitably hung (although hanging nets in direct sunlight should be avoided, as sunlight can affect insecticidal activity).

Indoor residual spraying

IRS is the application of a residual insecticide to potential malaria vector resting surfaces, such as internal walls, eaves and ceilings of houses or structures (including domestic animal shelters), where such vectors are likely to come into contact with the insecticide. IRS with a WHO-prequalified product is recommended for large-scale deployment in most malaria-endemic locations. IRS is most effective where the vector population is susceptible to the insecticide(s) being applied, where the majority of mosquitoes feed and rest indoors, and where most structures are suitable for spraying. In deciding whether to deploy IRS, programmes should consider whether achieving the target coverage of IRS is feasible.

Humanitarian emergencies

The first priorities for malaria control in a humanitarian emergency are prompt and effective diagnosis and treatment *[47]*. Deployment of ITNs and IRS have been shown to provide protection against malaria in the limited number of studies that have been carried out in the chronic phase of emergencies *[48][49][50][51][52][53][54]* (Messenger *et al unpublished evidence*). However, deployment of such interventions may be logistically challenging during the acute phase of a humanitarian emergency. In the following sections, recommendations regarding the deployment of ITNs and IRS are provided.

Some vector control interventions and personal protection measures have been specifically designed for deployment in emergency situations. Such interventions include insecticide-treated plastic sheeting (ITPS), which can be used to construct temporary shelters; insecticide-impregnated blankets or topsheets, which may be included in emergency relief kits provided at the outset of an emergency; repellents; and treating cattle with insecticides. For all of these interventions, a limited number of studies have evaluated their efficacy in humanitarian emergencies *[54]* (Messenger *et al unpublished evidence*) and, as such, the evidence base on the effectiveness of these interventions against malaria is currently insufficient to formulate recommendations.

As in more stable settings, the appropriateness and effectiveness of vector control in humanitarian emergencies will depend on:

- the malaria infection risk;
- the behaviour of the human population (e.g. mobility, where they are sleeping or being exposed to vector mosquitoes); and
- the behaviours of the local vector population (e.g. indoor resting, indoor biting, early evening or night biting).

In humanitarian emergencies, further consideration must be given to whether the delivery of vector control interventions is feasible. This may depend on:

- the type of shelter available (e.g. ad hoc refuse materials, plastic sheeting, tents, more permanent housing); and
- the available infrastructure, resources and human capacity to deliver vector control.

Strong recommendation for , High certainty evidence

Pyrethroid-only nets (2019)

Pyrethroid-only long-lasting insecticidal nets (LLINs) should be deployed for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

- *WHO recommends ITNs that have been prequalified by WHO for deployment in protecting populations at risk of malaria.*
- *ITNs are most effective where the principal malaria vector(s) bite predominantly at night after people have retired under their nets.*
- *ITNs can be used both indoors and outdoors, wherever they can be suitably hung (though hanging nets in direct sunlight should be avoided, as sunlight can affect insecticidal activity).*

Practical Info

The current WHO recommendation for ITNs applies only to those mosquito nets that have been prequalified by WHO and

that contain only an insecticide of the pyrethroid class (categorized as 'pyrethroid-only LLINs').

As with all insecticide-based interventions, the insecticide resistance profile of the vectors within the area of deployment should be assessed. If pyrethroid-resistance is detected, pyrethroid-PBO ITN or pyrethroid-chlorfenapyr ITNs should be considered for distribution, and pyrethroid-pyrproxyfen ITNs may be considered, instead of pyrethroid-only nets (see the following recommendations on the other types of nets).

ITNs are generally acceptable to most communities. In many malaria-endemic countries, untreated nets were in use for many years prior to the introduction of ITNs and, even where there is not a long history of their use, they have become familiar tools for preventing mosquito bites. Individuals often appreciate the extra privacy afforded by a net, as well as its effectiveness in controlling other nuisance insects. In very hot climates, ITNs may be less acceptable, as they are perceived to reduce air flow, making it too hot to allow for a comfortable sleep. In areas where mosquito densities are low or where malaria transmission is low, individuals and communities may perceive less benefit to using nets.

When deploying ITNs, coverage must be optimized such that both personal and community-level effects are maximized and maintained in endemic settings. Post-distribution monitoring of nets is essential, reporting their durability, usage and coverage. Evaluation of the impact on vectors, such as their abundance, EIR and behaviour, and insecticide resistance status can be used to inform and guide future deployment.

Nets should be handled and disposed of appropriately to minimize risk to human and animal health and of environmental contamination. WHO recommends that old nets are not burned in the open air but are buried, preferably in non-permeable soil and away from water sources. Burning may lead to the release of dioxins, which are harmful to human health. The insecticides used on nets are toxic to aquatic organisms and so should not be disposed of in water.

Evidence To Decision

Benefits and harms

The systematic review *[55]* reported that ITNs significantly reduce all-cause child mortality (rate ratio: 0.83; 95% CI: 0.77–0.89; high-certainty evidence), incidence of *P. falciparum* malaria (rate ratio: 0.55; 95% CI: 0.48–0.64; high-certainty evidence), prevalence of *P. falciparum* malaria (risk ratio: 0.83; 95% CI: 0.71–0.98; high-certainty evidence), and incidence of severe malaria disease (rate ratio: 0.56; 95% CI: 0.38–0.82; high-certainty evidence) compared to no nets.

No undesirable effects were identified in the systematic review. However, the panel noted that brand new nets recently removed from packaging may cause slight, transitory irritation to skin, eyes, nose, etc. Some users complain that the nets are too hot to sleep under, especially during the warmer seasons. As with any insecticide-based intervention, ITNs may also play a role in insecticide resistance development in *Anopheles* vectors, and there is a risk of environmental contamination with potential toxic effects on animals if nets are not handled or disposed of carefully (see section on Practical Info).

Certainty of the Evidence

High

The systematic review determined that, overall, the evidence that ITNs have an impact on malaria was high compared to no nets and compared to untreated nets.

Resources and other considerations

The table below, compiled by the GDG, lists resources that should be considered for the deployment of ITNs. Note that this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated enumerators • Transport logisticians and drivers • Stock managers • Distribution team staff (including those trained in behaviour change

	communication [BCC]) • Teachers/health facility staff, where appropriate, trained for distribution channel • Entomologists for quality control (QC) assessments • Environmental assessment support staff
Training	• Training in enumeration, distribution, logistics management, BCC, monitoring and evaluation (M&E) and quality assurance assessments.
Transport	• Shipping of ITNs may require large trucks for transport of containerized nets from port of entry to centralized warehouses and onward to the district or other level. • Vehicles to provide transport of ITNs and potentially distributors to the community (last mile) to enumerate persons/households, provide BCC and distribute ITNs • Vehicle maintenance costs • Fuel
Supplies	• ITNs • Inventory management forms • Recipient lists, distribution forms, including recipient sign-off sheets, daily distribution reports, inventory status reports, recipient status reports, and BCC materials (e.g. flip charts, posters, banners, staff clothing) • M&E data collection forms • ITN quality/durability assessment materials – e.g. cone bioassay material
Equipment	• Computer and communication equipment
Infrastructure	• Appropriate national and regional storage • Adequate lower level storage for ITNs at the district/school/health facility • Office space for management • Insectary to maintain mosquitoes exposed in QC assessments
Communication	• Communication with other ministries and sectors e.g. environment, transport • Communication with the general public, e.g. through the education sector and advertising on local media to encourage uptake and appropriate use and care of ITNs • Communication with the community/local leaders
Governance/ programme management	• Distribution supervisors • BCC supervision • M&E survey support for assessing coverage and use • QC supervision

Justification

The systematic review *[55]* followed the original 2003 analysis, which included insecticide-treated curtains and ITNs together and included two studies solely evaluating insecticide-treated curtains and one study evaluating both ITNs and insecticide-treated curtains. There was no obvious heterogeneity that would lead to a subgroup analysis to examine whether the effects were different, and the results from studies evaluating insecticide-treated curtains were consistent with the results of those evaluating ITNs. The GDG drew on the analysis to make recommendations related to ITNs only.

The systematic review *[55]* reported high-certainty evidence that, compared to no nets, ITNs are effective at reducing the rate of all-cause child mortality, the rate of uncomplicated episodes of *P. falciparum*, the incidence rate of severe malaria episodes, and the prevalence of *P. falciparum*. ITNs may also reduce the prevalence of *P. vivax*, but here the evidence of an

effect was less certain.

Compared to untreated nets, there was high certainty evidence that ITNs reduce the rate of uncomplicated episodes of *P. falciparum* and reduce the prevalence of *P. falciparum*. There was moderate certainty evidence that ITNs also reduce all-cause child mortality compared to untreated nets. The effects on the incidence of uncomplicated *P. vivax* episodes and *P. vivax* prevalence were less clear.

The systematic review did not identify any undesirable effects of pyrethroid ITNs.

Research Needs

- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection), as well as potential harms and/or unintended consequences of new types of nets and insecticides in areas where resistance to pyrethroids is high.
- Determine the comparative effectiveness and durability of different pyrethroid-only net types.
- Determine the effectiveness of nets in situations of residual/outdoor transmission.
- Determine the impact of ITNs in transmission 'hotspots' and elimination settings.

Conditional recommendation for , Moderate certainty evidence

Pyrethroid-PBO ITNs (2022)

Pyrethroid-PBO ITNs instead of pyrethroid-only LLINs can be deployed for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission where the principal malaria vector(s) exhibit pyrethroid resistance.

The conditionality of this recommendation is largely driven by the current higher unit cost of pyrethroid-PBO ITNs compared to pyrethroid-only LLINs and therefore the uncertainty of their cost-effectiveness. Furthermore, as PBO is less wash-resistant than pyrethroids, its bioavailability declines faster over the three-year estimated life of an ITN; therefore, the added impact of pyrethroid-PBO ITNs over that of pyrethroid-only LLINs may decline over time. The evidence comes from two sites in eastern Africa with pyrethroid resistance and not from other geographies where transmission levels and vector characteristics may vary. PBO acts by inhibiting certain metabolic enzymes, primarily oxidases, and so are likely to provide greater protection than pyrethroid-only LLINs where mosquitoes display mono-oxygenase-based insecticide resistance mechanisms.

In deciding whether pyrethroid-PBO ITNs may be appropriate in their context, malaria programmes should:

- *consider the deployment of pyrethroid-PBO ITNs in areas where resistance to pyrethroids in local vectors has been detected;*
- *determine whether resources are adequate to cover the extra cost of pyrethroid-PBO ITNs, while ensuring that coverage of populations at risk of malaria is not affected;*
- *note that WHO recommends that ITNs prequalified by WHO be selected for deployment.*

Practical Info

Given that the evidence indicates that unwashed pyrethroid-PBO ITNs are more effective than pyrethroid-only LLINs in areas with pyrethroid resistance up to 25 months post-deployment, the decision on whether to switch from pyrethroid-only LLINs to pyrethroid-PBO ITNs, or another ITN product designed to provide enhanced efficacy in areas of pyrethroid resistance, should be guided by resource availability. WHO recommends that pyrethroid-PBO ITNs be used where pyrethroid resistance is confirmed using standard procedures *[22]*. Given that pyrethroid-PBO nets are designed to provide improved impact against resistant mosquitoes in which pyrethroid resistance is, at least in part, conferred by a monooxygenase-based resistance mechanism, determining the presence of such resistance mechanisms in local vector populations will provide additional information to help target deployment.

In deciding whether to use potentially more expensive pyrethroid-PBO ITNs, malaria programmes should consider the impact this switch may have on vector control coverage. Deployment of pyrethroid-PBO ITNs must only be considered in situations where coverage with effective vector control (primarily ITNs or IRS) will not be reduced. The primary goal must be to ensure continued access and use of ITNs or IRS at levels that ensure optimal coverage for all people at risk of malaria as part of an intervention package. Post-distribution monitoring of nets to estimate coverage in terms of access to and use of nets and other malaria interventions is recommended.

Pyrethroid-PBO ITNs should not be considered a tool that can alone effectively manage insecticide resistance in malaria vectors. Despite the recent recommendation of other ITN classes and associate product, the development and evaluation of

ITNs treated with non-pyrethroid insecticides and other innovative vector control interventions for deployment across all settings continues to remain a priority to provide alternatives for use in a comprehensive IRM strategy.

The systematic review reported that the washing of pyrethroid-PBO ITNs may result in lower mosquito mortality and higher blood-feeding success than the washing of pyrethroid-only LLINs. The durability of pyrethroid-PBO ITNs compared to pyrethroid-only LLINs has been questioned previously based on wash-resistance data. The added epidemiological and entomological impact of pyrethroid-PBO ITNs depends on the bioavailability and retention of PBO on/in the net. If this is reduced significantly over time and/or declines with washing, the greater impact of pyrethroid-PBO ITNs over pyrethroid-only LLINs in terms of protection against malaria may be limited to less than three years. In addition, at present, it is unknown how differences in the design/composition of pyrethroid-PBO ITNs affect their relative efficacy. A series of experimental hut trials with entomological end-points using non-inferiority designs have recently been completed with as a means to provide clarity in this respect *[56]*. As part of M&E activities, data collected by programmes on net durability would provide information on the life span of pyrethroid-PBO ITNs under field conditions and hence on the period over which the additional impact is maintained.

Programmes that decide to switch from pyrethroid-only LLINs to pyrethroid-PBO ITNs based on concerns regarding continued effectiveness and/or insecticide resistance status of local vectors, should not revert back to the use of pyrethroid-only LLINs thereafter. Instead, programmes should plan for continued deployment of pyrethroid-PBO ITNs in that geographic area or develop plans for deployment of other equally or more effective new interventions once these are covered by a WHO recommendation.

Evidence To Decision

Benefits and harms

The systematic review *[59]* included two trials *[58][57]* from the United Republic of Tanzania and the Republic of Uganda that compared the epidemiological impact of pyrethroid-PBO ITNs against malaria to that of pyrethroid-only LLINs. Both trials were conducted in areas with highly pyrethroid-resistant mosquitoes, defined by the review team as mosquitoes demonstrating <30% mortality in discriminating dose assays. The review provided high- to moderate-certainty evidence that malaria parasite prevalence was lower where pyrethroid-PBO nets were deployed at four time points post net distribution (4–6 months: OR: 0.74; 95% CI: 0.62–0.89, 9–12 months: OR: 0.72; 95% CI: 0.61–0.86, 16–18 months: OR: 0.88; 95% CI: 0.74–1.04, and 21–25 months: OR: 0.79; 95% CI: 0.67–0.95).

The review also reported entomological outcomes, mosquito mortality and mosquito blood-feeding success derived from experimental hut studies. In areas classified by the authors as having highly pyrethroid-resistant mosquitoes, unwashed pyrethroid-PBO ITNs were found to result in higher mosquito mortality and lower blood-feeding success compared to unwashed pyrethroid-only LLINs. Comparing washed pyrethroid-PBO ITNs to washed pyrethroid-only LLINs, however, the review reported that it was unclear whether the washed pyrethroid-PBO ITNs had a greater effect on mosquito mortality, although the washed pyrethroid-PBO ITNs did decrease the blood-feeding success of mosquitoes.

In areas defined as having moderate, low (defined by the review team as 31–60% and 61–90% mosquito mortality, respectively, in discriminating dose assays) or no pyrethroid insecticide resistance, the review did not identify any studies with epidemiological outcomes. Regarding entomological outcomes, mosquito mortality was only shown to be higher with unwashed pyrethroid-PBO ITNs compared to unwashed pyrethroid-only LLINs in those areas with moderate insecticide resistance. Little or no difference was seen in terms of mosquito mortality or blood-feeding rates when washed or unwashed pyrethroid-PBO ITNs were used in areas with low or no resistance compared to pyrethroid-only LLINs.

Given that the systematic review was limited to two studies with malaria outcomes, a number of potential effect modifiers could not be examined. However, as with pyrethroid-only LLINs, the GDG concluded that the extent of the impact of pyrethroid-PBO ITNs is likely to vary in different settings and will depend on a number of factors, such as the behaviour of the main malaria vectors and their level and mechanism(s) of insecticide resistance, the parasite prevalence in that area, and the usage of nets within a community.

The systematic review did not report any harms or unintended consequences of the intervention. However, the GDG noted that, compared to pyrethroid-only LLINs, pyrethroid-PBO ITNs may play an as yet unknown role in the development of insecticide resistance in *Anopheles* mosquito vectors, such as increasing selection pressure for non-oxygenase resistance mechanisms or perhaps increasing the intensity of oxygenase resistance. In the absence of empirical evidence, this potential undesirable effect was judged to be small.

Certainty of the Evidence

Moderate

The systematic review assessed that the overall certainty of evidence that pyrethroid-PBO ITNs have an impact on malaria parasite prevalence was moderate.

Values and preferences

No research was identified regarding preferences and values. The GDG judged that there was probably no important uncertainty or variability.

Resources

Similar resources, other than the cost of the ITN itself, are needed for the deployment of the different ITN products that are now available within the WHO recommended classes. (See table provided under 'Resources and other considerations' for pyrethroid-only ITNs.)

Based on the available cost data, the GDG judged that there are currently additional costs associated with deploying pyrethroid-PBO and other types of ITNs over pyrethroid-only LLINs. Due to the likely scale of ITN deployment, any additional cost per net would amount to a considerable additional budget associated with a switch away from pyrethroid-only LLINs, which would need to be met in order to maintain coverage. The GDG, however, remarked that unit costs change over time and, as they do, a review will be needed to determine whether this cost discrepancy remains. National programmes are encouraged to pay specific attention to the commodity cost, as this will also vary depending on required quantities and lead-times and will be a key ingredient to the separately developed guidance on ITN prioritization.

Apart from the higher cost of the net, the GDG identified no additional resource requirements associated with a switch from pyrethroid-only LLINs to pyrethroid-PBO ITNs. Based on experience to date, pyrethroid-PBO ITNs require similar resources to those identified for the distribution of pyrethroid-only LLINs (see table provided under “Resources and other considerations” for pyrethroid-only LLINs). It would be necessary to assess the insecticide resistance status in the principal vector(s) in the area where deployment is planned in order to determine whether pyrethroid resistance is present and thus to justify such deployment. However, regular insecticide resistance testing by means of bioassays should form part of routine programme monitoring operations and therefore should already be part of the budget. Further information justifying the use of pyrethroid-PBO ITNs could be generated using standard WHO procedures *[22]* to determine if a monooxygenase-based mechanism is at least partially involved in conferring pyrethroid resistance.

The systematic review reported that cost-effectiveness analyses comparing pyrethroid-PBO ITNs and pyrethroid-only LLINs are currently not available *[59]*. The GDG concluded that the cost-effectiveness of pyrethroid-PBO ITNs compared to pyrethroid-only LLINs may vary. In areas of pyrethroid resistance, pyrethroid-PBO ITNs may have greater impact on malaria than pyrethroid-only LLINs during the period for which the PBO is bioavailable. However, PBO is less wash-resistant than pyrethroids and its bioavailability therefore declines faster over the three-year estimated life of an ITN. The added impact of pyrethroid-PBO ITNs over that of pyrethroid-only LLINs may be lost or decline considerably over time.

In addition to the issue of durability, the cost-effectiveness may also depend on a number of potential effect modifiers, such as the malaria transmission level and vector characteristics in an area. Lastly, the GDG was concerned that, given flatlined funding for malaria *[4]*, the procurement of pyrethroid-PBO ITNs may negatively impact programmes’ ability to maintain ITN coverage of at-risk populations. Due to the current moderately higher cost of this commodity, there is a risk that existing net coverage could not be maintained if no additional funds were made available to cover the additional expenditure required to purchase the same quantity of nets as previously deployed.

Equity

The impact on the equity of using pyrethroid-PBO ITNs instead of pyrethroid-only LLINs was judged to vary by the GDG. If switching to more costly pyrethroid-PBO ITNs resulted in lower coverage of those at risk of contracting malaria with preventive tools, equity would likely be reduced. However, if the switch resulted in no reduction in coverage and

those populations who were previously provided with pyrethroid-only LLINs were then protected against malaria by a slightly more effective intervention, equity would likely increase.

Acceptability

No research was identified regarding the acceptability of pyrethroid-PBO ITNs. However, the GDG judged that such nets would be equally acceptable to key stakeholders, given that they are by-and-large physically the same as and used similarly to pyrethroid-only LLINs.

Feasibility

No research was identified regarding the feasibility of implementing pyrethroid-PBO ITNs. Nevertheless, the GDG judged that distributing such nets would be equally feasible as for pyrethroid-only LLINs.

Justification

Pyrethroid-PBO ITNs combine pyrethroids and a synergist, which acts by inhibiting certain metabolic enzymes, primarily oxidases, within the mosquito that would otherwise detoxify or sequester insecticides before they could reach their target site in an insect. Therefore, compared to a pyrethroid-only LLIN, a pyrethroid-PBO ITNs should have an increased killing effect on malaria vectors that express elevated oxidases, which is commonly associated with pyrethroid resistance.

The systematic review *[59]* identified and included two trials *[57][58]*, both from eastern Africa, evaluating parasite prevalence in areas where pyrethroid-PBO ITNs were deployed compared to pyrethroid-only LLINs. Both trials were conducted in areas with highly pyrethroid-resistant mosquitoes, defined by the review team as mosquitoes demonstrating <30% mortality in discriminating dose assays. Parasite prevalence was reduced by approximately 20% up to 25 months after distribution. The Tanzanian trial has been extended further to establish whether this effect lasts the full duration of an LLIN's intended 36-month life span, but results are not yet publicly available.

Although the two epidemiological trials included in the review were from areas where pyrethroid resistance was determined to be high, the methods used by the authors to determine the level of resistance and the categorization of the different bands of resistance intensity were not consistent with those recommended by WHO *[22]*. In many parts of Africa, as well as other parts of the world, pyrethroid resistance is becoming more prevalent and is generally increasing in intensity in the presence of continued selection pressure *[4]*. The panel therefore concluded that pyrethroid-PBO ITNs are likely to offer greater protection against malaria than pyrethroid-only LLINs in most areas where pyrethroid resistance is detected and mediated by elevated oxidases, regardless of resistance intensity.

When moving from the evidence provided to a decision on the strength of the recommendation, the GDG concluded that the recommendation should be conditional rather than strong for this intervention. In the context of guideline development, a conditional recommendation reflects the lower strength of a recommendation and one for which the GDG concludes that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs. The conditionality of this recommendation was based on the fact that the available evidence was only from African sites with pyrethroid resistance, rather than from other geographies; the moderate additional benefit of deploying pyrethroid-PBO ITNs compared to pyrethroid-only LLINs; the overall moderate certainty of the results; the higher unit cost of pyrethroid-PBO ITNs compared to pyrethroid-only LLINs; and the uncertainty of cost-effectiveness.

Research Needs

WHO encourages additional high-quality research to generate further evidence on:

- the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of pyrethroid-PBO ITNs in areas where the mechanisms of resistance in vector species are not oxidase-based and in areas of lower malaria transmission intensity;
- contextual factors (e.g. acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to pyrethroid-PBO ITNs;
- the durability of pyrethroid-PBO ITNs.

Strong recommendation for , Moderate certainty evidence

New

Pyrethroid-chlorfenapyr ITNs vs pyrethroid-only LLINs (2023)

Pyrethroid-chlorfenapyr ITNs should be deployed instead of pyrethroid-only LLINs for prevention of malaria in adults and children in areas with pyrethroid resistance.

Note: Recommendations on deployment of pyrethroid-chlorfenapyr nets were separated into two distinct recommendations for better clarity, but share the same evidence to decision, justification, practical info and research needs. Please refer to the following section.

Evidence To Decision

Certainty of the Evidence Moderate

Conditional recommendation for , Moderate certainty evidence

New

Pyrethroid-chlorfenapyr ITNs vs pyrethroid-PBO ITNs (2023)

Pyrethroid-chlorfenapyr ITNs can be deployed instead of pyrethroid-PBO ITNs for prevention of malaria in adults and children in areas with pyrethroid resistance.

The conditionality of the recommendation to deploy pyrethroid-chlorfenapyr ITNs instead of pyrethroid-PBO ITNs is based on the GDG's judgement that the balance of desirable and undesirable effects probably favours pyrethroid-chlorfenapyr ITNs over pyrethroid-PBO ITNs. However, the evidence for this recommendation is from only one trial in Africa.

In deciding whether to deploy pyrethroid-chlorfenapyr ITNs instead of pyrethroid-only LLINs or pyrethroid-PBO ITNs, malaria programmes should:

- *determine whether resources are adequate to cover the extra costs compared to pyrethroid-only LLINs or pyrethroid-PBO ITNs, while ensuring optimal coverage of populations at risk of malaria;*
- *generate additional information or conduct analyses with the aim of maximizing impact through targeted deployment (e.g. stratification of malaria risk, assessment of the characteristics of local vectors, such as pyrethroid resistance mechanisms). ITNs for prevention of malaria in adults and children in areas with pyrethroid resistance; and*
- *note that WHO recommends that ITNs prequalified by WHO be selected for deployment.*

Practical Info

Given that pyrethroid-chlorfenapyr ITNs are designed to provide improved impact against insecticide-resistant mosquitoes, pyrethroid resistance in potential target areas should be confirmed using standard procedures *[22]*, as should the susceptibility of local vectors to chlorfenapyr. In any case, pyrethroid-chlorfenapyr ITNs should not be considered a tool that alone can effectively manage insecticide resistance in malaria vectors.

As with all malaria interventions, post-distribution monitoring of ITNs to estimate coverage in terms of access to and use of ITNs is recommended. WHO also recommends that programmes conduct studies of ITN survival, which includes assessments of ITN integrity, each time a campaign uses a new product such as pyrethroid-chlorfenapyr ITNs. Such studies will provide information on the product's life span under field conditions and thus enable estimation of the period over which the additional impact against malaria may be maintained. The systematic review reported that, two years after deployment, 34% of pyrethroid-chlorfenapyr ITNs were torn (defined as hole area ≥ 790 cm^2) and therefore not fit for use, compared to 28% of pyrethroid-only LLINs and 43% of pyrethroid-PBO ITNs.

Evidence To Decision

Benefits and harms

Given that the systematic review [Barker *et al unpublished evidence*] was limited to two studies with malaria outcomes, a number of potential effect modifiers could not be examined. The GDG concluded that the extent of the impact of pyrethroid-chlorfenapyr ITNs is likely to vary by setting and will depend on several factors such as intensity of malaria transmission, behaviour of the main malaria vectors, the level and mechanism(s) of insecticide resistance, and the usage of ITNs within a community. The GDG also noted that both the type and dosage of pyrethroid on the pyrethroid-only LLINs and on pyrethroid-chlorfenapyr ITNs (alphacypermethrin) differed from those on the pyrethroid-PBO ITNs (permethrin), and this may influence the impact against malaria. Furthermore, the GDG observed that the resistance mechanism of the vector population at the study site was not reported. If the pyrethroid resistance in the study was not due to P450-based mechanisms, the effect of the pyrethroid-PBO ITNs may have been underestimated, as these nets would not have offered the same level of protection than in areas where resistance is conferred, at least partly, by P450-based mechanisms.

The systematic review reported [Barker *et al unpublished evidence*] that one trial *[61]* recorded 90 (44.1%) adverse events in the group assigned to the pyrethroid-only LLINs, 17 (8.5%) in the pyrethroid-chlorfenapyr ITN group and 17 (8.5%) in the pyrethroid-PBO ITN group. The authors also narratively reported that skin irritation was the most commonly reported adverse event; however, no adverse event was assessed as serious. While five deaths were reported in the cohort, three of these were from drowning, one was due to severe malaria and one to pneumonia; all of these deaths were judged to be unrelated to the study interventions.

The review also reported data on ITN integrity from the United Republic of Tanzania *[61]*. The numbers (proportion) of torn ITNs (defined as hole area ≥ 790 cm^2 and therefore not serviceable) were reported as 86 (28%) in the pyrethroid-only LLIN group, 96 (34%) in the pyrethroid-chlorfenapyr ITN group and 81 (43%) in the pyrethroid-PBO ITN group.

The GDG noted that, compared to pyrethroid-only LLINs, pyrethroid-chlorfenapyr ITNs may exert an as yet unknown selection pressure for the development of resistance to pyrrole insecticides and non-oxygenase resistance mechanisms in *Anopheles* mosquito vectors.

Overall, the GDG judged that the extent of undesirable effects associated with pyrethroid-chlorfenapyr ITNs was small compared to either pyrethroid-only LLINs or pyrethroid-PBO ITNs and that the overall balance of effects probably favours pyrethroid-chlorfenapyr ITNs.

Certainty of the Evidence

Moderate

Based on the systematic review [Barker *et al unpublished evidence*], the GDG concluded that the overall certainty of evidence that pyrethroid-chlorfenapyr ITNs have an impact against malaria was moderate.

Values and preferences

No research was identified regarding preferences and values. The GDG judged that there was probably no important uncertainty or variability associated with pyrethroid-chlorfenapyr ITNs.

Resources

Similar resources, other than commodity costs, would be needed for the deployment of pyrethroid-chlorfenapyr ITNs as those listed for pyrethroid-only LLINs. (See table provided under “Resources and other considerations” for pyrethroid-only LLINs.)

Based on the cost data reported by the study in the United Republic of Tanzania *[61]*, pyrethroid-chlorfenapyr ITNs were estimated to cost US$ 3.02 per ITN, while pyrethroid-only LLINs and pyrethroid-PBO ITNs were estimated to cost US$ 2.07 and US$ 2.98 per ITN, respectively. Based on these data, the GDG judged that there are currently moderate additional costs associated with deploying pyrethroid-chlorfenapyr ITNs instead of pyrethroid-only LLINs. Due to the scale of existing ITN coverage, the moderate additional cost per ITN could amount to considerable additional costs

associated with a switch from pyrethroid-only LLINs to pyrethroid-chlorfenapyr ITNs, which would need to be met in order to maintain the same population coverage.

The GDG, however, remarked that unit costs change over time and often decrease as new technologies are brought to scale. As pyrethroid-chlorfenapyr ITNs are scaled up, further review will be needed to determine whether this cost difference remains. National programmes are encouraged to pay specific attention to the commodity cost, as this will also vary depending on required quantities and lead-times and will be a key ingredient to the separately developed guidance on ITN prioritization.

Insecticide resistance status of the principal vector(s) in the area where deployment is planned should be assessed to justify deployment of pyrethroid-chlorfenapyr nets. However, regular insecticide resistance testing by means of bioassays *[22]* should already be part of routine monitoring operations and programme budgets.

The systematic review reported that the study conducted in the United Republic of Tanzania *[61]* carried out cost-effectiveness analyses that compared pyrethroid-chlorfenapyr ITNs and pyrethroid-PBO ITNs to pyrethroid-only LLINs over the two-year period of the trial. Pyrethroid-chlorfenapyr ITNs were estimated to avert 152 DALYs [SD 72] per 10 000 total population, while pyrethroid-PBO ITNs averted 37 DALYs [SD 72] per 10 000 population. When considering the costs of malaria diagnosis and treatment, pyrethroid-chlorfenapyr ITNs were reported to be less costly (incremental cost US$ 2894 [SD 1129] per 10 000 population) than pyrethroid-PBO ITNs (US$ 4816 [SD 1360]) from all perspectives. From societal and household perspectives, pyrethroid-chlorfenapyr ITNs would be more effective and less costly than either pyrethroid-only LLINs or pyrethroid-PBO ITNs over a two-year period. The GDG concluded that the cost-effectiveness would probably favour pyrethroid-chlorfenapyr ITNs over pyrethroid-only LLINs and pyrethroid-PBO ITNs.

The GDG was concerned that, given flatlined funding for malaria *[4]*, the procurement of pyrethroid-chlorfenapyr ITNs may negatively impact the ability of programmes to maintain ITN coverage of at-risk populations. Due to the current moderately higher cost of this commodity, there is a risk that programmes may not be able to maintain existing ITN coverage or coverage of other malaria interventions if no additional funds to cover the higher costs are made available. Some pragmatic prioritization guidance *[3]* has been provided with a view to supporting programmes in decision-making around the deployment of new types of nets in resource-constrained environments.

Equity

The GDG judged that the impact on the equity of using pyrethroid-chlorfenapyr ITNs instead of pyrethroid-only LLINs or pyrethroid-PBO ITNs is variable. If switching from pyrethroid-only LLINs to more costly pyrethroid-chlorfenapyr ITNs would result in lower coverage of preventive interventions for those at risk of malaria, equity may be reduced. However, if the switch resulted in no reduction in coverage (due to increased funding or price reduction) and those populations who were previously provided with pyrethroid-only LLINs were then protected from malaria by a more effective intervention, equity would likely increase.

Acceptability

No research was identified regarding the acceptability of pyrethroid-chlorfenapyr ITNs. However, the GDG judged that such ITNs would be acceptable to key stakeholders, given that they are largely similar to pyrethroid-only LLINs and pyrethroid-PBO ITNs in terms of their appearance, design and use, and given that they are currently available at a cost similar to that of pyrethroid-PBO ITNs.

Feasibility

Although no research was identified regarding the feasibility of implementing pyrethroid-chlorfenapyr ITNs, the GDG judged that deploying these ITNs would be as feasible as deploying pyrethroid-only LLINs or pyrethroid-PBO ITNs.

Justification

Pyrethroid-chlorfenapyr ITNs combine two active ingredients: a pyrethroid and a pyrrole insecticide. They are designed to

kill mosquitoes that are resistant to pyrethroids and, as such, fall into the second class of ITNs recognized by WHO. Pyrrole insecticides such as chlorfenapyr disrupt adenosine 5'-triphosphate production in the mosquito's mitochondria, thereby reducing the target insects' ability to produce energy and leading to cell dysfunction and subsequent death. Pyrethroids, meanwhile, target voltage-gated sodium channels associated with the nervous system of the insect, which results in muscular paralysis and rapid death. Due to its different mode of action, chlorfenapyr is, therefore, unlikely to show any cross-resistance to standard neurotoxic insecticides such as pyrethroids. Furthermore, death of the insect may occur 24–48 hours after exposure to chlorfenapyr, in contrast to pyrethroids, which result in a more rapid kill. The different entomological mode and site of action of chlorfenapyr may reduce selection pressure for insecticide resistance. By including two active ingredients in an ITN, the likelihood of the mosquitoes being resistant to both is greatly reduced. Therefore, compared to pyrethroid-only LLINs or pyrethroid-PBO ITNs, pyrethroid-chlorfenapyr ITNs should have an increased killing effect against pyrethroid-resistant malaria vectors and thus a greater impact against malaria.

The systematic review [Barker *et al unpublished evidence*] identified and included two trials *[61][62]* from eastern and western Africa evaluating the impact of pyrethroid-chlorfenapyr ITNs on incidence of clinical malaria and prevalence of malaria infection, compared to pyrethroid-only LLINs or pyrethroid-PBO ITNs. Both trials were conducted in areas with high malaria transmission (malaria infection prevalence in children under 10 years of age recorded as 20–40%) and pyrethroid-resistant mosquitoes. Compared to pyrethroid-only LLINs, incidence of clinical malaria (defined as malaria symptoms, i.e. current fever with a temperature ≥ 37.5°C or fever in the past 48 hours, plus malaria parasitaemia) was reduced by approximately 55% one year after deployment of pyrethroid-chlorfenapyr ITNs and by 40% two years post-deployment. Prevalence of malaria infection (regardless of symptoms) was reduced by approximately 20% one year after deployment and by approximately 45% two years post-deployment. Compared to pyrethroid-PBO ITNs, pyrethroid-chlorfenapyr ITNs had little or no effect on incidence of clinical malaria one year after their deployment. However, after two years, incidence was reduced by 35%. Prevalence of malaria infection was reduced by approximately 20% one year post-deployment and by 30% two years post-deployment. The trials in Benin and the United Republic of Tanzania are continuing and will investigate whether the protective effect lasts the full duration of an LLIN's intended 36-month life span. Results are not available yet.

When moving from the evidence provided by the systematic review to a decision as to the strength of the recommendation, the GDG concluded that there should be a strong recommendation to deploy pyrethroid-chlorfenapyr ITNs instead of pyrethroid-only LLINs in areas where malaria vectors are resistant to pyrethroids. This was due to the large effect against malaria and the high certainty that the benefits of deploying pyrethroid-chlorfenapyr ITNs instead of pyrethroid-only LLINs would outweigh any harms. However, the panel concluded that the recommendation to deploy pyrethroid-chlorfenapyr ITNs instead of pyrethroid-PBO ITNs in areas of insecticide resistance should be conditional. This was based on the fact that the available evidence was from only one trial in the United Republic of Tanzania, where intensity of malaria transmission is high and *An. funestus* is the primary malaria vector, which in turn limits generalizability of the findings to other geographies with different anopheline vectors and eco-epidemiological characteristics. Furthermore, deploying pyrethroid-chlorfenapyr ITNs was associated with a moderate additional benefit compared to pyrethroid-PBO ITNs two years after ITN deployment, but with little or no difference in malaria outcomes one year after deployment.

Research Needs

WHO encourages additional high-quality research to generate further evidence on:

- the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/ unintended consequences of pyrethroid-pyriproxyfen ITNs in areas with insecticide resistance traits in the local primary vectors that differ from those of the available studies;
- contextual factors (e.g. acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to use of pyrethroid-chlorfenapyr ITNs; and
- the durability of pyrethroid-chlorfenapyr ITNs under field conditions.

Conditional recommendation for , Moderate certainty evidence

New

Pyrethroid-pyriproxyfen ITNs vs pyrethroid-only LLINs (2023)

Pyrethroid-pyriproxyfen ITNs can be deployed instead of pyrethroid-only LLINs for prevention of malaria in adults and children in areas with pyrethroid resistance.

The conditionality of the recommendation to deploy pyrethroid-pyriproxyfen ITNs instead of pyrethroid-only LLINs is based on the GDG's concerns that the available evidence indicates poor cost-effectiveness of pyrethroid-pyriproxyfen ITNs compared to pyrethroid-only LLINs and that the extra resources currently required to purchase these ITNs may negatively impact on coverage and equity.

In deciding whether pyrethroid-pyriproxyfen ITNs should be deployed instead of pyrethroid-only LLINs, malaria programmes should:

- *determine whether resources are adequate to cover the extra cost compared to pyrethroid-only LLINs, while ensuring optimal coverage of populations at risk of malaria;*
- *generate additional information or conduct analyses with the aim of maximizing impact through targeted deployment (e.g. stratification of malaria risk, assessment of the characteristics of local vectors, such as pyrethroid resistance mechanisms); and*
- *note that WHO recommends that ITNs prequalified by WHO be selected for deployment.*

Note: Recommendations on deployment of pyrethroid-pyriproxifen nets were separated into two distinct recommendations for better clarity, but share the same evidence to decision, justification, practical info and research needs. Please refer to the following section.

Evidence To Decision

Certainty of the Evidence Moderate

Conditional recommendation against , Moderate certainty evidence

New

Pyrethroid-pyriproxyfen ITNs vs pyrethroid-PBO ITNs (2023)

Pyrethroid-pyriproxyfen ITNs are not recommended for deployment over pyrethroid-PBO ITNs for prevention of malaria in adults and children in areas with pyrethroid resistance.

The conditionality of the recommendation against the deployment of pyrethroid-pyriproxyfen ITNs instead of pyrethroid-PBO ITNs is based on the GDG's judgement that the balance of effects favours pyrethroid-PBO ITNs over pyrethroid-pyriproxyfen ITNs and that, based on current cost and efficacy data, pyrethroid-PBO ITNs are more cost-effective. The GDG acknowledged that evidence to support this recommendation is derived from only a single trial in Africa.

Practical Info

Given that pyrethroid-pyriproxyfen ITNs are designed to provide improved impact against resistant mosquitoes, pyrethroid resistance in potential target areas should be confirmed using standard procedures *[22]*, as should susceptibility of the local vectors to pyriproxyfen. In any case, pyrethroid-pyriproxyfen ITNs should not be considered a tool that alone can effectively manage insecticide resistance in malaria vectors.

As with all malaria interventions, post-distribution monitoring of ITNs to estimate coverage in terms of access to and use of ITNs is recommended. WHO also recommends that programmes conduct studies of ITN survival each time a campaign uses a new product such as pyrethroid-pyriproxyfen ITNs, including assessment of ITN integrity. Such studies will provide information on the life span of the product under field conditions and thus enable estimation of the period over which the additional impact against malaria may be maintained. The systematic review reported that, two years after deployment, 39% of pyrethroid-pyriproxyfen ITNs were torn (defined as having a total hole area ≥ 790 cm^2 and therefore assumed to be not fit for use), compared to 28% of pyrethroid-only LLINs and 43% of pyrethroid-PBO ITNs.

Evidence To Decision

Benefits and harms

Given that the systematic review was limited to three studies with malaria outcomes, a number of potential effect modifiers could not be examined. The GDG concluded that the extent of the impact of pyrethroid-pyriproxyfen ITNs is likely to vary by setting and will depend on several factors, such as intensity of malaria transmission, behaviour of the main malaria vectors, the level and mechanism(s) of insecticide resistance, and the usage of ITNs within a community. The GDG also noted that, across the studies, different pyrethroids (either permethrin or alphacypermethrin) were used in the ITNs and the impact on malaria may vary by the pyrethroid used. However, the panel's overall judgement was that the anticipated desirable effects of pyrethroid-pyriproxyfen ITNs compared to pyrethroid-only LLINs would be moderate. Compared to pyrethroid-PBO ITNs, the GDG considered the benefits to be minor.

The trial from the United Republic of Tanzania *[61]* included in the systematic review reported 90 (44.1%) adverse events in the pyrethroid-only LLIN group, 80 (38.8%) in the pyrethroid-pyriproxyfen ITN group and 17 (8.5%) in the pyrethroid-PBO ITN group. The authors also narratively reported that skin irritation was the most commonly reported adverse event; however, no adverse event was assessed as serious. While five deaths were reported in the cohort, three of these were from drowning, one was due to severe malaria and one was due to pneumonia; all deaths were judged to be unrelated to the study interventions.

The review also reported data from the same trial *[61]* on ITN integrity. The numbers (proportion) of ITNs that were torn (defined as hole area ≥ 790 cm^2) were reported as 86 (28%) in the pyrethroid-only LLIN group, 109 (39%) in the pyrethroid-pyriproxyfen ITN group and 81 (43%) in the pyrethroid-PBO ITN group.

Overall, the GDG judged the magnitude of undesirable effects associated with pyrethroid-pyriproxyfen ITNs to be small compared to pyrethroid-only LLINs. However, compared to pyrethroid-PBO ITNs, the undesirable effects were judged to be large. Overall, the GDG concluded that, compared to pyrethroid-only LLINs, the balance of effects probably favours pyrethroid-pyriproxyfen ITNs, but when comparing pyrethroid-pyriproxyfen ITNs to pyrethroid-PBO ITNs, the balance of effects was judged to favour the comparator, namely pyrethroid-PBO ITNs.

Certainty of the Evidence

Moderate

Based on the systematic review, the GDG concluded that the overall certainty of evidence that pyrethroid-pyriproxyfen ITNs have an impact against malaria was moderate, compared to both pyrethroid-only LLINs and pyrethroid-PBO ITNs.

Values and preferences

No research was identified regarding preferences and values. The GDG judged that there was probably no important uncertainty or variability associated with pyrethroid-pyriproxyfen ITNs.

Resources

Apart from the higher commodity cost of pyrethroid-pyriproxyfen ITNs, similar resources would be needed for their deployment as those listed for pyrethroid-only LLINs. (See table provided under "Resources and other considerations" for pyrethroid-only LLINs.)

Based on cost data reported by the study in the United Republic of Tanzania *[61]*, pyrethroid-pyriproxyfen ITNs were estimated to cost US$ 3.68 per ITN, while pyrethroid-only LLINs and pyrethroid-PBO ITNs were estimated to cost US$ 2.07 and US$ 2.98 per ITN, respectively. Based on these data, the GDG judged that there are currently moderate additional costs associated with deploying pyrethroid-pyriproxyfen ITNs instead of pyrethroid-PBO ITNs. Based on the likely scale of ITN deployment, this moderate additional cost per ITN could amount to considerable additional costs associated with a switch to pyrethroid-pyriproxyfen ITNs, which would need to be met to maintain the same population coverage. The GDG, however, remarked that unit costs change over time and often decrease as new technologies are brought to scale. As pyrethroid-pyriproxyfen ITNs are scaled up, further review will be needed to determine whether this cost difference remains. National programmes are encouraged to pay specific attention to the commodity cost, as this will also vary depending on required quantities and lead-times and will be a key ingredient to the separately developed guidance on ITN prioritization .

To justify the deployment of pyrethroid-pyriproxyfen nets, the insecticide resistance status of the principal vector(s) in the area where deployment is planned should be assessed. However, regular insecticide resistance testing by means of bioassays *[22]* should already be part of routine monitoring operations and programme budgets.

The systematic review reported that the study conducted in the United Republic of Tanzania *[61]* carried out cost-effectiveness analyses comparing pyrethroid-pyriproxyfen ITNs and pyrethroid-PBO ITNs with pyrethroid-only LLINs over the two-year period of the trial. Pyrethroid-pyriproxyfen ITNs were estimated to incur 9 DALYs [SD 71] per 10 000 total population, while pyrethroid-PBO ITNs averted 37 DALYs [SD 72] per 10 000 population. When considering the costs of malaria diagnosis and treatment, pyrethroid-pyriproxyfen ITNs were reported to be the more costly (incremental cost US$ 9621 [SD 1327] per 10 000 population), whereas pyrethroid-PBO ITNs were less costly (US$ 4816 [SD 1360]) from all perspectives. The GDG concluded that the cost-effectiveness would probably favour pyrethroid-only LLINs or pyrethroid-PBO ITNs over pyrethroid-pyriproxyfen ITNs.

The GDG was concerned that, given flatlined funding for malaria *[4]*, the procurement of pyrethroid-pyriproxyfen ITNs may negatively impact the ability of programmes to maintain ITN coverage of at-risk populations while not improving impact. Due to the current moderately higher cost of this commodity, there is a risk that programmes may not be able to maintain existing ITN coverage or coverage of other malaria interventions if no additional funds to cover the additional costs are made available. Some pragmatic prioritization guidance *[3]* has been provided with a view to supporting programmes in decision-making around the deployment of new types of nets in resource-constrained environments.

Equity

The GDG judged that the impact on the equity of using pyrethroid-pyriproxyfen ITNs instead of pyrethroid-only LLINs or pyrethroid-PBO ITNs would vary. If switching from either of these types of nets to more costly pyrethroid-pyriproxyfen ITNs resulted in lower coverage of preventive interventions for those at risk of malaria, equity may be reduced. However, if the switch resulted in no reduction in coverage (due to increased funding or a price reduction) and those populations who were previously provided with potentially less effective pyrethroid-only LLINs were then protected from malaria by a potentially slightly more effective intervention, equity may increase.

Acceptability

No research was identified regarding the acceptability of pyrethroid-pyriproxyfen ITNs. However, the GDG judged that such ITNs would be acceptable to key stakeholders, given that they are largely similar to pyrethroid-only LLINs and pyrethroid-PBO ITNs in terms of their appearance, design and use.

Feasibility

Although no research was identified regarding the feasibility of implementing pyrethroid-pyriproxyfen ITNs, the GDG judged that deploying such ITNs would be as feasible as deploying pyrethroid-only LLINs or pyrethroid-PBO ITNs.

Justification

Pyrethroid-pyriproxyfen ITNs combine a pyrethroid insecticide and an insect growth regulator (IGR). The two ingredients have different entomological effects. The pyrethroid insecticide rapidly kills mosquitoes by targeting voltage-gated sodium channels associated with the nervous system of the insect. The IGR is a hormone mimic that does not directly kill insects, but disrupts their growth and reproduction. Mosquitoes that are not killed by the pyrethroid may be sterilized and/or have their fecundity reduced, thereby preventing multiplication of the insecticide-resistant mosquitoes. Pyriproxyfen has also shown some impact on a mosquito's life span. Pyrethroid-pyriproxyfen ITNs, therefore, fall into the third class of ITNs recognized by WHO, which consists of ITNs primarily designed to sterilize and/or reduce the fecundity of insecticide-resistant mosquitoes. It is unlikely that mosquitoes exposed to ITNs that combine a pyrethroid and an IGR will be resistant to both active ingredients due to their different modes of action and limited to no selection pressure exerted so far for pyriproxyfen resistance. As such, pyrethroid-pyriproxyfen ITNs could have a greater impact against malaria than pyrethroid-only LLINs in areas with pyrethroid-resistant malaria vectors.

The systematic review [Barker *et al unpublished evidence*] identified and included three trials *[61][62][63]* from western and

eastern Africa, evaluating the impact of pyrethroid-pyriproxyfen ITNs on incidence of clinical malaria and prevalence of malaria infection, compared to either pyrethroid-only LLINs or pyrethroid-PBO ITNs. All trials were conducted in areas of high malaria transmission (malaria infection prevalence in children under 10 years of age recorded by the trials as 20–40% and as 50–70% in children under 5) and pyrethroid-resistant mosquitoes. Compared to pyrethroid-only LLINs, incidence of clinical malaria (defined as malaria symptoms, i.e. current fever of temperature ≥ 37·5°C or fever in the past 48 hours, plus malaria parasitaemia) decreased by approximately 20% one year after deployment of pyrethroid-pyriproxyfen ITNs and by 15% two years post-deployment. Prevalence of malaria infection (regardless of symptoms) was reduced by approximately 30% one year post-deployment and by approximately 20% two years post-deployment. Compared with pyrethroid PBO ITNs, the use of pyrethroid-pyriproxyfen ITNs, the use of pyrethroid-pyriproxyfen ITNs was associated with a two-fold higher incidence of clinical malaria one year after ITN deployment, with a slightly increased or no effect on incidence two years post-deployment. There was no effect on prevalence of malaria infection one or two years post-deployment. The trial in Benin is continuing and will investigate whether the impact against malaria varies for the full duration (36-month life span) of an LLIN. Results are not available yet.

The GDG concluded on a conditional recommendation to deploy pyrethroid-pyriproxyfen ITNs instead of pyrethroid-only LLINs in areas where malaria vectors are resistant to pyrethroids. The recommendation for deployment was based on the moderate effect against malaria and the GDG's judgement that the benefits probably outweighed any harms of deploying pyrethroid-pyriproxyfen ITNs instead of pyrethroid-only LLINs. The conditionality, however, was stipulated based on the panel conclusion that pyrethroid-pyriproxyfen ITNs were less cost-effective than pyrethroid-only LLINs and, due to the higher unit cost of pyrethroid-pyriproxyfen ITNs, extra resources would be required to replace pyrethroid-only LLINs with these dual active ingredient ITNs. Unless additional resources are provided, a switch to pyrethroid-pyriproxyfen ITNs would result in reduced coverage of populations at risk of malaria, thereby negatively affecting coverage and equity.

The panel conditionally recommended against the deployment of pyrethroid-pyriproxyfen ITNs instead of pyrethroid-PBO ITNs in areas of insecticide resistance. This decision was based on the lack of evidence of pyrethroid-pyriproxyfen ITNs having a greater impact against malaria compared to pyrethroid-PBO ITNs; the balance of effects favours pyrethroid-PBO ITNs over pyrethroid-pyriproxyfen ITNs. Based on these results and the current unit costs of pyrethroid-pyriproxyfen ITNs, pyrethroid-PBO ITNs are currently more cost-effective. Extra resources would be required while there would be no benefit of deploying pyrethroid-pyriproxyfen ITNs instead of pyrethroid-PBO ITNs, and, in the absence of additional resources, this would result in reduced coverage of malaria interventions for populations at risk of malaria, thereby negatively affecting equity. The GDG also acknowledged that the available evidence on the efficacy of pyrethroid-pyriproxyfen ITNs compared to pyrethroid-PBO ITNs was from only one trial conducted in the United Republic of Tanzania, where malaria transmission is high and *An. funestus* is the primary malaria vector, which in turn limits generalizability of the findings to other geographies with different anopheline vectors and eco-epidemiological characteristics.

Research Needs

WHO encourages additional high-quality research to generate further evidence on:

- the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of pyrethroid-pyriproxyfen ITNs in areas with insecticide resistance traits in the local primary vectors that differ from those of the available studies;
- contextual factors (e.g. acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to use of pyrethroid-pyriproxyfen ITNs;
- the durability of pyrethroid-pyriproxyfen ITNs over the expected life span of an LLIN (three years).

Strong recommendation for , High certainty evidence

Insecticide-treated nets: Humanitarian emergency setting (2022)

Insecticide-treated nets (ITNs) should be deployed for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission affected by a humanitarian emergency.

This recommendation is limited to classes of ITNs currently recommended by WHO. As with ITNs deployed in more stable settings, WHO recommends that ITNs that are prequalified by WHO be selected for use in humanitarian emergencies.

When considering deployment of ITNs in humanitarian emergencies, the infrastructure, access, logistical capacity and resources available must be taken into account, as these may influence the feasibility and cost of procuring and deploying nets.

Practical Info

In deciding whether to deploy ITNs in emergency settings, consideration must be given to whether ITNs are appropriate for that setting, taking into account vector characteristics, human behaviour and available infrastructure. ITNs are most effective where the principal malaria vector(s) bite predominantly at night after people have retired under their nets and where the mosquitoes are susceptible to the insecticides used to treat the nets. Data will need to be collected to assess whether these criteria are met. There may be more limited capacity to gather such data in humanitarian emergencies than in more stable settings. In addition to assessing whether ITNs are appropriate, consideration of the feasibility of deploying nets in a particular emergency setting is important. Depending on the infrastructure, access, logistical capacity and resources available, procuring and distributing nets may be more challenging than in more stable settings. Instability in such settings may challenge long-term planning and so result in shorter lead times and consequently higher costs. It is also important to determine whether the shelters or housing structures in such settings are suitable for hanging a net. In some situations, the structure may have nowhere to hang a net or it may be too small to adequately accommodate a net.

Other considerations for the deployment, monitoring and evaluation of nets apply equally to emergency and non-emergency settings. Please consult the practical information under the WHO recommendations for the different ITN classes. However, as for collecting data to assess whether nets are suitable in an area, the feasibility and capacity to regularly collect information for M&E in emergency settings must be assessed.

Evidence To Decision

Benefits and harms

The systematic review *[54]* (Messenger *et al unpublished evidence*) assessed the epidemiological impact of pyrethroid-only LLINs against malaria compared to no nets in areas affected by humanitarian emergencies in the chronic phase – in the Republic of Union of Myanmar, on the Myanmar–Thailand border and in the Islamic Republic of Pakistan *[48][49][50][53]*; no studies were found from areas in the acute phase of an emergency. The review presented evidence that pyrethroid-only LLINs were associated with reduced *P. falciparum* parasite incidence (rate ratio: 0.55; 95% CI: 0.37–0.79; four studies; high-certainty evidence) and *P. falciparum* parasite prevalence (rate ratio: 0.60; 95% CI: 0.40–0.88); two studies; high-certainty evidence) compared to no nets. Deployment of pyrethroid-only LLINs was reported to probably result in reduced *P. vivax* parasite incidence (rate ratio: 0.69; 95% CI: 0.51–0.94; three studies; moderate-certainty evidence). Little or no difference was seen in *P. vivax* parasite prevalence (risk ratio: 1.00; 95% CI: 0.75–1.34; two studies; low-certainty evidence).

The systematic review did not report any unintended consequences of the intervention. However, the GDG noted that the potential undesirable effects identified for the use of ITNs in stable settings are also likely to apply in humanitarian emergencies. The GDG also noted that if nets are deployed in settings where the population is accommodated in tents or small houses (structures that are commonly shelters in emergency settings), uptake and use may be limited because the restricted space may not allow the net to be hung easily and the net may encroach on the space required for other household activities. The GDG judged these potential undesirable effects to be minimal.

Although the studies included in the systematic review were limited to the use of pyrethroid-only LLINs, the likely benefits extend to other types of ITNs that are recommended by WHO for large-scale deployment in more stable settings (e.g. pyrethroid-PBO nets). The GDG judged the balance of benefits and harms to favour the use of ITNs that have been recommended for use in more stable settings to prevent and control malaria in humanitarian emergency settings.

Certainty of the Evidence

High

The systematic review assessed that the overall certainty of the evidence that pyrethroid-only LLINs have an impact on malaria in humanitarian emergency settings was high.

Values and preferences

No research was identified regarding preferences and values. The GDG judged that there was probably no important uncertainty or variability.

Resources

Based on cost data published in 2021 *[35]*, the median economic cost of ITNs was US$ 1.39 per person protected per year, drawing on data from non-emergency settings. The GDG noted that the cost of deploying nets in humanitarian emergency settings may be higher than in stable settings for a number of reasons. First, the cost of transporting nets may increase, particularly for locations that are difficult to access. Second, in some emergency settings, there may be a need to establish human capacity for net delivery, which could incur further cost. Finally, given the nature of emergency settings, the necessity for immediate deployment of interventions may require shorter lead times for procurement, resulting in higher costs of the commodity. The GDG judged that deploying ITNs would therefore involve moderate costs and cost more than deploying ITNs in stable settings.

A review of the cost and cost-effectiveness of malaria control interventions *[35]* in more stable settings reported that the cost-effectiveness of ITNs compared to no ITNs was US$ 5.85 per episode averted, US$ 1281.97 per death averted, and US$ 44.51 per disability-adjusted life year (DALY) averted. The GDG noted that the cost-effectiveness of deploying pyrethroid-only LLINs may depend largely on the setting: the cost-effectiveness may vary with the infrastructure in the setting and available capacity, as well as the malaria transmission level in the area of deployment. The GDG judged that, while there may be some upfront costs to deliver nets in such settings, given the associated benefits to protecting such vulnerable populations, deploying pyrethroid-only LLINs would be cost-effective compared to no nets.

Equity

Providing ITNs to populations in areas with ongoing malaria transmission affected by humanitarian emergencies was judged by the GDG to result in increased equity, as populations in these settings are at increased risk of malaria infection.

Acceptability

No research was identified regarding the acceptability of pyrethroid-only LLINs in emergency settings. Nevertheless, the GDG judged that ITNs would be acceptable to key stakeholders, given that they are generally well accepted in more stable settings. The acceptability may improve further over time as users see the benefit to protecting themselves from malaria.

Feasibility

No research was identified regarding the feasibility of implementing pyrethroid-only LLINs in humanitarian emergency settings. The GDG judged that distributing ITNs would be feasible, but consideration would need to be given to whether:

- the sleeping structures in the setting are amenable to having nets installed;
- nets can be procured in time and within the given budget;
- there is sufficient human capacity to deliver nets in the emergency setting; and
- there are sufficient resources available to cover potential extra costs to access the population, particularly hard-to-reach populations and those affected by conflict.

Justification

The systematic review *[54]* (Messenger *et al unpublished findings)* compared pyrethroid-only LLINs to no nets in terms of malaria outcomes in areas affected by humanitarian emergencies. The review concluded that deploying pyrethroid-only LLINs was associated with reductions in *P. falciparum* parasite incidence, *P. falciparum* parasite prevalence and *P. vivax* parasite incidence compared to no nets. It was unclear whether pyrethroid-only LLINs reduced *P. vivax* parasite prevalence in these settings. The included studies were all from emergencies in the chronic phase in Asia – in the Republic of Union of Myanmar, on the Myanmar–Thailand border, and in the Islamic Republic of Pakistan. Deploying nets in the acute stage of an emergency may differ from deploying nets once some infrastructure has been established, due to numerous logistical challenges. Humanitarian emergencies in other parts of the world may differ in terms of the available capacity, infrastructure, community behaviour and acceptance.

Given that the systematic review only identified and included four trials, a number of potential effect modifiers could not be examined. However, as for pyrethroid-only LLINs deployed in more stable settings, the impact of nets may vary depending on, for example, the behaviour of the mosquito species, the level and mechanism(s) of insecticide resistance, parasite prevalence, and net usage by the population.

While the review included studies that only examined the impact of pyrethroid-only LLINs, other ITNs recommended by WHO in more stable settings are likely to have a similar balance of benefits and harms to those deployed in humanitarian emergencies. Important considerations regarding resource needs, acceptability and feasibility when deploying pyrethroid-only LLINs in emergency settings should largely apply to other WHO-recommended ITNs. Based on the review findings and these considerations, the GDG judged that the desirable effects of deploying WHO-recommended ITNs, not just pyrethroid-only LLINs, in humanitarian emergencies compared to no nets would outweigh the undesirable effects. Based on the high certainty of the findings from emergency settings and the feasibility, acceptability and cost-effectiveness of ITNs in more stable settings, the panel felt that the recommendation should be classified as strong.

Research Needs

WHO encourages funding of high-quality research to generate further evidence on:

- the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/ unintended consequences of ITNs in the acute phase of humanitarian emergencies (where logistics and priorities may differ); and
- contextual factors (i.e. acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to products from the different ITN classes covered by a WHO recommendation deployed in humanitarian emergencies.

Good practice statement

Achieving and maintaining optimal coverage with ITNs for malaria prevention and control (2019)

To achieve and maintain optimal ITN coverage, countries should apply mass free net distribution through campaigns, combined with other locally appropriate delivery mechanisms such as continuous distribution using antenatal care (ANC) clinics and the Expanded Programme on Immunization (EPI).

Recipients of ITNs should be advised (through appropriate communication strategies) to continue using their nets beyond the three-year expected lifespan, irrespective of the condition and age of the net, until a replacement net is available.

Practical Info

To achieve and maintain optimal ITN coverage, countries should apply a combination of mass free net distribution through campaigns and continuous distribution through multiple channels, in particular through ANC clinics and the EPI. Mass campaigns are the only proven cost-effective way to rapidly achieve high and equitable coverage. Complementary continuous distribution channels are also required because coverage gaps can start to appear almost immediately post-campaign due to net deterioration, loss of nets, and population growth.

Mass campaigns should distribute one ITN for every two persons at risk of malaria. However, for procurement purposes, the calculation to determine the number of ITNs required needs to be adjusted at the population level, since many households have an odd number of members. Therefore, a ratio of one ITN for every 1.8 persons in the target population should be used to estimate ITN requirements, unless data to inform a different quantification ratio are available. In places where the most recent population census is more than five years old, countries can consider including a buffer (e.g. adding 10% after the 1.8 ratio has been applied) or using data from previous ITN campaigns to justify an alternative buffer amount. Campaigns should also normally be repeated every three years, unless available empirical evidence justifies the use of a longer or shorter interval between campaigns. In addition to these data-driven decisions, a shorter distribution interval may be justified during humanitarian emergencies, as the resulting increase in population movement may leave populations uncovered by vector control, potentially increasing their risk of infection as and the risk of epidemics.

Continuous distribution through ANC and EPI channels should remain functional before, during and after mass distribution campaigns. In determining the optimal mix of ITN delivery mechanisms to ensure optimal coverage and maximized efficiency, consideration should be given to the required number of nets, the cost per net distributed and coverage over time. For example, during mass distribution campaign years, other delivery schemes may need to be altered to avoid-over supply of ITNs.

“Top-up” campaigns (i.e. ITN distributions that take into account existing nets in households and provide each household only with the additional number of nets needed to bring it up to the target number) are not recommended. Substantial field experience has shown that accurate quantification for such campaigns is generally not feasible and the cost of accounting for existing nets outweighs the benefits.

There should be a single national ITN plan and policy that includes both continuous and campaign distribution strategies. This should be developed and implemented under the leadership of the NMP, based on an analysis of local opportunities and constraints, and identification of a combination of distribution channels with which to achieve optimal coverage and minimize gaps. This unified plan should include a comprehensive net quantification and gap analysis for all public sector ITN distribution channels. As much as possible, the plan should include major ITN contributions by the private sector.

Therefore, in addition to mass campaigns, the distribution strategy could include:

- ANC, EPI and other child health clinics: These should be considered high-priority continuous ITN distribution channels in countries where these services are used by a large proportion of the population at risk of malaria, as occurs in much of sub-Saharan Africa.
- Schools, faith- and community-based networks, and agricultural and food-security support schemes: These can also be explored as channels for ITN distribution in countries where such approaches are feasible and equitable. Investigating the potential use of these distribution channels in complex emergencies is particularly important.
- Occupation-related distribution channels: In some settings, particularly in Asia, the risk of malaria may be strongly associated with specific occupations (e.g. plantation and farm workers and their families, miners, soldiers and forest workers). In these settings, opportunities for distribution through channels such as private sector employers, workplace programmes and farmers’ organizations may be explored.
- Private or commercial sector channels: These can be important channels for supplementing free ITN distribution through public sector channels. Access to ITNs can also be expanded by facilitating the exchange of vouchers or coupons provided through public sector channels for a free or subsidized ITN at participating retail outlets. ITN products distributed through the private sector should be regulated by the national registrar of pesticides in order to ensure that product quality is in line with WHO recommendations.

The procurement of ITNs with attributes that are more costly (e.g. nets of conical shape) is not recommended for countries in sub-Saharan Africa, unless nationally representative data clearly show that the use of ITNs with particular attributes increases significantly among populations at risk of malaria. To build an evidence base to support the purchase of more costly nets, investigation into the population's preferences and whether adhering to those preferences translates into increased use of ITNs may also be warranted, particularly in situations where standard nets are unlikely to suit the lifestyle of specific population groups at risk of malaria, such as may be the case for nomadic populations.

The life spans of ITNs can vary widely among individual nets used within a single household or community, as well as among nets used in different settings. This makes it difficult to plan the rate or frequency at which replacement nets need to be procured and delivered. All malaria programmes that have undertaken medium- to large-scale ITN distributions should conduct ITN durability monitoring in line with available guidance to inform appropriate replacement intervals. Where there is evidence that ITNs are not being adequately cared for or used, programmes should design and implement BCC activities aimed at improving these behaviours.

In countries where untreated nets are widely available, NMPs should promote access to ITNs. Strategies for treating untreated nets can also be considered, for example, by supporting access to insecticide treatment kits.

As NMPs implement different mixes of distribution methods in different geographic areas, there will be a need to accurately track ITN coverage at subnational levels. Subnational responses should be triggered if coverage falls below programmatic targets. Tracking should differentiate among the contributions of various delivery channels to overall ITN coverage.

Countries should generate data on defined standard indicators of coverage and access rates in order to ascertain whether optimal coverage has been achieved and maintained. The data should also inform changes in implementation in order to improve performance and progress towards the achievement of programmatic targets. Currently, the three basic survey indicators are: i) the proportion of households with at least one ITN; ii) the proportion of the population with access to an ITN within their household; and iii) the proportion of the population reporting having slept under an ITN the previous night (by age [<5 years; 5–14 years; 15+ years], gender and access to ITN).

Justification

In December 2017, WHO published updated recommendations on *Achieving and maintaining universal coverage with LLINs for malaria control [64]*. These recommendations were developed and revised based on expert opinion through broad consultation, including multiple rounds of reviews by the Malaria Policy Advisory Group (MPAG). Under the section on "practical information", these recommendations have been summarized and slightly revised to clarify that these recommendations are not specific to LLINs, but apply to ITNs in general.

Good practice statement

Management of old ITNs (2019)

Old ITNs should only be collected where there is assurance that: i) communities are not left without nets, i.e. new ITNs are distributed to replace old ones; and ii) there is a suitable and sustainable plan in place for safe disposal of the collected material.

If ITNs and their packaging (bags and baling materials) are collected, the best option for disposal is high-temperature incineration. They should not be burned in the open air. In the absence of appropriate facilities, they should be buried away from water sources and preferably in non-permeable soil.

Recipients of ITNs should be advised (through appropriate communication strategies) not to dispose of their nets in any water body, as the residual insecticide on the net can be toxic to aquatic organisms (especially fish).

Practical Info

It is important to determine whether the environmental benefits outweigh the costs when identifying the best disposal option for old ITNs and their packaging. For malaria programmes in most endemic countries, there are limited options for dealing with ITN collection. Recycling is not currently a practical option in most malaria-endemic countries (with some exceptions for countries with a well-developed plastics industry). High-temperature incineration is likely to be logistically difficult and expensive in most settings. In practice, when malaria programmes have retained or collected packaging material in the process of distributing ITNs, it has mostly been burned in the open air. This method of disposal may lead to the release of dioxins, which are harmful to human health.

If such plastic material (with packaging an issue at the point of distribution and old ITNs an intermittent issue at household level when the net is no longer in use) is left in the community, it is likely to be re-used in a variety of ways. While the insecticide exposure entailed by this kind of re-use has yet to be fully studied, the expected negative health and environmental impacts of leaving the waste in the community are considered to be less than amassing it in one location and/or burning it in the open air.

Since the material from nets represents only a small proportion of total plastic consumption, it will often be more efficient for old ITNs to be dealt with as part of larger and more general solid-waste programmes. National environment management authorities have an obligation to consider and plan for what happens to old ITNs and packaging materials in the environment in collaboration with other relevant partners.

Justification

Currently, ITNs and the vast majority of their packaging (bags and baling materials) are made of non-biodegradable plastics *[65]*.The large-scale deployment of ITNs has given rise to questions as to the most appropriate and cost-effective way to deal with the resulting plastic waste, particularly given that most endemic countries do not currently have the resources to manage ITN collection and waste disposal programmes.

A pilot study was conducted to examine patterns of ITN usage and disposal in three African countries (the Republic of Kenya, the Republic of Madagascar and United Republic of Tanzania). Findings of this pilot study, along with other background information were used to generate recommendations through the WHO Vector Control Technical Expert Group (VCTEG) and MPAG on best practices with respect to managing waste.

The following are the main findings from the pilot study and other background material:

- ITNs entering domestic use in Africa each year contribute approximately 100 000 tonnes of plastic and represent a per capita rate of plastic consumption of 200g per year. This is substantial in absolute terms; however, it constitutes only approximately 1% to 5% of the total plastic consumption in Africa and thus is small compared to other sources of plastic

and other forms of plastic consumption.

- The plastic from ITNs is treated with a small amount of pyrethroid insecticide (less than 1% per unit mass for most products), and plastic packaging is therefore considered a pesticide product/container.
- Old ITNs and other nets may be used for a variety of alternative purposes, usually due to the perceived ineffectiveness of the net, loss of net physical integrity or presence of another net.
- ITNs that no longer serve a purpose are generally disposed of at the community level along with other household waste by discarding them in the environment, burning them in the open, or placing them into pits.
- ITN collection was not implemented on a large scale or sustained in any of the pilot study countries. It may be feasible to recycle ITNs, but it is not practical or cost-effective at this point, as there would need to be specialized adaptation and upgrading of recycling facilities before insecticide-contaminated materials could be included in this process.
- Two important and potentially hazardous practices are: i) routinely removing ITNs from bags at the point of distribution and burning discarded bags and old ITNs, which can produce highly toxic fumes including dioxins, and ii) discarding old ITNs and their packaging in water, as they may contain high concentrations of residual insecticides that are toxic to aquatic organisms, particularly fish.
- Insecticide-treated plastics can be incinerated safely in high-temperature furnaces, but suitable facilities are lacking in most countries. Burial away from water sources and preferably in non-permeable soil is an appropriate method to dispose of net bags and old ITNs in the absence of a suitable high-temperature incinerator.
- In most countries, ministries of environment (national environment management authorities) are responsible for setting up and enforcing laws/regulations to manage plastic waste broadly. Although some countries have established procedures for dealing with pesticide-contaminated plastics, it is unrealistic to expect NMPs to single-handedly address the problem of managing waste from ITNs. Environmental regulations; leadership and guidance from national environmental authorities; and oversight from international agencies, such as the United Nations Environment Programme, are all necessary.

Strong recommendation for , Low certainty evidence

Indoor residual spraying (2019)

IRS should be deployed for the prevention and control of malaria in children and adults living in areas with ongoing malaria transmission.

WHO recommends that WHO-prequalified insecticidal products be selected for IRS use and that these be selected based on the insecticide susceptibility of the local malaria vector(s). IRS is considered an appropriate intervention where:

- *the majority of the vector population feeds and rests indoors;*
- *people mainly sleep indoors at night;*
- *the malaria transmission pattern is such that the population can be protected by one or two rounds of IRS per year; and*
- *the majority of structures are suitable for spraying.*

Practical Info

IRS is considered an appropriate intervention where:

- the majority of the vector population tends to feed and rest indoors;
- people mainly sleep indoors at night;
- the malaria transmission pattern is such that the population can be protected by one or two rounds of IRS per year;
- the majority of structures are suitable for spraying.

When selecting insecticides to be used for IRS, it is important to investigate the resistance profile of the local vectors in order to select insecticides to which the vectors are susceptible.

Insecticide formulations currently used for IRS fall into five major insecticide classes with three modes of action, based on their primary target site in the vector. WHO-prequalified products have been assessed for their safety, quality and entomological efficacy, which includes evaluation of their mortality effect on mosquitoes when applied to a range of interior surfaces of dwellings found in malaria-endemic areas.

Sodium channel modulators

- Pyrethroids: alphacypermethrin, deltamethrin, lambda-cyhalothrin, etofenprox, bifenthrin
- Organochlorines (e.g. DDT): No prequalified product available

Acetylcholinesterase inhibitors

- Organophosphates: malathion, fenitrothion, pirimiphos-methyl
- Carbamates: bendiocarb, propoxur

Nicotinic acetylcholine receptor competitive modulators

- Neonicotinoids: clothianidin

IRS products using four of these insecticide classes have been prequalified by WHO; as of August 2020, there were no organochlorine IRS formulations prequalified, including DDT. This means that no DDT product has been assessed by WHO for its efficacy, safety and quality for vector control, and no inspection of manufacturing sites has been conducted. Unlike the other four classes covered by WHO's recommendation for IRS, DDT has been classified as a persistent organic pollutant. As such, its production and use are strictly restricted by an international agreement known as the Stockholm Convention on Persistent Organic Pollutants *[66]*. The Convention's objective is to protect both human health and the environment from persistent organic pollutants. When the Stockholm Convention was established in 2004, it provided an exemption for the production and use of DDT for disease vector control, mainly because of the absence of equally effective and efficient alternatives at the time. The recent expansion of products available for IRS and overall expansion of vector control interventions has provided additional options.

WHO actively supports the promotion of chemical safety and, together with the United Nations Environment Programme, shares a common commitment to the global goal of reducing and eventually eliminating the use of DDT, while minimizing the burden of vector-borne diseases. DDT use for malaria vector control has declined over the years and WHO supports continuation of this trend.

In some areas, the use of DDT may be warranted. The decision to use DDT for malaria vector control needs to be based on a detailed analysis that considers all other potential options for vector control and provides clear reasoning for choosing DDT over the other options. WHO considers DDT to be a last resort, not a first choice. If DDT is selected, it should be used under strict control measures and only for the intended purpose. Its use requires that the conditions set by the Stockholm Convention be met. Effective use and safe storage of DDT rely on compliance with well-established and well-enforced rules and regulations in accordance with national guidelines and following WHO technical guidance provided in the WHO *Operational manual for IRS for malaria transmission, control and elimination [67]*. Where DDT is deployed, it is essential for adequate resources and technical support to be in place to ensure the sound management of this persistent organic pollutant.

Countries that are using DDT for malaria vector control need to regularly (at least once every two years) reassess whether there is a justified continued need for DDT. The outcome of such assessment should be reported to the WHO Global Malaria Programme and to the Secretariat of the Stockholm Convention as part of the formal reporting process *[66]*.

When selecting products and formulations, residual efficacy needs to continue for at least three months after the application of the insecticide to the substrate (usually cement, mud or wood) *[68]*. Insecticides are available in various formulations to increase their longevity on different surfaces.

Community acceptance of IRS is critical to the programme's success, particularly as it requires householders to grant permission for spray teams to enter their house. It also involves disruption to the household, requiring householders to remove personal items from their house prior to spraying. Furthermore, some insecticide formulations leave unsightly residue on sprayed surfaces. Repeated, frequent spraying of houses over extended periods can lead to refusal by householders. Reduced acceptance has been an impediment to effective IRS implementation in various parts of the world *[69]*. It is therefore important to develop information, education and communication (IEC) strategies to keep the community informed and to ensure full support and cooperation.

In areas with ongoing malaria transmission, optimal coverage of IRS should be maintained. Implementation of the intervention should take place prior to the onset of the peak transmission season. Following application of the insecticide(s),

it is important to monitor the residual activity.

The WHO *Operational manual for IRS for malaria transmission, control and elimination [67]* aims to assist malaria programme managers, entomologists and public health officers in designing, implementing and sustaining high-quality IRS programmes.

Evidence To Decision

Benefits and harms

The systematic review *[70]* reported that IRS may reduce malaria incidence (risk ratio [RR]: 0.12; 95% CI: 0.04–0.31; one study; low-certainty evidence) and parasite prevalence (RR: 0.24; 95% CI: 0.17–0.34; one study; low-certainty evidence) compared to no IRS. The GDG noted that evidence from the programmatic implementation of IRS over many years has reported reductions in all-cause child mortality, malaria mortality, *P. falciparum* incidence and prevalence, and incidence of severe disease compared to no IRS.

The systematic review also compared IRS to pyrethroid-only ITNs in areas of intense and unstable malaria transmission. It concluded that in areas of intense malaria transmission, IRS may reduce malaria incidence compared to ITNs (RR: 0.88; 95% CI: 0.78–0.98; one study; low-certainty evidence), but there may be little or no difference between IRS and ITNs in terms of parasite prevalence (RR: 1.06; 95% CI: 0.91–1.22; one study; very low-certainty evidence). Comparing IRS with ITNs in areas of unstable transmission, the review reported that IRS may be associated with increased malaria incidence (RR: 1.48; 95% CI: 1.37–1.60; one study; low-certainty evidence) and parasite prevalence (RR: 1.70; 95% CI: 1.18–2.44; one study; low-certainty evidence) compared to ITNs.

No undesirable effects were identified in the systematic review. However, IRS may play an as yet undetermined role in insecticide resistance development in *Anopheles* vectors.

Certainty of the Evidence

Low

The systematic review assessed that the overall certainty of the evidence that IRS has an impact on malaria was low.

Resources and other considerations

The table below, compiled by the GDG lists resources that should be considered for the deployment of IRS. Note that this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated enumerators • Transport logisticians, drivers • Stock managers • Spray personnel • Entomologists for QC assessments • Environmental assessment support staff
Training	• Training in enumeration, logistics management, spray technique, environmental safety, personal protective equipment (PPE) use and maintenance, spray pump operation and maintenance, insecticide mixing and clean-up, entomological quality assessments, BCC and M&E
Transport	• Movement of insecticide requires environmentally compliant vehicles and ground transport plans. Spray team movement typically requires significant numbers of small vehicles capable of movement across challenging roads/terrain. Individual spray personnel may in some cases also require bicycles. • Transportation of pesticide-contaminated spray pumps and clothing to clean-up sites typically using spray team transportation

	• Insecticide-contaminated residues and packaging must be transported from remote clean-up sites under an environmentally compliant transport plan often using small trucks. • Vehicles to provide transport for staff that provide BCC and entomological staff and associated supplies for QC wall cone bioassays • Vehicle maintenance costs • Fuel
Supplies	• PPE • Spray pump repair parts • Insecticide and packaging (including return/clean packaging) • Soap/bathing materials • Inventory management forms • Documentation paperwork/forms or electronic devices • Entomological supplies for wall cone bioassays and maintenance of adult mosquitoes • M&E data collection forms
Equipment	• Computer and communication equipment • Spray pumps appropriate for the specific insecticide • Collection tanks/wash buckets and cleaning supplies (varies with insecticide)
Infrastructure	• Appropriate national and regional/provincial storage • Temporary insecticide storage depots at the local level • Office space for management • Clean-up sites (soak pits/evaporation pools) • Training facilities with spray practice capacity • Insectary to maintain mosquitoes exposed in QC wall cone bioassays
Communication	• Communication with other ministries and sectors, e.g. environment, transport • Communication with the general public, e.g. through the education sector and advertising on local media to encourage uptake • Communication with the community/local leaders
Governance/ programme management	• Spray team supervisors / district or higher level supervisors / clean-up site managers • BCC supervision • M&E support for QC • Entomology supervisors for QC testing

Justification

When carried out correctly, IRS has historically been shown to be a powerful intervention to reduce adult mosquito vector density and longevity and, therefore, to reduce malaria transmission. However, despite its long tradition and the large body of associated operational experience, few randomized controlled trials (RCTs) have been conducted on IRS. Therefore, the availability of data suitable for use in the meta-analysis was limited *[70]* and the certainty of evidence reported by the systematic review was low. The GDG considered that despite the low certainty of the evidence, a strong recommendation for the intervention is warranted based on the fact that a number of implementation trials and programmatic data have demonstrated impact against malaria. The GDG considered that this body of evidence, when viewed as a whole, provides higher certainty evidence (compared to the evidence from the systematic review) of the effectiveness of IRS as a malaria prevention and control intervention. The GDG judged that, based on the systematic review comparing IRS and ITNs, ITNs are an equally effective alternative intervention in areas where local vectors are susceptible to the insecticides being used *[70]*.

An updated systematic review of data on IRS interventions from recent studies, RCTs and other designs is being undertaken to further support this recommendation or modify it as appropriate.

Research Needs

- Generate further evidence on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms and/or unintended consequences of IRS.
- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of IRS in urbanized areas with changing housing designs.
- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of IRS using new insecticides in areas where mosquitoes are resistant to currently deployed insecticides.
- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) of IRS in areas with different mosquito behaviours (such as in areas with outdoor transmission).
- Given the relatively high cost of implementing IRS, especially in the context of growing insecticide resistance and when delivering IRS in more remote areas, there is a need to investigate new approaches to delivering IRS to increase the cost-effectiveness of this intervention.

Conditional recommendation for , Very low certainty evidence

Indoor residual spraying: Humanitarian emergency setting (2022)

IRS can be deployed for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission affected by a humanitarian emergency.

The conditionality of this recommendation is largely driven by the very low certainty of the evidence that IRS reduces malaria in such settings and due to concerns around feasibility and cost.

When deciding whether IRS may be appropriate for prevention and control of malaria in humanitarian emergency settings, programmes should consider:

- *whether the structures are suitable for spraying. Some shelters provided in emergency settings may not be suitable for application of insecticides, such as open-sided structures and those built from materials that affect the residual nature of the insecticides;*
- *whether the target coverage of IRS can be feasibly achieved in the setting;*
- *whether there are sufficient resources to cover the relatively high costs associated with an IRS programme. In such settings, transport of commodities to hard-to-reach areas, coupled with the need to quickly procure items and establish human capacity to deliver the intervention, is likely to incur higher costs than when deploying IRS in more stable settings.*

As with the deployment of IRS in more stable settings, WHO recommends that WHO-prequalified insecticides be selected for IRS use in humanitarian emergencies. It is important to ensure that the vector population is susceptible to the insecticide selected for spraying.

Practical Info

In deciding whether to deploy IRS in emergency settings, as in more stable settings, consideration must be given to whether IRS is a suitable intervention for that setting, taking into account vector characteristics, human behaviour and available infrastructure. IRS is considered an appropriate intervention where the majority of the vector population feeds and rests indoors; the vectors are susceptible to the insecticide that is being deployed; people mainly sleep indoors at night; the majority of structures are suitable for spraying; and where high enough coverage can be achieved to provide community-level protection. Data will need to be collected to assess whether these criteria are met. Data on vector composition, density, behaviour and insecticide susceptibility prior to deploying IRS not only provide information as to whether IRS is suitable in that setting, but also provide baseline information against which changes can be detected and monitored. Combined with data on coverage, this information can be used to gauge the effectiveness and efficiency of IRS. However, there may be more limited capacity to regularly gather such data in humanitarian emergencies than in more stable settings. Data are also required on the structures present in humanitarian emergencies to assess whether they are amenable to IRS. Open-sided structures or those with surfaces constructed from materials that impact the residual nature of the spray may not be suitable.

Initiating any IRS programme requires a well-defined management system to be established with dedicated human, logistical, transport and financial resources. Programmes and implementing partners should consider whether the logistical needs

(acquisition of commodities and equipment, recruitment of personnel and transport) can be met in emergency situations with the available resources within the given timeframe. Timeliness is a key factor in obtaining the maximum benefits from IRS; the spray should be applied over the shortest period of time just prior to the onset of the transmission season. As with ITNs, instability in humanitarian emergencies may reduce the options for long-term planning, resulting in shorter lead times for establishing a programme and acquiring supplies and equipment than in more stable settings. If commodities and personnel have to be sourced at short notice, procurement costs may be higher. Costs may also increase if more expensive means of transport are required for deployment in more remote, less accessible areas or those affected by conflict.

As with more stable settings, ensuring optimal coverage to provide community-level protection is critical. To support this community acceptance of IRS is essential. Given that in some humanitarian emergencies, the local language may differ to that of the affected population, consideration should be given to whether messaging needs to be adapted.

Evidence To Decision

Benefits and harms

The systematic review *[54]* (Messenger *et al unpublished evidence)* assessed the epidemiological impact of IRS against malaria compared to no IRS in areas affected by humanitarian emergencies in the chronic phase; no studies were found from areas in the acute phase of an emergency. One RCT was carried out in the Republic of the Sudan *[71]* and two controlled before-after studies and one cross-sectional study were conducted in the Islamic Republic of Pakistan *[51][72][73]*. While the incidence of *P. falciparum* was lower with IRS, only one observational study contributed to this evidence (rate ratio: 0.57; 95% CI: 0.53–0.61; very low-certainty evidence). There was little to no difference in *P. falciparum* parasite prevalence between arms (rate ratio: 1.31; 95% CI: 0.91–1.88; one study; low-certainty evidence). *P. vivax* parasite incidence was lower compared to no IRS (rate ratio: 0.51; 95% CI: 0.49–0.52; one study; very low-certainty evidence); however, only one observational study was included. Little or no difference was seen in *P. vivax* parasite prevalence between arms (OR: 0.74; 95% CI: 0.25–2.14; two studies; very low-certainty evidence).

The GDG judged that the extent of the desirable effects of IRS compared to no IRS is likely to vary depending on a number of factors. Many of these factors also apply to more stable settings: IRS works best when the majority of vectors rest indoors and are susceptible to the insecticides used; where people sleep indoors; where the population is not nomadic; and where the structures are sprayable and not too scattered. The suitability of structures for spraying is an important factor to consider in emergency settings. Tents are often used to provide emergency shelter and not all tent material will allow the application of the insecticide by spraying; in some areas, structures are open-sided. It may be that IRS is more appropriate in the chronic phase of an emergency than in the acute phase due to the type of shelter, infrastructure and human capacity likely to have been established by this later stage.

The systematic review did not report any unintended consequences of the intervention. However, the GDG noted that undesirable effects may be similar to those that may arise when deploying IRS in non-emergency settings (see “Evidence to decision” section of the recommendation for IRS). These undesirable effects were judged by the GDG to be minimal.

The GDG judged the balance of benefits and harms to probably favour the use of IRS against malaria compared to no IRS in humanitarian emergency settings.

Certainty of the Evidence

Very low

The systematic review assessed the overall certainty of evidence that IRS has an impact on malaria in humanitarian emergency settings to be very low.

Values and preferences

No research was identified regarding preferences and values. The GDG judged that there was probably no important uncertainty or variability.

Resources

The resources needed for IRS in humanitarian emergencies are, at a minimum, the same as those needed for delivery of

IRS in more stable settings (see “Resources and other considerations” table, section 4.1.1), but the overall cost is likely to be higher due to the various logistical issues noted below. Based on cost data published in 2021 *[35]* the median economic cost per person protected per year was estimated to be US$ 5.70 in stable settings. As in stable settings, establishing an IRS programme in an area for the first time requires a great amount of resources. In emergency settings, increased costs are assumed to be associated with transporting commodities and personnel to areas where access is limited by geography or conflict, the fact that shorter lead times for procurement generally result in higher cost of goods, and the need to quickly establish capacity (recruitment and training of personnel, establishment of operation sites, i.e. stores, soak pits, and wash areas) to protect the at-risk population and avoid a potential malaria epidemic. The GDG therefore judged that deploying IRS in such settings would likely involve high costs.

Data from a review of the cost and cost-effectiveness of malaria control interventions deployed in stable settings *[35]* reported that the cost-effectiveness of IRS compared to no IRS was US$ 840.44 per death averted and US$ 25.16 per DALY averted. The GDG noted that the cost-effectiveness of deploying IRS is likely to vary depending on the malaria transmission level in the area of deployment and other contextual factors. However, the GDG judged that IRS is likely to be cost-effective compared to no IRS, given the benefits of protecting vulnerable populations from malaria in such settings.

Equity

Providing IRS to populations in areas with ongoing malaria transmission affected by humanitarian emergencies was judged by the GDG to result in increased equity by providing the most vulnerable with an effective malaria prevention intervention

Acceptability

No research was identified regarding the acceptability of IRS in emergency settings. Despite the lack of evidence, the GDG judged that IRS is likely to be acceptable to key stakeholders, given that IRS is generally accepted in more stable settings.

Feasibility

No evidence was included in the systematic review and no studies were identified by the GDG regarding the feasibility of implementing IRS in humanitarian emergency settings.

The GDG judged that the feasibility of IRS would vary, likely depending on whether:

- the structures in such settings are amenable to being sprayed; open-sided structures and certain surface materials would not be suitable for spraying;
- commodities can be acquired and skilled personnel recruited with the resources available within the given timeframe;
- access to the population is feasible, which may involve higher costs than in more stable settings.

The GDG noted that IRS may be more feasible in the chronic phase of a humanitarian emergency, when shelter, general infrastructure and human resources are better established than in the acute stages. In the acute phase of an emergency, there may be other competing demands on resources and overall capacity.

Justification

The systematic review *[54]* (Messenger *et al unpublished evidence)* included four studies conducted in the Islamic Republic of Pakistan and The Republic of the Sudan that compared IRS versus no IRS on malaria outcomes in areas affected by humanitarian emergencies. The review included only one observational study showing that *P. falciparum* was reduced, but the certainty of evidence was considered to be very low. One RCT showed no effect of IRS on *P. falciparum* parasite prevalence (low-certainty evidence). IRS was reported to reduce both *P. vivax* parasite incidence and prevalence based on two observational studies, but the certainty of evidence was assessed to be very low. All studies were conducted during the

chronic phase of the emergency. Deploying IRS in the acute stage of an emergency may differ from employing IRS once some infrastructure has been established, due to numerous logistical challenges.

Given that the systematic review only identified and included four studies, a number of potential effect modifiers could not be examined, and the generalizability of the findings was limited. Humanitarian emergencies in other parts of the world may differ in terms of available capacity, infrastructure, community behaviour and acceptance. As for many vector control interventions, the impact of IRS may vary in different settings depending on a number of factors, such as the behaviour of the mosquito species, the level and mechanism(s) of insecticide resistance in vectors, parasite prevalence, and coverage of IRS in the population. As with deploying IRS in more stable settings, IRS will only be effective where vectors rest primarily indoors and mosquitoes are susceptible to the insecticide being deployed.

The review findings provided little evidence of an impact on malaria outcomes in humanitarian emergencies. Given the effectiveness of IRS programmes in reducing malaria burden in more stable settings, however, the GDG judged that the desirable effects of deploying IRS compared to no IRS in humanitarian emergencies would likely outweigh the undesirable effects. Given the low certainty of the evidence, the panel felt that the recommendation should be classified as conditional. Considerations of feasibility and the cost and cost-effectiveness of implementing IRS in such settings were viewed by the GDG as important. In humanitarian emergencies, the shelters provided may not be amenable to spraying and there may be higher costs associated with deploying IRS in such settings than in more stable ones.

Research Needs

WHO encourages funding of high-quality research to generate further evidence on:

- the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/ unintended consequences of IRS in the acute phase of humanitarian emergencies (where logistics and priorities may differ);
- contextual factors (i.e. acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to IRS deployed in humanitarian emergencies.

4.1.2 Co-deploying ITNs and IRS

Conditional recommendation against , Moderate certainty evidence

Prioritize optimal coverage with either ITNs or IRS over combination (2019)

The co-deployment of ITNs and IRS is not recommended for prevention and control of malaria in children and adults in areas with ongoing malaria transmission. Priority should be given to delivering either ITNs or IRS at optimal coverage and to a high standard, rather than introducing the second intervention as a means to compensate for deficiencies in the implementation of the first intervention.

In settings where optimal ITN coverage, as specified in the strategic plan, has been achieved and where ITNs remain effective, additionally implementing IRS may have limited utility in reducing malaria morbidity and mortality. Given the resource constraints across malaria-endemic countries, it is recommended that effort be focused on good-quality implementation of either ITNs or IRS, rather than deploying both in the same area. However, the combination of these interventions may be considered for resistance prevention, mitigation or management should sufficient resources be available.

Practical Info

Given the resource constraints across malaria-endemic countries, the deployment of a second vector control intervention on top of optimal coverage with an existing one should only be considered as part of a broader prioritization analysis aimed at achieving maximum impact with the available resources. In many settings, a switch from ITNs to IRS or vice versa, rather than their combination, is likely to be the only financially feasible option. Deployment of either intervention needs to ensure optimal coverage of populations at risk of malaria and ensure they are delivered to a high standard. Further guidance on best practices for ensuring high-quality deployment of interventions is provided in the WHO *Indoor residual spraying: An operational manual for IRS for malaria transmission, control and elimination [67]* and in the *Alliance for Malaria Prevention toolkit*.

Evidence To Decision

Benefits and harms

- No benefit of adding IRS to areas where pyrethroid-only ITNs are being used was identified in systematic review.
- In areas of confirmed pyrethroid resistance, IRS with a non-pyrethroid insecticide may increase effectiveness against malaria.
- No undesirable effects were identified in systematic review. However, the cost of combining two interventions will significantly increase commodity and operational costs.

Certainty of the Evidence

Moderate

The certainty of evidence identified in the systematic review showing no benefit to adding IRS in situations where ITNs are already being used was graded as moderate.

Resources and other considerations

- The degree of pyrethroid resistance and its impact on the effectiveness of pyrethroid-only ITNs should be considered.
- The status of vector resistance to the proposed IRS active ingredient needs to be known.
- In resource-constrained situations, it is unlikely to be financially feasible to deploy both ITNs and IRS.

Justification

The systematic review published in 2019 *[74]* on the deployment of IRS in combination with ITNs (specifically pyrethroid-only LLINs) provided evidence that, in settings where there is optimal coverage with ITNs and where these remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. WHO guidance was developed accordingly to emphasize the need for good-quality implementation of either ITNs or IRS, rather than deploying both in the same area *[75]*. However, the co-deployment of these interventions may be considered for resistance prevention, mitigation or management should sufficient resources be available

Insecticide resistance threatens the effectiveness of insecticidal interventions and hence is a key consideration in determining which vector control interventions to select to ensure maximum impact. One approach to the prevention, mitigation and management of vector insecticide resistance is the co-deployment (or combination) of interventions with different insecticides (see Section 4.1 on “Prevention, mitigation and management of insecticide resistance”). Therefore, WHO guidance developed based on the systematic review *[74]* differentiates between the effect of combined interventions on malaria morbidity and mortality versus the utility of this approach in a resistance management strategy *[75]*.

A summary of the conclusions (with minor updates for clarity) used to develop the above recommendations is as follows:

- In settings with high ITN coverage where ITNs remain effective, IRS may have limited utility in reducing malaria morbidity and mortality. However, IRS may be implemented as part of an IRM strategy in areas where ITNs are in use *[21]*.
- Malaria control and elimination programmes should prioritize the delivery of ITNs or IRS at optimal coverage and to a high standard, rather than introducing the second intervention as a means to compensate for deficiencies in the implementation of the first intervention.
- If ITNs and IRS are to be deployed together in the same geographical location, IRS should be conducted with a non-pyrethroid insecticide.
- Evidence is needed to determine the effectiveness of combining IRS and ITNs in malaria transmission foci, including in low transmission settings. Evidence is also needed from different eco-epidemiological settings outside of Africa.
- All programmes in any transmission setting that decide to prioritize the combined deployment of ITNs and IRS over other potential use of their financial resources should include a rigorous programme of M&E (e.g. a stepped wedge introduction of the combination) in order to confirm whether the additional inputs are having the desired impact. Countries that are already using both interventions should similarly undertake an evaluation of the effectiveness of the combination versus either ITNs or IRS alone.
- The approach of co-deploying interventions for resistance management was developed largely based on experience with agricultural pest management, and the evidence base from public health remains weak.

Research Needs

- Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms and/or unintended consequences of co-deploying non-pyrethroid IRS with ITNs vs ITNs only in areas with insecticide-resistant mosquito populations.
- Determine whether there are comparative benefits (incidence of malaria [infection or clinical] and/or prevalence of malaria infection), as well as potential harms/unintended consequences of combining non-pyrethroid IRS with ITNs vs IRS only in areas with insecticide-resistant mosquito populations.
- Determine the acceptability of co-deploying IRS and ITNs among householders and communities.
- Evaluate new tools for monitoring the quality of IRS and ITN interventions.

Good practice statement

Access to ITNs or IRS at optimal coverage levels (2019)

Access to effective vector control using ITNs or IRS at optimal coverage levels should be ensured for all populations at risk of malaria in most epidemiological and ecological settings.

Practical Info

Financial considerations such as cost and cost-effectiveness are major drivers of decision-making, and the selection of malaria vector control interventions and determination of their coverage should thus be embedded in a prioritization process that considers the cost and effectiveness of all available malaria interventions and aims at achieving maximum impact with the available resources. Evaluations of the relative cost and cost-effectiveness of ITNs and IRS are ongoing to inform revision of the guidelines.

Justification

ITNs can provide both personal and community-level protection when nets are deployed at the community rather than individual level, with the aim of providing sufficient nets to cover all household inhabitants. Similarly, IRS will have a greater effect on mosquito populations and therefore transmission if deployed at high coverage. It is therefore important to maximize access to ITNs or IRS in communities that are at risk of malaria. This will involve quantification of needs to enable access for all household inhabitants when placing procurement orders and putting in place appropriate delivery structures. For malaria vector control interventions recommended for large-scale deployment, namely ITNs and IRS, optimal coverage refers to providing populations at risk of malaria with access to ITNs coupled with health promotion to maximize use and ensuring timely replacement; or providing these populations with regular application of IRS. Either intervention should be deployed at a level that provides the best value for money while reflecting programmatic realities. In practice, this often means quantifying commodities to provide full access by the population at risk, while realizing that this will not result in 100% coverage or 100% access due to various system inefficiencies. Being cognizant of such constraints, decision-making should then consider other alternatives as part of the intervention package, ranging from chemoprevention to supplementary vector control, instead of pursuing the idealistic goal of providing full population coverage.

In terms of the relative effectiveness of IRS compared to pyrethroid-only ITNs, a systematic review published in 2010 *[70]* reported low-certainty evidence that, in areas of intense malaria transmission, IRS may be associated with lower malaria incidence, but no effect was evident for parasite prevalence. In areas of unstable transmission, ITNs may be associated with lower malaria incidence and prevalence; however, the certainty of evidence was determined to be very low. The panel therefore could not provide a definitive conclusion on the comparative effectiveness of these interventions. WHO currently views these two interventions as being equally effective ways of delivering an insecticide. The actual effectiveness in reducing the burden of malaria is dependent on the insecticide(s) used on the ITN or applied by IRS. Decisions on whether to deploy IRS or ITNs need to be informed by a number of factors, such as data on insecticide resistance, past and present experience of using interventions (including feasibility of deployment and acceptability and use by end-users), vector behaviours and the current options available within the context. Given these various considerations, the wide range of different contexts and the lack of correlation between insecticide resistance data assessed using bioassays and the actual effectiveness of an insecticidal intervention in controlling vectors, no general recommendation to guide the selection of ITNs over IRS can be made.

Good practice statement

No scale-back in areas with ongoing local malaria transmission (2019)

In areas with ongoing local malaria transmission (irrespective of both the pre-intervention and current level of transmission), vector control interventions should not be scaled back. Ensuring access to effective malaria vector control at optimal levels for all inhabitants of such areas should be pursued and maintained.

Practical Info

Access to effective vector control interventions will need to be maintained in the majority of countries and locations where malaria control has been effective. This includes settings with ongoing malaria transmission, as well as those in which transmission has been interrupted but some level of receptivity and importation risk remains. Malaria elimination is defined as the interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite species in a defined geographical area as a result of deliberate intervention activities. Following elimination, continued measures to prevent re-establishment of transmission are usually required *[30]*. Interventions are no longer required once eradication has been achieved. Malaria eradication is defined as the permanent reduction to zero of the worldwide incidence of infection caused by all human malaria parasite species as a result of deliberate activities.

There is a critical need for all countries with ongoing malaria transmission, and in particular those approaching elimination, to build and maintain strong capacity in disease and entomological surveillance and health systems. The capacity to detect and respond to possible resurgences with appropriate vector control relies on having the necessary entomological information (i.e. susceptibility status of vectors to insecticides, as well as their biting and resting preferences). Such capacity is also required for the detailed assessment of malariogenic potential, which is a pre-condition for determining whether vector control can be scaled back (or focalized).

If areas where transmission has been interrupted are identified, the decision to scale back vector control should be based on a detailed analysis that includes assessment of the receptivity and importation risk of the area, as well as an assessment of the active disease surveillance system, and capacity for case management and vector control response.

Justification

A comprehensive review of historical evidence and mathematical simulation modelling undertaken for WHO in 2015 indicated that the scale-back of malaria vector control was associated with a high probability of malaria resurgence, including for most scenarios in areas where malaria transmission was very low or had been interrupted *[76]*. Both the historical review and the simulation modelling clearly indicated that the risk of resurgence was significantly greater at higher EIRs and case importation rates, and lower coverage of active case detection and case management.

Once transmission has been reduced to very low levels approaching elimination, ensuring optimal access to vector control for at-risk populations remains a priority, even though the size and demographics of the at-risk populations may change as malaria transmission is reduced.

As malaria incidence falls and elimination is approached, increasing heterogeneity in transmission will result in foci with ongoing transmission in which vector control may need to be optimized and enhanced. Such foci may be the result of particularly high vectorial capacity, lapsed prevention and treatment services, changes in parasites that make the current strategies less effective, or reintroduction of malaria parasites by the movement of infected people or infected mosquitoes. Monitoring the coverage, quality and impact of vector control interventions is essential to maintain the effectiveness of control. Guidance on entomological surveillance across the continuum from control to elimination is provided elsewhere *[30]*.

Once elimination has been achieved, vector control may need to be continued by targeting defined at-risk populations to prevent reintroduction or re-establishment of local transmission.

It is acknowledged that malaria transmission can persist following the implementation of a widely effective malaria programme. The sources and risks of residual transmission may vary by location, time and the existing components of the current malaria programme. This variation is potentially due to a combination of both mosquito and human behaviours, such as when people live in or visit forest areas or do not sleep in protected houses, or when local mosquito vector species bite and/or rest outdoors and thereby avoid contact with IRS or ITNs/LLINs.

Once elimination has been achieved, optimal vector control coverage should be maintained in receptive areas where there is

a substantial risk of reintroduction.

4.1.3 Supplementary interventions

Larval source management (LSM)
LSM in the context of malaria control is the management of water bodies that are potential larval habitats for mosquitoes. Such management of water bodies is conducted to prevent the development of the immature stages (eggs, larvae and pupae) and hence the production of adult mosquitoes, with the overall aim of preventing or controlling transmission of malaria. There are four types of LSM:

- habitat modification: a permanent alteration to the environment, e.g. land reclamation, filling of water bodies;
- habitat manipulation: a recurrent activity, e.g. flushing of streams, drain clearance;
- larviciding: the regular application of biological or chemical insecticides to water bodies; and
- biological control: the introduction of natural predators into water bodies.

Topical repellents, insecticide-treated clothing and spatial/ airborne repellents
Topical repellents, insecticide-treated clothing and spatial/ airborne repellents have all been proposed as potential methods for preventing malaria in areas where the mosquito vectors bite or rest outdoors, or bite in the early evening or early morning when people are not within housing structures. These methods have also been proposed for specific population groups, such as those who live or work away from permanent housing structures (e.g. migrants, refugees, internally displaced persons, military personnel) or those who work outdoors at night. In these situations, the effectiveness of ITNs or IRS may be reduced. Repellents have also been proposed for use in high-risk groups, such as pregnant mothers. Despite the potential to provide individual protection against bites from malaria vectors, the deployment of the above personal protection methods in large-scale public health campaigns has been limited, at least partially due to the scarcity of evidence of their public health value. Daily compliance and appropriate use of repellents seem to be major obstacles to achieving such potential impact *[77]*. Individuals' use of the intervention to achieve personal protection faces the same obstacles.

Space spraying
Space spraying refers to the release of fast-acting insecticides into the air as smoke or as fine droplets as a method to reduce the numbers of adult mosquitoes in dwellings and also outdoors. Application methods include thermal fogging; cold aerosol distribution by handheld or backpack sprayers, ground vehicles or aerial means; and repetitious spraying by two or more sprays in quick succession. Space spraying is most often deployed in response to epidemics or outbreaks of mosquito-borne disease, such as dengue.

Housing modifications
In the context of malaria control, housing modifications are defined as any structural changes, pre- or post-construction, of a house that prevents the entry of mosquitoes and/or decreases exposure of inhabitants to vectors with the aim of preventing or reducing the transmission of malaria. Housing modifications may encompass a wide range of interventions – from those made at the outset in the structural design of the house and the choice of materials used, to modifications made to existing homes, such as the screening or closure of gaps. In 2018, the WHO Department of Public Health, Environmental and Social Determinants of Health published the WHO *Housing and health guidelines [78]*. This document brings together the most recent evidence to provide practical recommendations for reducing the health burden due to unsafe and substandard housing. The review concluded that improved housing conditions have the potential to save lives, prevent disease, increase quality of life, reduce poverty, and help mitigate climate change. It was, however, noted that further evidence was needed on the impact of improved housing in preventing vector-borne diseases.

Available evidence indicates that poor-quality housing and neglected peri-domestic environments are risk factors for the transmission of a number of vector-borne diseases such as malaria, arboviral diseases (e.g. dengue, yellow fever, chikungunya and Zika virus disease), Chagas disease and leishmaniasis *[79]*. Together with metal roofs, ceilings, and finished interior walls, the closing of open eaves, screening of doors and windows with fly screens or mosquito netting, and filling of holes and cracks in walls and roofs may reduce the mosquitoes' entry points into houses and potentially reduce transmission of malaria and other vector-borne diseases. A recent review indicated that housing quality is an important risk factor for malaria infection across the spectrum of malaria endemicity in sub-Saharan Africa *[80]*.

Structural housing interventions that may reduce exposure of inhabitants to mosquitoes fall largely into two categories:

1. Primary house construction:

- house designs, such as elevating houses (e.g. using stilts) and using fewer or smaller windows;
- construction materials, such as cement or brick walls, corrugated iron roofing, door designs with fewer openings, and closure of eaves that minimize entry holes for mosquitoes.

2. Modifications to existing house designs:

- non-insecticidal interventions, which include screening and covering potential entry points, filling eaves with

mud, sand, rubble or cement, installing ceilings and conducting wall maintenance to fill in any cracks;
- insecticidal interventions, which include insecticidal screening of mosquito entry points, particularly eaves, and the installation of lethal house lures.

Housing modifications are likely to be most effective against mosquitoes that display endophilic and/or endophagic behaviours (i.e. indoor resting and feeding, respectively).

Conditional recommendation for , Low certainty evidence

Larviciding (2019)

Insecticides can be regularly applied to water bodies (larviciding) for the prevention and control of malaria in children and adults as a supplementary intervention to ITNs or IRS in areas with ongoing malaria transmission where aquatic habitats are few, fixed and findable.

The conditionality of this recommendation is due to the low certainty of evidence, the impact being limited to non-extensive habitats, and concerns about feasibility.

When considering larviciding, programmes should note the following:

- *Larviciding only reduces vector density and so does not have the same potential for health impact as ITNs and IRS; ITNs provide protection from biting vectors and both ITNs and IRS reduce adult longevity.*
- *Larviciding should not be seen as a substitute for ITNs or IRS or a means to fill a coverage gap in areas with significant malaria risk; rather, larviciding represents a potential supplementary strategy for malaria control.*
- *Feasibility and cost-effectiveness should be taken into account; larviciding will generally be most cost-effective in areas where larval habitats are few, fixed and findable, and likely less feasible in areas where the aquatic habitats are abundant, scattered and variable.*

The following settings are potentially the most suitable for larviciding as a supplementary measure implemented alongside ITNs or IRS:

- *urban areas: where breeding sites are relatively few, fixed and findable in relation to houses (which are targeted for ITNs or IRS);*
- *arid regions: where larval habitats may be few and fixed throughout much of the year.*

Practical Info

Larviciding is most likely to be cost-effective in urban areas where the appropriate conditions are more likely to be present. Larviciding is not generally recommended in rural settings, unless there are particular circumstances limiting the larval habitats and specific evidence confirming that such measures can reduce malaria incidence in the local setting. Determining whether or not specific habitats have immature *Anopheles* larvae and are suitable for larviciding is essential and should be based on expert technical opinion and knowledge.

WHO's 2013 *Operational manual on larval source management [81]* concluded that ITNs and IRS remain the backbone of malaria vector control, but LSM represents an additional (supplementary) strategy for malaria control in Africa. Larviciding will generally be most effective in areas where larval habitats are few, fixed and findable, and likely less feasible in areas where the aquatic habitats are abundant, scattered and variable. Determination of whether or not specific habitats are suitable for larviciding should be based on assessment by an entomologist. The WHO operational manual focuses on sub-Saharan Africa, but the principles espoused are likely to hold for other geographic regions that fit the same criteria. The following settings are potentially the most suitable for larviciding as a supplementary measure implemented alongside ITNs or IRS:

- urban areas: where breeding sites are relatively few, fixed and findable in relation to houses (which are targeted for ITNs or IRS);
- arid regions: where larval habitats may be few and fixed throughout much of the year.

Larviciding is likely to be more acceptable in communities that have a good understanding of the lifecycle of mosquitoes and the link with the transmission of malaria or other diseases. Community members may have concerns about larvicides being applied to drinking water or other domestic water sources. A well-designed community sensitization programme is required to ensure that communities fully understand the intervention and that any concerns about health and safety aspects are

addressed.

Evidence To Decision

Benefits and harms

The systematic review *[82]* reported that larviciding for non-extensive larval habitats less than 1km^2 may have an effect in reducing malaria incidence (rate ratio: 0.24; one trial; low-certainty evidence) and parasite prevalence (risk ratio: 0.79; 95% CI: 0.71–0.89; two studies; low-certainty evidence) compared to no larviciding. However, it is not known whether larviciding has an effect on malaria incidence (OR: 1.97; 95% CI: 1.39–2.81; one study; very low-certainty evidence) or parasite prevalence (OR: 1.49; 95% CI: 0.45–4.93; one study; very low-certainty evidence) compared to no larviciding in large-scale aquatic habitats.

No undesirable effects were identified in the systematic review. However, larviciding may affect non-target fauna; communities may not accept its application to sources of drinking water or water used for other domestic purposes.

Certainty of the Evidence

Low

For larval habitats less than 1km^2, the systematic review assessed that the overall certainty of evidence that larviciding has an impact on malaria was low. In larger habitats, the certainty of evidence was judged to be very low.

Resources and other considerations

The table below compiled by the GDG lists resources that should be considered for implementing larviciding. Note that this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated larvicide operators and skilled entomological technicians, divided into separate teams for surveillance and application of larvicide • Transport logisticians and drivers • Stock managers • Mapping technicians and assistants • Environmental assessment support staff
Training	• *Anopheles* larval habitat identification and classification • Larvicide application and safety • Entomological sampling and identification of *Anopheles* mosquito larvae, pupae and adults • Training for awareness campaigns and to encourage acceptability
Transport	• Appropriate vehicles to provide transport of larvicide, equipment, entomological sampling materials and workers to the community • Vehicle maintenance costs • Fuel
Supplies	• Larvicide • PPE • Entomological supplies for larval monitoring and rearing/maintenance of adult mosquitoes
Equipment	• Larvicide application equipment • Larvae, pupae and adult monitoring equipment • Mosquito identification equipment, e.g. microscopes

	• Computer/communication equipment
Infrastructure	• Appropriate storage facilities for larvicide and equipment • Office space for management • Insectary for collected larvae and to rear/maintain mosquitoes
Communication	• Communication with other ministries and sectors e.g. environment, transport, ministry of works/other infrastructure sectors and city/local councils • Communication with the general public e.g. through the education sector and media for awareness campaigns and to encourage acceptability • Communication with the community/local leaders
Governance/ programme management	• Supervision of mapping and application • Supervision of standard monitoring of larval, pupal and adult populations to assess entomological impact • Environmental impact assessment supervision

Justification

Larviciding is deployed for malaria control in several countries, including the Federal Republic of Somalia and the Republic of The Republic of the Sudan. However, the systematic review on larviciding conducted in 2019 *[82]* assessed that the certainty of evidence of impact on malaria incidence or parasite prevalence was moderate or low in non-extensive habitats. Since larviciding only reduces vector density, it does not have the same potential for health impact as ITNs and IRS – both of which reduce vector longevity (a key determinant of transmission intensity) and provide protection from biting vectors. As a result, larviciding should never be seen as a substitute for ITNs or IRS in areas with significant malaria risk.

Research Needs

- Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of larviciding.
- Evaluate new technologies for identifying aquatic habitats.

Larval habitat modification and/or larval habitat manipulation (2021)

No recommendation can be made because the evidence on the effectiveness of a specific larval habitat modification and/or larval habitat manipulation intervention for the prevention and control of malaria was deemed to be insufficient.

Practical Info

Although the available evidence that met the inclusion criteria for the systematic review was considered insufficient to develop specific recommendations, national programmes may decide to use environmental management (habitat modification and/or manipulation) to avoid the creation, and reduce the availability of, larval habitats, where deemed appropriate based on expert guidance and local knowledge. If such strategies are employed, the selection of the specific intervention(s) should be highly contextual, i.e. it should take into account the specific environment, the types of interventions relevant to that environment, the resources needed and their availability, the feasibility of the intervention(s), acceptability by local stakeholders and potential impact on equity. The selection should also take into account previous experience either gained locally or from other areas of similar ecological and epidemiological characteristics where such intervention(s) have been implemented. Additionally, the selection of the comparator should consider other interventions that are known to be cost-effective, for example, larviciding. Where the decision is taken to invest resources into larval habitat modification and/or larval habitat manipulation, the intervention(s) should be designed and conducted with the explicit aim of generating data to demonstrate effective malaria control, preferably supported with environmental and entomological data as secondary end-points.

When assessing the impact of environmental management against malaria, it is important that the testing of the

intervention(s) under investigation be conducted specifically for the purpose of preventing or controlling malaria by reducing the availability and productivity of larval habitats. For example, dams are generally constructed for water management, irrigation or power production purposes, not for malaria control. In fact, in some cases, their construction may result in increased larval production due to the creation of standing water bodies. The controlled release of water from the impoundment of a dam, however, is considered an example of habitat manipulation – a recurrent activity that potentially controls mosquito larvae by increasing the flow rate of downstream water with the aim of preventing mosquito development and so controlling malaria transmission. This is one example of the multitude of interventions that fall under the broad category of larval habitat modification and/or manipulation. To be able to generate evidence on the efficacy of larval habitat modification and/or manipulation in preventing malaria, and to facilitate the interpretation of the evidence once generated, it is important to well define the interventions that are being evaluated and, importantly, compare how the water conditions of larval habitats at the intervention and control sites are affected. For example, if the intervention aimed to increase the water flow to downstream areas, the evaluation should include an assessment of whether this was achieved, the extent to which this impacted the development of the immature and adult stages of the mosquito, and, ultimately, whether there was an epidemiological impact against malaria in the intervention arms compared to control areas. This information will then support the evolution of WHO guidance in this area and, ultimately, guide the choice and implementation of efficacious interventions.

Evidence To Decision

Benefits and harms

The systematic review (Martello *et al* *unpublished evidence*) identified two studies that investigated the impact of habitat manipulation by controlling the release of water from flood gates of dams or spillways (overflow channels) across streams to flush downstream areas with water against malaria. It is unknown whether larval habitat manipulation has an effect on malaria parasite prevalence compared to no larval habitat manipulation (relative risk: 0.01; 95% CI: 0.0–0.16; one study; very low-certainty evidence). It is unknown whether larval habitat manipulation combined with IRS has an effect on malaria clinical incidence compared to IRS alone (odds ratios or relative risks could not be calculated because the numbers of participants in each arm or at follow-up were not reported; one study; very low-certainty evidence).

Both studies were conducted in very specific settings.

No undesirable effects were identified in the systematic review.

Certainty of the Evidence

The systematic review assessed that the overall certainty of evidence that larval habitat manipulation had an impact on malaria was very low.

Values and preferences

No research was identified to determine preference and values. The GDG judged that there was probably no important uncertainty or variability.

Resources and other considerations

No research was identified that assessed cost effectiveness or resource needs.

Justification

The systematic review (Martello *et al* *unpublished evidence)* to inform WHO recommendations in this area identified only two controlled before-after studies meeting the inclusion criteria with epidemiological outcomes that investigated the impact of larval habitat manipulation alone. No studies investigating the impact of larval habitat modification on malaria outcomes were identified. Two other identified studies combined habitat manipulation with larviciding and so the effect of the two could not be separated. One study was conducted in an urban area of the Republic of the Philippines in 1960 and the other in a forested area of the Republic of India in 2008 where annual IRS was also conducted. The studies provided low- or very low-certainty evidence that the controlled release of water from flood gates of dams to discharge excess water or using

spillways (overflow channels) across streams to automatically flush downstream areas with water (continually or intermittently) reduced clinical malaria incidence or parasite prevalence. The evidence was downgraded due to the lack of appropriate randomization or poor statistical reporting. The studies examined very specific interventions, each studied in a single site, which the GDG judged would limit their generalizability. The systematic review reported a number of other studies with only entomological outcomes investigating a wide range of highly heterogeneous interventions falling under the broad term of larval habitat manipulation and/or modification, some of which may only be appropriate in specific ecologies. Given the broad range of interventions and settings in which larval habitat manipulation and/or modification may be applied, the GDG judged that the potential impact, feasibility, acceptability and resource needs for each intervention are likely to be highly variable.

Although it is acknowledged that there is a wealth of historical research on environmental management of malaria, the literature did not meet the eligibility criteria to be included in this systematic review. Therefore, there remains a continued need to robustly demonstrate the epidemiological impact of environmental management (habitat modification and/or manipulation) on malaria incidence and prevalence through further well-designed intervention studies.

Research Needs

The GDG encourages funding of high-quality research on the impact of habitat manipulation and/or modification on malaria transmission to inform the development of specific WHO recommendations in this area. A number of evidence gaps and associated requirements were identified:

- Determine the impact (incidence of clinical malaria and/or prevalence of malaria infection) and potential harms/ unintended consequences of the different interventions.
- Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).
- Detailed descriptions are needed of the interventions deployed, as well as larval habitat types and vector species targeted. The impact of the intervention on the water conditions of the larval habitats should be assessed, i.e. properties of the habitat that the intervention aims to modify such as water flow, volume, sunlight penetration, salinity or other physical conditions.
- Evidence is needed on contextual factors, (i.e. acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to larval habitat modification and/or manipulation is needed.

Larvivorous fish (2019)

No recommendation can be made because no evidence on the effectiveness of larvivorous fish for the prevention and control of malaria was identified.

Evidence To Decision

Benefits and harms

No studies reporting epidemiological outcomes against malaria were identified in the systematic review *[83]*. The review reported that there was no clear evidence of an effect on larval densities (very low-certainty evidence), but larvivorous fish may reduce the number of habitats positive for anopheline larvae (low-certainty evidence). The GDG noted that fish can serve as an additional source of nutrition.

No undesirable effects were identified in the systematic review.

The GDG recognized that there are specific settings in which the intervention is currently implemented, and in these specific settings programme staff consider it to be effective.

Certainty of the Evidence

The systematic review did not identify any eligible studies demonstrating the effect of larvivorous fish on malaria transmission or disease outcomes.

Resources and other considerations

- There is evidence that this intervention would require mosquito aquatic habitats to be large, permanent and few.
- Local capacity for breeding fish, maintaining fish and monitoring aquatic habitats would be needed.
- The characteristics of settings in which this intervention might be applicable would be needed.

Justification

The systematic review conducted in 2017 on the use of larvivorous fish *[83]* did not identify any studies demonstrating impact on malaria and so there is insufficient evidence to support a recommendation. The GDG recognized that there are specific settings in which the intervention is currently implemented, and in these specific settings programme staff consider it to be effective. In some of the settings where larvivorous fish are being deployed, programmatic evidence exists; however, this was not determined appropriate for inclusion in the systematic review due to unsuitable study design or other concerns. The GDG acknowledged that there may be data at the country/programme level that it is not aware of.

Research Needs

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) and potential harms/unintended consequences of the use of larvivorous fish.

Conditional recommendation against , Low certainty evidence

Topical repellents (2019)

The deployment of topical repellents in areas with ongoing malaria transmission is not recommended if the aim is to prevent and control malaria at the community level.

The panel recommended against the implementation of topical repellents with the aim of controlling malaria at the community level, given the lack of evidence of a significant impact. To achieve community-level impact, it is likely that a high level of individual compliance would be needed. Further work is required to separate out the potential protective effects at the individual and/or community level and therefore fully assess the potential public health value of topical repellents.

Evidence To Decision

Benefits and harms

The systematic review *[77]* included six RCTs conducted in Cambodia, Lao People's Democratic Republic, the Plurinational State of Bolivia and the United Republic of Tanzania, and in specific populations in the Islamic Republic of Pakistan (refugees) and The Kingdom of Thailand (pregnant women). The review reported that it is unknown whether topical repellents have an effect on clinical malaria caused by *P. falciparum* (risk ratio: 0.65; 95% CI: 0.40–1.07; three studies; very low-certainty evidence), on *P. falciparum* parasitaemia (risk ratio: 0.84; 95% CI: 0.64–1.12; four studies; low-certainty evidence) or on *P. vivax* parasitaemia (risk ratio: 1.07; 95% CI: 0.80–1.41; three studies; low-certainty evidence).Topical repellents were not associated with any reduction in the number of clinical cases caused by *P. vivax* (risk ratio: 1.32; 95% CI: 0.99–1.76; two studies; low-certainty evidence)

Based on expert opinion and in line with current WHO recommendations, topical repellents may still be useful in providing personal protection against malaria.

No undesirable effects were identified in the systematic review.

Certainty of the Evidence

Low

The systematic review assessed that the overall certainty of the evidence that topical repellents have an impact on malaria at the community level was very low.

Resources and other considerations

Adherence to daily application remains a major limitation.

Justification

The RCTs included in the systematic review conducted in 2018 *[77]* provided low certainty evidence of a possible effect of topical repellents on malaria parasitaemia (*P. falciparum* and *P. vivax*). The evidence is insufficiently robust to determine whether topical repellents have an effect on clinical malaria.

Research Needs

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) and potential harms/unintended consequences of topical repellents for individuals in specific settings and target populations.

Conditional recommendation against , Low certainty evidence

Insecticide-treated clothing (2019)

Deployment of insecticide-treated clothing is not recommended for the prevention and control of malaria at the community level in areas with ongoing malaria transmission; however, insecticide-treated clothing may be beneficial as an intervention to provide personal protection against malaria in specific population groups.

The GDG recommended against the deployment of insecticide-treated clothing due to the lack of evidence of an impact in the general population. In the absence of ITNs, there is some evidence that insecticide-treated clothing may reduce the risk of malaria infection in specific populations such as refugees and military personnel.

Evidence To Decision

Benefits and harms

Two RCTs were included in the systematic review *[77]*. Studies were conducted in specific populations in the Republic of Colombia (military personnel) and the Islamic Republic of Pakistan (Afghan refugees). The review reported that insecticide-treated clothing may have a protective effect against clinical malaria caused by *P. falciparum* (risk ratio: 0.49; 95% CI: 0.29–0.83; two studies; low-certainty evidence) and *P. vivax* (risk ratio: 0.64; 95% CI: 0.40–1.01; two studies; low-certainty evidence) i*n these populations* in the absence of ITNs.

No evidence was available on epidemiological effects in the general at-risk population.

No undesirable effects were identified in the systematic review.

Certainty of the Evidence

Low

The systematic review assessed that the overall certainty of the evidence that insecticide-treated clothing in specific populations has an impact on malaria was low.

Resources and other considerations

Such clothing may be beneficial as a tool to provide personal protection against malaria in specific population groups (refugees, military personnel).

Justification

The systematic review carried out in 2018 *[77]* provided low-certainty evidence that insecticide-treated clothing may have protective efficacy against *P. falciparum* and *P. vivax* cases, at least in certain specific populations (refugees, military personnel and others engaged in occupations that place them at high risk) and where ITNs are not in use. There was no evidence

available on epidemiological effects in the general at-risk population.

Research Needs

- Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of insecticide-treated clothing in the general population.
- Identify approaches to enhance acceptability/desirability and increase uptake and adherence.
- Develop formulations that improve the durability of insecticidal efficacy.

Spatial/Airborne repellents (2019)

No recommendation can be made because the evidence on the effectiveness of spatial/airborne repellents for the prevention and control of malaria was deemed to be insufficient.

Evidence To Decision

Benefits and harms

The systematic review *[77]* included two RCTs conducted in China and the Republic of Indonesia. The meta-analysis showed that spatial repellents had no impact against malaria parasitaemia (risk ratio: 0.24; 95% CI: 0.03–1.72; very low-certainty evidence).

No undesirable effects were identified in the systematic review.

Certainty of the Evidence

The systematic review assessed that the overall certainty of the evidence that spatial/airborne repellents have an impact on malaria was very low.

Justification

The systematic review published in 2018 *[77]* concluded that there is very low-certainty evidence that spatial or airborne repellents may have protective efficacy against malaria parasitaemia. Therefore, no recommendation on the use of spatial/airborne repellents in the prevention and control of malaria can be made until more studies assessing malaria epidemiological outcomes have been conducted.

Research Needs

- Determine the impact (incidence of malaria [infection or clinical)] and/or prevalence of malaria infection) and potential harms/unintended consequences of spatial/airborne repellents.
- Develop spatial repellent insecticide formulations that provide a long-lasting effect.

Conditional recommendation against , Very low certainty evidence

Space spraying (2019)

Space spraying is not recommended for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission; IRS or ITNs should be prioritized instead.

The panel recommended against the deployment of space spraying to control malaria, given the lack of evidence of impact against malaria. Due to the short-lived nature of the insecticides used, space spraying is generally costly and wasteful of resources.

Evidence To Decision

Benefits and harms

The systematic review *[84]* included a single interrupted time series study from the Republic of India in the meta-analysis, which was conducted more than 30 years ago. No impact on malaria cases per month was reported (step rate ratio: 1.00; 95% CI: 0.51–1.92; slope rate ratio: 0.85; 95% CI: 0.79–0.91).

The panel judged that any anticipated desirable effect of space spraying is likely to be small, as the insecticide formulations used are short-lived. *Anopheles* mosquitoes are generally considered to be less susceptible to space spraying than *Culex* or *Aedes*.

No undesirable effects were identified by systematic review.

Certainty of the Evidence

Very low

The systematic review assessed that the overall certainty of the evidence that space spraying has an impact on malaria was very low.

Resources and other considerations

Specialist technical equipment would be required to undertake space spraying. Combined with the human resource needs and the need for large amounts of insecticide, the costs are anticipated to be high, especially given the low residual effect of the chemicals used. Cost-effectiveness is considered to be limited for this intervention.

Justification

Only observational study was identified by the systematic review and the certainty of the evidence was graded as very low *[84]*. The lack of data from RCTs, other trial designs or quasi-experimental studies has therefore hampered a comprehensive assessment of this intervention and the review concluded that it is unknown whether space spraying causes a reduction in the incidence of malaria. The anticipated desirable effects of space spraying are likely to be small, as the insecticide formulations used are short-lived. *Anopheles* mosquitoes are generally considered to be less susceptible to space spraying than *Culex* or *Aedes*. Space spraying is frequently applied when cases are at their peak, which is followed by a decline in cases, whether or not control measures are applied. Nevertheless, space spraying is often deployed in response to outbreaks of mosquito-borne disease. Due to the high visibility of this intervention, the decision to use this approach is usually made to demonstrate that the authorities are taking action in response to the outbreak. This practice should be strongly discouraged given the limited evidence of the intervention's effectiveness, the high cost and the potential wastage of resources. The GDG therefore felt it necessary to develop a clear recommendation against space spraying for malaria control.

Research Needs

- Determine the impact (incidence of malaria (infection or clinical) and/or prevalence of malaria infection) and potential harms/unintended consequences of space spraying, particularly in emergency situations.

Conditional recommendation for , Low certainty evidence

House screening (2021)

Screening of residential houses can be used for the prevention and control of malaria in children and adults in areas with ongoing malaria transmission.

The GDG determined that a conditional recommendation should be given for house screening because of the low- to moderate-certainty evidence of an impact against malaria. Furthermore, programmes would need to consider a number of local contextual factors when considering screening of residential houses as a public health strategy, such as:

- *how the intervention will be delivered and maintained;*
- *whether the structure and condition of the residential houses in the community allow for the installation of screening;*
- *the feasibility and resources needed for implementation, especially if deployed on a large scale.*

Programmes should note that this recommendation addresses the use of screening of windows, ceilings, doors and/or eave spaces, and does not cover other ways of blocking entry points into houses.

Practical Info

If house screening is being considered as a means to prevent malaria, it is important to identify who the end-user will be and how the intervention will be implemented, i.e. whether screening of houses will be a tool that the programme promotes for individuals or communities to implement at their own cost, or whether it will be undertaken as a programmatic initiative. Depending on the approach, the resources needed, feasibility, uptake and impact on equity may vary and would need to be considered.

Screening of houses may be done post-construction or could be a standard feature for new homes. Intersectoral collaboration, for example, between health, housing and environmental sectors, is crucial in the implementation of house screening. It is also important to consider what standards and criteria, if any, need to be set for screening materials and designs, as they are for buildings.

Screening of residential houses should be part of an IVM approach as promoted under the GVCR *[16]*. Deployment of interventions recommended for large-scale deployment (such as ITNs or IRS) should be maintained, and communities should be encouraged to continue using ITNs regularly or allow their houses to be sprayed, even if screening has been installed.

In settings where national or local government authorities are not able to provide screening of residential houses as a public health strategy (e.g. due to feasibility/resource challenges), they should promote its use in affected communities.

If house screening is deployed or adopted by communities to prevent malaria, post-distribution monitoring of the intervention is needed to assess material durability, usage and coverage. This information should guide how regularly screens require replacement or repair and provide information on the sustainability of the intervention.

Evidence To Decision

Benefits and harms

The systematic review *[85]* included two cRCTs conducted in the Federal Democratic Republic of Ethiopia and the Republic of the Gambia that compared screened houses (without insecticide) to unscreened houses. There was low-certainty evidence that screening may reduce clinical malaria incidence caused by *P. falciparum* (rate ratio: 0.38; 95% CI: 0.18–0.82; one trial, low-certainty evidence) and parasite prevalence (risk ratio: 0.84; 95% CI: 0.60–1.17; one trial; low-certainty evidence). Anaemia was also reduced (risk ratio: 0.61; 95% CI: 0.42–0.89; one trial, moderate-certainty evidence). Screening may reduce the EIR, as both trials showed lower estimates in the intervention arm.

The systematic review noted from a pooled analysis of the two studies that individuals living in screened houses (covered eaves, windows and doors) were 16% less likely to sleep under a mosquito net (risk ratio: 0.84; 95% CI: 0.65–1.09; two trials, 203 participants). However, the results from the two studies were discrepant: In the Federal Democratic Republic of Ethiopia, the study *[86]* found no difference in ITN use in screened or unscreened homes, while

the study *[87]* in the Republic of the Gambia found that reported use of ITNs was lower in houses with screened ceilings (26%, 70/272) than in control houses (35%, 57/162; p=0.04). In the Gambian study, the number of mosquitoes in the house were reduced, which could have resulted in fewer participants feeling the need to use a net to prevent biting.

None of the other pre-specified outcomes (all-cause mortality; other disease incidence; adverse effects; unintended effects other than bed net usage) were reported in the included studies.

Based on the evidence presented in the review, the GDG judged that in some settings there may be potential undesirable effects associated with house screening; however, all of the potential effects identified by the GDG were judged to be small:

- Inhabitants of screened houses may stop or reduce their use of other effective interventions such as ITNs, especially if house screening is perceived to greatly reduce mosquito entry and/or be sufficient alone to protect against malaria. The decline or discontinuation in the use of interventions is likely not limited to those deployed with house screening; if any intervention that is deployed in conjunction with another is perceived to be sufficiently effective alone, use of the co-deployed intervention may decline.
- Screening of available entry points for mosquitoes into the house may result in reduced airflow and ventilation, and increased indoor temperatures compared to unscreened openings. While the GDG remarked that, as a result, occupants may open doors and windows (thereby negating the benefit of screening and, in turn, increasing the risk of mosquito exposure), in Côte d'Ivoire this was not the case. Households with screened openings did not differ from those with no screening in terms of opening and closing windows *[88]*. Reduced airflow and ventilation has been shown to result in increased respiratory problems and infections *[89]* and increased indoor air pollution, which negatively affects human health *[90][91][92]*. However, if household inhabitants routinely close entry points at night, such as windows, screening these openings would allow for increased airflow and ventilation compared to when they are closed, thereby reducing indoor temperatures as shown in the Republic of the Gambia *[93][94]*.

Certainty of the Evidence

Low

The systematic review assessed that the overall certainty of the evidence that house screening has an impact on malaria was low.

Values and preferences

No research was identified regarding preferences and values. The GDG judged that there was probably no important uncertainty or variability.

Resources

Resources needed for the screening of houses may depend on whether the intervention is deployed by the programme or implemented by the community. The table below, compiled by the GDG, lists resources that should be considered. Note that this table does not include resource needs for product selection or assessment of impact of the intervention.

Line Item (Resource)	Resource Description
Staff	• Competent, trained, supervised and adequately remunerated skilled carpenters/ construction workers/community members • BCC staff • Transport logisticians and drivers • Demonstrators/teachers • M & E staff
Training	• Training in appropriate construction/modification and/or installation techniques

	• Training for awareness campaigns and to encourage uptake
Transport	• Vehicles to provide transport of material and workers to the community to support installation and maintenance of the intervention and to provide BCC • Vehicle maintenance costs • Fuel
Supplies	• Adequate construction material for screening (including but not limited to wood/ screen, fasteners) • BCC materials (e.g. flip charts, posters, banners, staff clothing) • M&E data collection forms
Equipment	• Construction tools/equipment • Computer/communication equipment
Infrastructure	• Storage space for construction materials • Office space for management
Communication	• Communication with other ministries and sectors e.g. environment, transport, housing, city/local councils and large infrastructure projects, as well as coordination with local building regulators • Communication with the community/local leaders • Communication with the general public, e.g. through the education sector and media for awareness and to encourage uptake
Governance/ programme management	• Construction/installation supervisors • BCC supervision • M&E survey support for coverage

Equity

National programmes considering the adoption of screening of residential houses as a public health strategy should assess how the implementation of a screening programme would affect health equity in the community. Depending on how the intervention is deployed, the effect on equity may vary. For example, if individuals are encouraged to screen houses themselves, equity may be reduced. If the intervention is deployed at the programme level, it may be increased. The impact on equity may also depend on house structure and conditions, as some features may not allow for screening.

Acceptability

The studies included in the systematic review used in-depth interviews and focus group discussions to assess community acceptance of the intervention. In both studies, participants reported that the intervention reduced the number of indoor mosquitoes and house flies. Most participants in both trials chose to have screening after the duration of the trial. Additionally, participants in the study from the Republic of the Gambia reported a reduction in entry of other animals, such as bats, cockroaches, earwigs, geckos, mice, rats, snakes, and toads. In both trials, participants expressed concern that screening would be damaged by domestic animals and children, or that it would become dirty. In the Ethiopian study, some participants reported that they made further efforts to reduce mosquito entry after screening installation, such as filling in wall openings with mud.

Feasibility

National programmes considering the adoption of screening of residential houses as a public health strategy should

assess:

- whether the structure and condition of the residential houses in the community allow for the installation of screening and are accessible;
- whether adequate resources are available, particularly if houses require screening to be made bespoke and if there is a need to renovate some houses to enable screening;
- the level of community buy-in (acceptability and/or willingness to implement the intervention);
- the feasibility of implementation if it is on a large scale, including the impact on resource use and potential changes in cost-effectiveness of the programme, and also taking into account the values, preferences and cultural norms of the main stakeholders; and
- how the intervention will be delivered and maintained.

Justification

The systematic review *[85]* identified only two eligible published studies assessing the impact of housing modifications on malaria epidemiological outcomes conducted in the Federal Democratic Republic of Ethiopia and the Republic of the Gambia . Both studies investigated the impact of house screening (screening of windows, ceilings, doors and/or eaves) with untreated materials against malaria. The authors concluded that screening may reduce clinical malaria incidence, parasite prevalence, prevalence of anaemia and EIR. In the trials included in the systematic review, research teams deployed screening at the community level and, as a result, there is currently no evidence as to the benefits and harms of individuals or communities deploying screens themselves. The review identified several studies that were yet to be published on the efficacy of insecticide-treated screening, eave tubes or other forms of housing modifications, but the data were not available at the time for inclusion in the review.

Given that only two trials were included in the review, a number of potential effect modifiers could not be examined, and the generalizability of the findings was limited. The panel concluded that untreated screening of residential houses may prevent malaria and reduce malaria transmission, and that these desirable effects would outweigh the undesirable effects. However, in translating this evidence into a recommendation strength, the GDG concluded that the recommendation should be conditional due to the low- to moderate-certainty evidence and based on a number of contextual factors. The panel judged that policy-makers considering house screening should assess the feasibility, acceptability, impact on equity and resources needed for screening houses in their contexts in order to determine whether such an intervention would be appropriate for their setting.

Research Needs

WHO encourages funding of high-quality research on the impact of interventions under the broad category of “housing modifications” to further inform the development of specific WHO recommendations. Results from four trials awaiting publication are likely to enrich the current evidence base on housing modifications for preventing malaria and controlling malaria transmission. Publication of these studies is strongly encouraged.

A number of specific evidence gaps and associated requirements were identified:

- Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of house screening, as well as other housing modification interventions deployed alone or in combination.
- Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).
- Evidence is needed on contextual factors (i.e. acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences) related to house screening, as well as other housing modification interventions.
- Determine the resource needs, costs and cost-effectiveness of various deployment options for house screening (at the programme, community and individual level).
- Develop deployment mechanisms and foster community buy-in for house screening and other housing modification interventions.

4.1.4 Research needs

WHO’s guideline development process for new vector control interventions relies on evidence from at least two well-designed and well-conducted studies with epidemiological endpoints to demonstrate the public health value of the

intervention. If the initial two studies generate contradictory or inconsistent results or suffer from design limitations that preclude comprehensive assessment of an intervention's potential public health value, further trials with epidemiological endpoints may be required. As such, WHO encourages the use of appropriate study designs, including the generation of baseline data and appropriate follow-up times that consider the characteristics of the intervention and its intended deployment, expected durability/residual efficacy and replacement intervals, and the epidemiology (e.g. pathogen transmission intensity) of the selected study site. WHO encourages studies to be conducted for durations that maximize the likelihood that the study objectives and targeted statistical power will be robustly achieved so as to strengthen the evidence used to inform deliberations by a GDG regarding a potential WHO recommendation. Detailed descriptions of the setting, interventions deployed, and vector species targeted are required. Investigators are encouraged to share their study design and methodology with WHO prior to commencing the study in order to enable the VCAG to validate whether the data generated are likely to provide quality evidence to inform the development of a WHO recommendation. High research standards should be employed in conducting, analysing and reporting studies, ensuring that studies are adequately powered, and appropriate randomization methods and statistical analyses are used. WHO requires studies to be conducted in compliance with international ethical standards and good clinical and laboratory practices. Further information on evaluation standards for vector control interventions can be found in *Norms, standards and processes underpinning WHO recommendations on vector control [95]*.

Intervention	Research needs
Pyrethroid-only ITNs	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences* of new types of nets and insecticides in areas where resistance to pyrethroids is high.
	Determine the comparative effectiveness and durability of different net types.
	Determine the effectiveness of nets in situations of residual/outdoor transmission.
	Determine the impact of ITNs in transmission 'hotspots' and elimination settings.
Pyrethroid-PBO nets	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of pyrethroid-PBO nets from areas where the mechanisms of resistance in vector species are not oxidase-based and from areas of lower malaria transmission intensity.
	Further evidence is needed on the durability of pyrethroid-PBO nets.
ITNs in humanitarian emergencies	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of ITNs in the acute phase of humanitarian emergencies (where logistics and priorities may differ).
Indoor residual spraying (IRS)	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of IRS.
	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of IRS in urbanized areas with changing housing designs.
	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of IRS using new insecticides in areas where mosquitoes are resistant to currently deployed insecticides.
	Determine the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) of IRS in areas with different mosquito behaviours (such as in areas with outdoor transmission).
	Given the relatively high cost of implementing IRS, especially in the context of growing insecticide resistance, and when delivering IRS in remote areas, there is a need to investigate new approaches to the implementation of IRS to increase cost-effectiveness.
IRS in	Determine the impact (incidence of

humanitarian emergencies	malaria [infection or clinical] and/ or prevalence of malaria infection) and potential harms/unintended consequences of IRS in the acute phase of humanitarian emergencies (where logistics and priorities may differ).
Vector control in humanitarian settings	Further evidence is required on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of other vector control interventions in humanitarian emergencies.
Co-deploying IRS and ITNs	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of co-deploying IRS with ITNs vs ITNs alone from more settings, for example, areas with mosquito populations that are resistant to insecticides other than pyrethroids.
	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of combining ITNs with IRS vs IRS alone.
	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of switching from ITNs to IRS vs co-deployment of the two interventions.
	Determine the acceptability of combining IRS and ITNs among householders and communities.
	Evaluate new tools for monitoring the quality of IRS and ITN interventions is needed.
Larviciding	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of larviciding.
	Evaluate new technologies for identifying aquatic habitats.
Larval habitat manipulation/ modification	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) and potential harms/ unintended consequences of the different interventions. Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).
	Detailed descriptions are needed of the interventions deployed, as well as larval habitat types and vector species targeted. The impact of the intervention on the water conditions of the larval habitats should be assessed, i.e. properties of the habitat that the intervention aims to modify such as water flow, volume, sunlight penetration, salinity or other physical conditions.
Larvivorous fish	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) and potential harms/unintended consequences of the use of larvivorous fish.
Topical repellents	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) and potential harms/unintended consequences of topical repellents for individuals in specific settings and target populations.
Insecticide-treated clothing	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) and potential harms/unintended consequences of insecticide-treated clothing in the general population.
	Identify approaches to enhance acceptability/desirability and increase uptake and adherence.
	Develop formulations that improve the durability of insecticidal efficacy.
Spatial/ airborne	Determine the impact (incidence of malaria [infection or clinical] and/

repellents	or prevalence of malaria infection) and potential harms/unintended consequences of spatial/airborne repellents.
	Develop spatial repellent insecticide formulations that provide a long-lasting effect.
Repellents in general	Epidemiological and/or entomological evidence is needed on whether repellents cause diversion of malaria mosquitoes from a treated area to a neighbouring untreated area.
Space spraying	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) and potential harms/unintended consequences of space spraying, particularly in emergency situations.
House modifications	Further evidence is needed on the impact (incidence of malaria [infection or clinical] and/or prevalence of malaria infection) and potential harms/unintended consequences of house screening and other housing modification interventions deployed alone or in combination.
	Epidemiological evidence is required on the efficacy against malaria of the same intervention implemented in different settings (where vector species may differ).
	Determine the resources needs, costs and cost-effectiveness of various deployment options for house screening (at the programme-, community-, individual-level).
	Develop deployment mechanisms and foster community buy-in for house screening and other housing modification interventions.
Insecticide resistance management	Determine the impact (incidence of malaria [infection or clinical] and/ or prevalence of malaria infection) of different strategies for insecticide resistance management such as using rotations of insecticides, mosaics, etc.
	Determine the impact of insecticide resistance on key outcomes (malaria mortality, clinical disease and prevalence of infection).

* Harms/unintended consequences may include undesirable effects on individuals, the community, mosquito bionomics and the environment.

Other research needs and evidence gaps required to further update guidance were identified as follows:

- evidence on the linkage or correlation between the epidemiological and entomological end-points used to demonstrate impact;
- evidence on contextual factors (i.e. structural challenges and opportunities, acceptability, feasibility, resource use, cost-effectiveness, equity, values and preferences in various settings) related to different vector control interventions deployed in stable and humanitarian emergency situations;
- evidence on the use of tools to monitor recommended vector control interventions;
- evidence to support the resources listed and other considerations for resource use provided under each recommended intervention in order to aid guidance on the prioritization of interventions (wherever possible, following examples provided in other WHO guidance and guidelines); and
- evidence of the benefits (incidence of clinical malaria and/ or or prevalence of malaria infection) and potential harms/ unintended consequences of deploying interventions in special situations, for example, a) to control outdoor transmission of malaria, and b) to protect specific populations with high occupational exposure to malaria.

4.2 Preventive chemotherapies

Chemoprevention and chemoprophylaxis are preventive chemotherapies that use antimalarial medicines to prevent malaria infection and disease. Chemoprevention uses full therapeutic courses of antimalarial medicines at prescheduled times, irrespective of infection status, to treat existing infections and prevent new infections and thus reduce malaria in people living in endemic areas. Chemoprophylaxis usually involves administration of sub-therapeutic doses of antimalarials to prevent new infections and is primarily used by non-immune people travelling to malaria endemic areas. Chemoprophylaxis is not addressed in detail in the current guidelines beyond the short description in this section.

Current WHO recommendations for chemoprevention include

the intermittent preventive treatment of malaria in pregnancy (IPTp), perennial malaria chemoprevention (PMC), previously known as intermittent preventive treatment in infants (IPTi), seasonal malaria chemoprevention (SMC), intermittent preventive treatment in school aged children (IPTsc), post-discharge malaria chemoprevention (PDMC) and mass drug administration (MDA) for malaria burden and transmission reduction, and mass relapse prevention. Each of these recommendations reflects the biological plausibility that a treatment course of an effective antimalarial will clear any existing, and prevent new, malaria infections. This underlying principle can inform the adaptation of recommendations to maximise impact in different settings.

The updated chemoprevention recommendations reflect the paradigm shift, outlined in the introduction, to provide greater flexibility to NMPs to adapt control strategies to suit their settings. Standard processes have been used to develop evidence-based recommendations which are not unduly restrictive. We no longer specify strict age groups, transmission intensity thresholds, numbers of doses or cycles, or specific drugs. The effectiveness of a chemoprevention programme will be influenced by a host of contextual and other factors (e.g. intensity of malaria transmission, extent of seasonal variation in transmission, the age group targeted by the chemoprevention programme, the preventive efficacy of the drugs used, the frequency of dosing, duration of protection of each treatment course, availability of drugs, coverage achieved, adherence to the recommended regimen) and by the mix of interventions being deployed in each setting. NMPs are therefore encouraged to consider local data to determine how best to tailor chemoprevention strategies to local needs and determine which age groups should be prioritized where, for how long, how frequently, and with which drugs. Subnational tailoring is increasingly needed, for example to recognize the variation in duration of the transmission season even within a country, meaning that 3, 4, 5 or more cycles of SMC may be warranted in different subnational areas.

To support decision making, each chemoprevention recommendation is accompanied by a summary of available research evidence, an explanation of how this was used to inform the recommendation and practical information regarding key considerations for implementation.

Protection for travellers to malaria-endemic areas

The primary target for these guidelines is people living in endemic areas and no formal recommendations regarding preventive chemotherapy are currently included for non-immune people travelling to malaria endemic regions.

People growing up in endemic countries will increasingly be non-immune as malaria control improves. However, epidemiological changes will be heterogeneous and future guidelines will need to consider the use of chemoprophylaxis among people growing up in areas without malaria (e.g. some urban settings) who then travel within their own country to places where malaria is endemic (e.g. many rural settings). The potential of chemoprophylaxis for people at risk of occupational exposure to malaria (e.g. farmers, miners) also warrants consideration. Readers interested in the use of antimalarial agents to prevent malaria in people travelling from non-endemic settings to areas of malaria transmission are directed to the WHO International travel and health guidance *[2]*.

In summary, travellers should start chemoprophylaxis before entering an endemic area, to assess tolerability and, for slowly eliminated drugs, to build up therapeutic concentrations. Malaria may be prevented by taking drugs that inhibit liver-stage (pre-erythrocytic) development (causal prophylaxis) or drugs that kill asexual blood stages (suppressive prophylaxis). Causal prophylactics (atovaquone + proguanil) can be stopped soon after leaving an endemic area, whereas suppressive prophylactics must be taken for at least 4 weeks after leaving the area in order to eliminate asexual parasites emerging from the liver weeks after exposure.

4.2.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

Intermittent preventive treatment of malaria in pregnancy (IPTp) is the administration of a treatment course of an antimalarial medicine at predetermined intervals, regardless of whether the pregnant woman is infected with malaria. Malaria infection during pregnancy poses substantial risks not only to the mother, but also to her fetus and the newborn.

This updated IPTp recommendation builds on evidence from seven trials that informed the previous recommendation (2012)[1] for the use of at least three doses of sulfadoxine-pyrimethamine (SP) for IPTp during antenatal care (ANC) visits in the second and third trimester of the first and second pregnancies to improve birth outcomes. The initial evidence also demonstrated that IPTp reduced maternal anaemia and infection with malaria. This update assessed the potential effects of gravidity, malaria transmission intensity, and SP resistance on the effectiveness of IPTp-SP, and the recommendation has been revised accordingly.

[1]The evidence showed that, compared to two doses, three or more doses of IPTp-SP increased mean birthweight by 56g (95% CI: 29–83g higher; high-certainty evidence); reduced the number of low birthweight infants (relative risk: 0.80; 95% CI: 0.69–0.94; high-certainty evidence); reduced placental parasitaemia (relative risk: 0.51; 95% CI: 0.38–0.68; high-certainty evidence); and probably reduced maternal parasitaemia (relative risk: 0.68; 95% CI: 0.52–0.89; moderate-certainty evidence).

Strong recommendation for , Moderate certainty evidence

Intermittent preventive treatment of malaria in pregnancy (2022)

In malaria-endemic areas, pregnant women of all gravidities should be given antimalarial medicine at predetermined intervals to reduce disease burden in pregnancy and adverse pregnancy and birth outcomes.

- *Sulfadoxine-pyrimethamine (SP) has been widely used for malaria chemoprevention during pregnancy and remains effective in improving key pregnancy outcomes.*
- *IPTp-SP should start as early as possible in the second trimester and not before week 13 of pregnancy.*
- *Doses should be given at least one month apart, with the objective of ensuring that at least three doses are received.*
- *Antenatal care (ANC) contacts remain an important platform for delivering IPTp. Where inequities in ANC service and reach exist, other delivery methods (such as the use of community health workers) may be explored, ensuring that ANC attendance is maintained and underlying inequities in ANC delivery are addressed.*
- *IPTp is generally highly cost-effective, widely accepted, feasible for delivery and justified by a large body of evidence generated over several decades.*

Practical Info

Antimalarial medicine

WHO recommends that the medicines used for IPTp be different from those used as first-line malaria treatment. SP has been widely used for chemoprevention during pregnancy and has been shown to be efficacious, safe, well tolerated, available and inexpensive. A drug regimen that can be administered as a directly observed single dose, such as SP, is preferable to a multi-day regimen.

The Guideline Development Group did not formally consider alternative drug regimens to SP for IPTp, or their associated costs. However, recent studies of dihydroartemisinin-piperaquine (DHAP) in areas of high SP resistance have shown that, although superior to SP in reducing malaria during pregnancy, the use of DHAP did not translate into better pregnancy outcomes; SP was associated with better fetal growth, resulting in higher mean birthweights in all gravidae (Gutman *et al* *unpublished evidence* *(a)*).

Transmission

In areas of moderate to high *P. falciparum* transmission, IPTp-SP should be given to all pregnant women. Whether there continues to be a role for IPTp in areas where malaria transmission has fallen to low levels is uncertain. There is evidence that even in areas with *Pf*PR_{2-10} < 3%, IPTp-SP reduces maternal anaemia and may reduce low birthweight, as well as maternal and placental infection (Gutman *et al* *unpublished evidence* *(a)*). Some of these effects may not be due to the effects of IPTp-SP on malaria. There is currently insufficient data to define the level of transmission below which IPTp-SP may cease to be cost-effective. Challenges of IPTp reintroduction after withdrawal caution against discontinuing IPTp-SP following a recent reduction in malaria transmission.

Pregnancy

IPTp improves a wide range of outcomes in women in their first and second pregnancies, including maternal and placental infection, maternal anaemia and low birthweight (Gutman *et al* *unpublished evidence* *(a)*). There is now evidence that IPTp also reduces maternal infection in third or subsequent pregnancies, but there are currently too few trials to evaluate effects on other outcomes in these women (Gutman *et al* *unpublished evidence* *(a)*). Administering IPTp to all pregnant women regardless of number of pregnancies facilitates ease of IPTp implementation for health workers.

Dosage

IPTp-SP should ideally be administered as directly observed therapy (DOT) with three tablets of SP (each tablet containing 500 mg/25 mg SP), for the total required dosage of 1500 mg/75 mg SP.

Schedule

IPTp-SP should not be given before week 13 of pregnancy due to an increased risk of fetal malformation. IPTp-SP should start in the second trimester and doses should be given at each scheduled ANC contact until the time of delivery, provided that doses are at least one month apart. At least three doses of IPTp-SP should be received during pregnancy.

Delivery

ANC contacts remain an important platform for delivering IPTp, and so inequities in ANC service and reach should be addressed. Research on alternative approaches to IPTp delivery (e.g. through community health workers) may identify

opportunities to increase coverage, while ensuring that ANC attendance is maintained. This may be useful for supporting IPTp delivery while measures to address ANC inequities are implemented. Consideration should be given to contextual factors such as the values and preferences of end-users, costs, coverage and sustainability of alternative delivery platforms.

Drug resistance
IPTp-SP appears to select for antifolate resistance mutations associated with low to moderate increases in drug resistance. However, there is no convincing evidence of selection favouring key mutations, such as *dhps*A581G, which is associated with the loss of IPTp-SP efficacy (Plowe *unpublished evidence*). There is also insufficient evidence to withhold IPTp-SP in areas where the prevalence of *dhps*A581G exceeds a threshold of 10% (Plowe *unpublished evidence*). Although the ability of IPTp-SP to clear existing infections and prevent new ones is compromised in areas of high to very high resistance, the intervention still reduces low birthweight and maternal anaemia. Consequently, IPTp-SP should continue to be used in areas of high SP resistance until more effective alternatives for malaria chemoprevention are found.

Contraindications
IPTp is not recommended for pregnant women before week 13 of pregnancy, or those with severe acute illness, or who are unable to take oral medication, or women who during the last 30 days received a dose of any of the drugs being used for IPTp, or those allergic to any of the components of SP. IPTp-SP should not be given to individuals receiving a sulfa-based medicine as treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole) for HIV. High doses of folic acid (daily dose ≥ 5 mg) have been shown to counteract the efficacy of SP as an antimalarial, and only low-dose formulations (i.e. 0.4 mg daily) should be co-administered with SP.

Other considerations
Information about IPTp should be fully accessible to pregnant women. As with all health interventions, consent should be obtained from the pregnant woman prior to administering IPTp.

Evidence To Decision

Benefits and harms

In the mother

- **Anaemia**: IPTp-SP may reduce maternal anaemia (risk ratio: 0.90; 95% CI: 0.87–0.93; low-certainty evidence) and increase maternal haemoglobin (mean difference: 0.19 g/dL higher; 95% CI: 0.15–0.22 g/dL higher; low-certainty evidence) for each dose of SP in all gravidae. The effect is lower but remains significant in the highest SP resistance areas[1] (relative risk reduction: 8.2%; 95% CI: 3–13%). IPTp-SP also reduced maternal anaemia in areas with *Pf*PR_{2-10} < 3% (risk ratio: 0.91; 95% CI: 0.85–0.97).
- **Placental and maternal malaria infection at delivery**: IPTp-SP probably reduces placental infection (risk ratio: 0.78; 95% CI: 0.74–0.84; moderate-certainty evidence) and maternal malaria infection at delivery (risk ratio: 0.80; 95% CI: 0.75–0.85; moderate-certainty evidence) for each dose of SP in all gravidae, compared to no IPTp-SP. Overall, IPTp-SP was associated with a 20% reduction (95% CI: 16–24%) in placental or maternal malaria at delivery compared to no IPTp-SP. The effect was greater in first and second pregnancies (24%; 95% CI: 19–29%) than in third or subsequent pregnancies (17%; 95% CI: 13–20%). There was a trend towards reduced efficacy with increased resistance, with a relative risk of 28% (95% CI: 20–36%) in the lowest resistance stratum and 22% (95% CI: 14–29%), 8% (95% CI: 0–7%) and -5% (95% CI: -16–5%) in the moderate, high and very high resistance strata, respectively. The effect of IPTp-SP in areas with *Pf*PR_{2-10} < 3% was variable (risk ratio for maternal malaria: 0.73; 95% CI: 0.53–1.01; and for placental malaria: 0.89; 95% CI: 0.68–1.15).
- **Adverse events**: IPTp-SP had a pooled prevalence of serious adverse events of 3.84% (95% CI: 2.20–5.88%) and a pooled prevalence of adverse events of 14.3% (95% CI: 4.9–27.5%). In two trials comparing IPTp-SP to placebo or case management, the pooled risk ratio showed that IPTp-SP may reduce maternal adverse events (risk ratio: 0.56; 95% CI: 0.30–1.01; moderate-certainty evidence). Skin reactions were rarely reported, with a pooled prevalence of 0.4% (95% CI: 0.2–0.7%) among all women who took IPTp-SP and with no significant increase in the two trials comparing IPTp-SP to placebo or case management (pooled risk ratio: 1.24; 95% CI: 0.34–4.58).
- **Maternal death**: The effect of IPTp-SP on maternal death is poorly documented. It is possible that IPTp-SP results in little to no difference in maternal death (risk ratio: 1.17; 95% CI: 0.49–2.80; low-certainty evidence).

None of the studies in the systematic review reported on **malaria infection**, **severe malaria**, or **maternal hospitalization**.

In the fetus and infant

- **Birthweight**: IPTp-SP probably reduces low birthweight for each dose of SP compared to no IPTp-SP (risk ratio: 0.75; 95% CI: 0.71–0.78; low-certainty evidence) for all gravidae. The point estimate is slightly higher in first and second pregnancies (26%; 95% CI: 21–31%) than in third or subsequent pregnancies (21%; 95% CI: 16–26%). Compared to no IPTp-SP, each dose of IPTp-SP probably increases mean birthweight for babies born to women of all gravidae (mean difference: 57 g higher; 95% CI: 44–69 g; moderate-certainty evidence). IPTp-SP was associated with a mean increase in birthweight of 67 g (95% CI: 50–85 g) in babies born to women in their first and second pregnancies and 43 g (95% CI: 26–60 g) in third or subsequent pregnancies. The relative risk reduction in low birthweight decreased with increasing SP resistance, remaining significant in high-resistance areas (relative risk reduction: 23%; 95% CI: 16–29%), but becoming non-significant in the highest SP resistance areas (relative risk reduction: 16%; 95% CI: -4–32%). Mean difference in birthweight was 65 g (95% CI: 44–87 g), 66 g (95% CI: 45–88 g) and 46 g (95% CI: 27–66 g) in the lowest, middle and high SP resistance areas, respectively. There was a non-significant mean difference of 11 g (95% CI: -9–32 g) in the highest resistance areas.
- **Adverse pregnancy outcomes**: Each dose of IPTp-SP may reduce preterm delivery compared to no IPTp-SP (risk ratio: 0.76; 95% CI: 0.71–0.81; very low-certainty evidence). However, the evaluation of preterm delivery and number of SP doses is complicated because prematurity inherently reduces the opportunity to receive more SP doses. It is uncertain whether IPTp-SP reduces stillbirths and spontaneous abortions compared to no IPTp-SP (risk ratio: 0.68; 95% CI: 0.59–0.78; very low-certainty evidence).

None of the studies in the systematic review reported on **malaria infection, anaemia, severe malaria, hospital admissions**, or **death**.

More information on the evidence can be found in the systematic review (Gutman *et al* *unpublished evidence* *(a)*).

[1] Resistance was defined as low (Ala437Gly < 75% in Central/West Africa or Lys540Glu < 40% in Eastern/Southern Africa), medium (Ala437Gly ≥ 75% in Central/West Africa or Lys540Glu 40–60% and AlaA581Gly < 5% in Eastern/Southern Africa), high (Lys540Glu ≥ 60 & Ala581Gly < 5% in Eastern/Southern Africa) and very high (Lys540Glu ≥ 60% and *dhps* Ala581Gly ≥ 5% in Eastern/Southern Africa).

Certainty of the Evidence

Moderate

The certainty of evidence across the outcomes ranged from very low to moderate, with a number of the outcomes deemed important by the GDG classed as moderate-certainty evidence. The GDG noted sustained impact of IPTp-SP across all transmission and resistance settings. Consequently, the overall certainty of evidence for the outcomes of interest was considered moderate by the GDG. This reflects the large number of observational studies contributing useful information to these updated guidelines, building on the initial more robust data from randomized controlled trials.

More information on the certainty of evidence assessments can be found in the ‘research evidence’ tab associated with this recommendation online or in the annex of the pdf version.

Values and preferences

Preferences and values of the target population were determined by:

- consultation with civil society, which indicated that chemoprevention to prevent malaria disease in pregnant women was seen as a priority in endemic areas (CS4ME *unpublished evidence*);
- a synthesis of contextual factors from studies of IPTp-SP, although these lacked data on how IPTp-SP was valued (Rodriguez *et al* *unpublished evidence*).

The GDG vote on values and preferences was equally split between “probably no important uncertainty or variability” and “possibly important uncertainty or variability” in how the outcomes of IPTp are valued across contexts. The vote was repeated and remained split. Those who voted for the latter felt that IPTp may be valued differently depending on the transmission and resistance context. The consensus of the GDG was not to say that values and preferences vary but rather to highlight the two positions.

More information can be found in the civil society consultation report (CS4ME *unpublished evidence*).

Resources

An individually randomized, placebo-controlled trial in a moderately intense transmission setting in Mozambique found IPTp-SP to be a highly cost-effective intervention *[96]*. Based on data from 2007, the financial cost of delivering two doses of IPTp-SP through ANC was about US$ 435.79 per 1000 pregnant women. Delivering two doses of IPTp-SP to 1000 pregnant women resulted in a total health system cost saving of US$ 422.74, 43% of which was attributed to reduced hospital admissions. Consequently, the net intervention cost was US$ 13.17 per 1000 pregnant women. IPTp-SP led to substantial household cost savings for women seen in the outpatient department (US$ 33.89 in direct costs; 95% CI: 6.10–77.20; and US$ 83.79 in indirect costs; 95% CI: 29.60–148.30). However, it did not lead to statistically significant household cost savings for women who required admission for malaria (US$ 8.20 in direct costs; 95% CI: -42.80–55.80; and US$ 11.44 in indirect costs; 95% CI: -20.50–42.70). Delivering IPTp-SP to 1000 pregnant women was expected to avert 18.9 (95% CI: 4.4–33.8) neonatal deaths, or 555.2 (95% CI: 129.0–992.0) disability-adjusted life years (DALYs). This study determined threshold values of some variables beyond which IPTp-SP was no longer cost-effective. These were when ANC attendance is lower than 37.5%, the protective efficacy of IPTp-SP against maternal infection is lower than 15%, maternal clinical malaria incidence is lower than 0.15 person-year at risk, or the maternal case fatality ratio is lower than 0.15%.

Based on the data from Mozambique, the intervention costs of delivering two doses of IPTp-SP were US$ 41.46 per DALY averted versus US$ 7.28 per DALY averted for three doses *[96][97]*. The cost of one dose of IPTp-SP was reported to be between US$ 0.63 and US$ 0.79 *[97][98]*.

The GDG considered that there were negligible costs and savings associated with implementing IPTp-SP and the certainty of the evidence on the resources required was moderate. The GDG determined that IPTp is probably cost-effective compared to no intervention.

More information on the evidence can be found in the summary of contextual factors report (Rodriguez *et al* *unpublished evidence*).

Equity

Age, marital status, religion, and living in a rural area were found to influence the uptake of IPTp-SP in 13 studies. Women under 20 years old were generally the least likely to receive three doses of IPTp-SP, with those between 25 and 34 most likely to receive IPTp-SP. Socioeconomic considerations including education level, employment status and wealth index affected uptake of IPTp. Higher uptake was associated with being married and higher education, and some studies found a strong association between employment status and IPTp-SP uptake. Many studies reported that women in the “middle” to “richest” wealth index had higher uptake of IPTp-SP compared to those in the “poorest” to “poorer” wealth categories, including receipt of at least three doses of IPTp-SP. Rural residence was inconsistently associated with improved IPTp-SP uptake. Studies conducted in Burkina Faso, Côte d’Ivoire, and Sierra Leone reported that women who lived in rural areas were more likely to take the recommended doses of IPTp-SP, while studies in Ghana, Malawi and Nigeria reported that urban residence was associated with higher IPTp-SP uptake compared to rural residence. Living more than 5 km from a health facility was also associated with poorer uptake of IPTp-SP.

The GDG considered that the health equity of IPTp varies depending on contextual factors, especially those influencing access to ANC services. IPTp programmes that address inequities will likely improve coverage of IPTp and improve pregnancy outcomes.

More information on the evidence can be found in the summary of contextual factors report (Rodriguez *et al* *unpublished evidence*).

Acceptability

IPTp has been widely accepted by pregnant women. Greater knowledge about IPTp has been shown to increase acceptance and uptake of the intervention. ANC attendance is a main driver influencing patient acceptance of IPTp-SP.

Numerous studies have reported increased uptake of IPTp-SP with early initiation of education and counselling sessions at ANC, specifically during the first trimester, as well as frequent ANC contacts. In general, women who were concerned about the side effects of SP were less likely to take the recommended number of doses of IPTp-SP.

The GDG considered IPTp to probably be acceptable to key stakeholders.

More information on the evidence can be found in the summary of contextual factors report (Rodriguez *et al unpublished evidence*).

Feasibility

Limited knowledge and training of staff on the prevention and management of malaria in pregnancy, including indications for IPTp-SP, contribute to poor uptake. Some health care workers expressed concerns over the lack of ongoing training to update their knowledge, although this was country- and site-dependent. Other issues that impaired the delivery of IPTp included stockouts of SP, under-prescribing of SP (< three doses), and inadequate staffing. DOT was generally, but not always, associated with improved uptake of IPTp-SP. Utilization of DOT was variable, with between 5% and 67% of pregnant women reporting taking IPTp-SP under DOT *[99][100][101][102]*.

The GDG considered IPTp implementation to be feasible, given that it is delivered through ANC.

More information on the evidence can be found in the summary of contextual factors report (Rodriguez *et al unpublished evidence*).

Justification

This recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *[103]*.

Sources of information

Recommendation development was informed by a systematic review (Gutman *et al unpublished evidence (a)*) and a report summarizing evidence from published studies on contextual factors related to IPTp implementation (Rodriguez *et al unpublished evidence*), including cost-effectiveness, feasibility, equity, values and acceptability. These sources of information were supplemented by a cross-cutting review on chemoprevention and drug resistance (Plowe *unpublished evidence*), a civil society consultation report on chemoprevention (CS4ME *unpublished evidence*) and contributions from the GDG membership, which included former and current national malaria programme representatives. The GDG was supported by a Steering Group, which included representatives from the WHO Departments for Sexual and Reproductive Health and Research and Child Health and Development.

The systematic review addressed the GDG's PICO (population, intervention, comparison, outcome) question regarding whether women of all gravidities should be given SP as malaria chemoprevention to reduce disease burden in pregnancy and/or adverse pregnancy and birth outcomes. In particular, the systematic review assessed the potential modifying effects of gravidity, malaria transmission intensity, and SP resistance on the effectiveness of IPTp-SP.

The main outcomes of interest considered by the GDG in the systematic review were maternal anaemia and low birthweight. Other outcomes of interest included maternal clinical malaria, placental infection, malaria infection, severe malaria, adverse events, hospitalization, and death; and fetal/infant adverse pregnancy outcomes (spontaneous abortion, stillbirth or preterm delivery), malaria infection, anaemia, severe malaria, hospital admissions, and death. Overall, 102 studies and 105 276 participants contributed to the systematic review. This included seven trials comparing IPTp-SP to placebo or passive case detection, 12 trials or cohorts following women who received IPTp-SP, and 83 observational studies. The studies covered all gravidae. All the included studies were conducted in sub-Saharan Africa, with more studies situated in Central and West Africa (59.3%) than in Eastern and Southern Africa (40.7%). Given that IPTp is an intervention that has proven to be effective, for ethical reasons, no new placebo-controlled trials have been conducted since the last update to the IPTp recommendation. This review therefore included a large number of observational studies.

Summary of judgements

The Evidence-to-Decision framework captures the evidence from the systematic review considered by the GDG. The GDG determined that the balance between desirable and undesirable effects favoured IPTp; negligible costs and savings were associated with IPTp implementation delivered through ANC contacts; the certainty of the evidence on required resources was moderate; and IPTp was probably cost-effective, probably acceptable to key stakeholders, and feasible to implement.

The GDG concluded that a strong recommendation should be made for IPTp based on its moderate beneficial effects, small undesirable effects, and moderate-certainty evidence.

Implementation

Please refer to the *WHO policy brief for the implementation of intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP) [100]* and the *WHO recommendations on antenatal care for a positive pregnancy experience [101]*. A manual for subnational tailoring of malaria interventions is under development and expected for publication in 2022.

Evaluation

The safety and impact of IPTp programmes should be routinely monitored. The effect of IPTp may be evaluated using routine data on hospital deliveries, clinic and/or community health worker data.

The WHO chemoprevention efficacy study (CPES) protocol should be used to monitor the efficacy of medicines used for chemoprevention. Although the potential effect of chemoprevention on the spread of drug resistance may be monitored by the analysis of molecular markers associated with treatment outcomes, the correlation between molecular markers and the efficacy of antimalarials for chemoprevention is unclear and results should be interpreted with caution. Given that SP continues to have positive outcomes for mother and baby even in areas of very high SP resistance, national malaria programmes may want to continue IPTp-SP programmes, despite worsening efficacy on malaria-specific outcomes.

Research Needs

Several evidence gaps were identified regarding IPTp. None should prevent adoption and implementation of IPTp. Nevertheless, impact could potentially be enhanced by determining:

- the effectiveness of alternative drug regimens for IPTp, including SP + diydroartemisinin-piperaquine (DHAP);
- the non-malarial effect of SP on pregnancy outcomes[2] ;
- the effectiveness of alternative approaches to IPTp delivery (e.g. community-based approaches) to improve uptake and address inequities in coverage compared to comparable investment in ANC services.

Data on the safety and effectiveness of alternatives to SP for IPTp will be reviewed by WHO when the relevant meta-analyses are available.

[2] Despite a near complete loss of its antimalarial effects in areas of very high SP resistance, SP continues to positively impact fetal growth and maternal anaemia. This may be mediated through a non-malarial pathway. This is consistent with the results of an individual patient data meta-analysis, including data from six trials comparing IPTp with DHAP vs IPTp with SP. These data showed that IPTp with DHAP was much more effective than SP in reducing malaria in areas of high SP resistance. However, this did not translate into better pregnancy outcomes, primarily because SP was associated with better fetal growth and thus higher mean birthweights in all gravidae. This may reflect the broad-spectrum antimicrobial properties of sulfadoxine, a long-acting sulfonamide, and the associated reduced risk of persistent bacterial infections, and/or its influence on the maternal gut microbiome, and/or its ability to reduce inflammation (Gutman *et al* *unpublished evidence (a)*).

4.2.2 Perennial malaria chemoprevention (PMC) - formerly intermittent preventive treatment of malaria in infants (IPTi)

Perennial malaria chemoprevention (PMC) is the administration of a full treatment course of an antimalarial medicine at predefined intervals, regardless of whether the child is infected with malaria, in order to prevent illness in moderate to high perennial malaria transmission settings. The goal of PMC is to protect young children by establishing preventive antimalarial drug concentrations in the blood that clear existing infections and prevent new ones during the age of greatest risk of severe malaria. Previously, this recommendation referred to intermittent preventive treatment in infants (IPTi). Since the initial recommendation, additional data have documented the value of malaria chemoprevention in children aged 12 to 24 months. The name has been changed to PMC because the updated recommendation no longer limits the intervention specifically to infants and reflects the malaria transmission settings in which the intervention should be considered.

Conditional recommendation for , Moderate certainty evidence

Perennial malaria chemoprevention (2022)

In areas of moderate to high perennial malaria transmission, children belonging to age groups at high risk of severe malaria can be given antimalarial medicines at predefined intervals to reduce disease burden.

- *Perennial malaria chemoprevention (PMC) schedules should be informed by the age pattern of severe malaria admissions, the duration of protection of the selected drug, and the feasibility and affordability of delivering each additional PMC course (see "Practical info").*
- *Sulfadoxine-pyrimethamine (SP) has been widely used for chemoprevention in Africa, including for PMC. Artemisinin-based combination therapies (ACTs) have been effective when used for PMC, but evidence is limited on their safety, efficacy, adherence to multi-day regimens, and cost-effectiveness in the context of PMC.*
- *Previously, PMC was recommended in infants (<12 months of age) as intermittent preventive treatment in infants (IPTi). Since the initial recommendation, new data have documented the value of malaria chemoprevention in children aged 12 to 24 months.*
- *The Expanded Programme on Immunization (EPI) platform remains important for delivering PMC. Other methods of delivery can be explored to optimize access to PMC and integration with other health interventions.*
- *Moderate to high perennial malaria transmission settings are defined as areas with P. falciparum parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000 [30]. These thresholds are indicative and should not be regarded as absolutes for determining applicability of the PMC recommendation.*

Practical Info

Antimalarial medicine

WHO recommends that medicines used for PMC be different from those used as first-line malaria treatment. SP has been widely used for chemoprevention in Africa and has been shown to be efficacious, safe, well tolerated, available and inexpensive. SP was evaluated in 10 trials for PMC, artesunate-amodiaquine (AS+AQ) in one trial, DHAP in one trial, and sulfadoxine-pyrimethamine + artesunate (SP+AS) in one trial *[106]*. All regimens were found to be effective in reducing clinical malaria. Although ACTs have been effective when used for PMC, evidence is limited on their safety (including potential cumulative toxicity), efficacy, adherence to multi-day regimens, and cost-effectiveness in the context of PMC in young children. A drug regimen that can be administered as a directly observed single dose, such as SP, is preferable to multi-day regimens.

Age group

The target age group should be identified using local data on the age distribution of malaria admissions and severe disease. Previously, PMC was recommended in infants (<12 months of age) as IPTi based on evidence generated in this age group and an appreciation of the disease burden they bear. Since the initial recommendation, additional data have documented the value of malaria chemoprevention in children aged 12 to 24 months. Three studies evaluated PMC doses in children aged 12 to 15 months *[107][108][109]*, and one study evaluated monthly doses in children up to 24 months *[110]*. Evidence from seasonal malaria chemoprevention (SMC) programmes, where the age of the target population overlaps with that of PMC, also shows that the impact of chemoprevention on disease burden can be sustained beyond infancy with additional doses. However, there is limited information on the safety and efficacy of malaria chemoprevention in children >15 months of age in perennial transmission settings.

Dosage

Children in age groups at increased risk of severe disease should be given a complete course of antimalarials, at their recommended treatment dose, as PMC. The drug dosage should be determined by the child's weight wherever possible, with dosing according to age only in situations where the child's weight is unknown.

Frequency

The PMC schedule should be informed by the length of protective efficacy of the selected drug, as well as the feasibility of delivering each additional PMC course. SP doses should be given at least one month apart. Eight trials have evaluated a range of 3–6 doses of SP for PMC in the first year of life. Four trials have evaluated 1–12 doses of SP for PMC in the second year of life. The safety and impact of PMC programmes should be routinely monitored.

Delivery

The EPI platform remains important for delivering PMC, especially in the first year of life, and it may be possible to make use of the EPI or other routine health visits, or establish new contacts to reach children over 1 year of age. Research on

alternative approaches for PMC delivery beyond the EPI schedules may be warranted. Consideration should be given to contextual factors such as values and preferences of end-users, costs, coverage and sustainability of alternative delivery platforms.

Drug resistance
The impact of drug resistance on the protection provided by PMC with SP is currently unclear. The duration of protection of SP has been shown to be 42 days in settings without parasite resistance mutations. This was reduced to 21 days in a setting where 89% of parasites carried the quintuple mutation *[111]*. In settings with a *Pfdhps*540 mutation frequency of up to 50%, 3–4 doses of PMC with SP reduced clinical malaria by 30% over the first year of life *[111]*. However, in the setting where the *Pfdhps*540 mutation frequency was 89%, no overall protective effect of PMC was observed *[111]*. The efficacy of SP for treatment is affected by the frequency of mutation-carrying parasites, but there is little evidence that the frequency of molecular markers predicts the efficacy of PMC.

Contraindications
PMC is not recommended for individuals receiving other forms of malaria chemoprevention (e.g. SMC or MDA). Although PMC and SMC could, in principle, be delivered to different age groups in the same geographical area, for example where there is perennial malaria transmission with seasonal peaks, there is no operational experience of the co-delivery of these strategies. There is currently no experience of co-administration of PMC with the RTS,S/AS01 malaria vaccine.

PMC is not recommended in children with severe acute illness or those who are unable to take oral medication, children who during the last 30 days received a dose of any of the drugs being used for PMC, or those allergic to any of the drugs being used for PMC. PMC with SP should not be given to individuals receiving a sulfa-based medication as treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole).

Other considerations
Information about PMC should be fully accessible to caregivers and key stakeholders, such as government officials and religious leaders. As with all health interventions, consent should be obtained from the caregiver on behalf of the child prior to administration of PMC.

Evidence To Decision

Benefits and harms

- **Clinical malaria**: PMC probably reduces the risk of clinical malaria compared to placebo or no PMC when using SP (rate ratio: 0.78; 95% CI: 0.69–0.88), AS-AQ (rate ratio: 0.75; 95% CI: 0.61–0.94), DHAP (rate ratio: 0.42; 95% CI: 0.33–0.54) (all moderate-certainty evidence), or SP+AS (rate ratio: 0.78; 95% CI: 0.62–0.97; high-certainty evidence).
- **Severe malaria**: PMC may reduce the risk of severe malaria compared to placebo or no PMC when using SP (rate ratio: 0.92; 95% CI: 0.47–1.81; low-certainty evidence), but may increase the risk of severe malaria when using DHAP (rate ratio: 1.29; 95% CI: 0.28–5.98; low-certainty evidence). There was no reported evidence on the effect of PMC with AS-AQ or SP+AS on severe malaria within the included studies.
- **Anaemia**: PMC probably reduces the risk of anaemia compared to placebo or no PMC when using SP (rate ratio: 0.82; 95% CI: 0.68–0.98), AS-AQ (rate ratio: 0.77; 95% CI: 0.53–1.12) or SP+AS (rate ratio: 0.72; 95% CI: 0.49–1.07) (all moderate-certainty evidence). No data were available on this outcome for DHAP in the meta-analysis.
- **All-cause hospital admissions**: PMC probably reduces hospital admissions compared to placebo or no PMC when using SP (rate ratio: 0.85; 95% CI: 0.78–0.93; moderate-certainty evidence) and probably has little effect when using AS-AQ (rate ratio: 0.98; 95% CI: 0.76–1.27; moderate-certainty evidence), SP+AS (rate ratio: 0.92; 95% CI: 0.71–1.20; moderate-certainty evidence) or DHAP (rate ratio: 1.58; 95% CI: 0.46–5.42; low-certainty evidence). Malaria-specific hospital admissions were not covered by the systematic review.
- **All-cause mortality**: PMC probably reduces the risk of death compared to placebo or no PMC when using SP (risk ratio: 0.93; 95% CI: 0.74–1.15; moderate-certainty evidence) or SP+AS (risk ratio: 0.83; 95% CI: 0.36–1.89; moderate-certainty evidence), and may reduce mortality when using DHAP (risk ratio: 0.33; 95% CI: 0.01–8.08; low-certainty evidence). Although available evidence suggests that AS-AQ probably increases the risk of death (risk ratio: 1.21; 95% CI: 0.58–2.55; moderate-certainty evidence), the actual effect varies, and it is possible that there is little or no difference.
- **Parasitaemia**: PMC probably reduces the risk of parasitaemia compared to placebo or no PMC when using SP (rate ratio: 0.66; 95% CI: 0.56–0.79; moderate-certainty evidence). No data were available on this outcome for AS-AQ, SP+AS or DHAP in the meta-analysis.

- **Adverse events**: In one study, the frequency of gastrointestinal symptoms was higher in children who received PMC with SP compared to placebo (risk ratio: 2.25; 95% CI: 1.51–3.35) *[107]*.
- **Potential drug–vaccine interactions and blood transfusions** were outcomes not covered by the systematic review. However, a study done in a subset of children enrolled in five randomized controlled trials in Ghana, Kenya, Mozambique and the United Republic of Tanzania found that PMC with SP did not affect the serological response to EPI vaccines *[110]*.

More information on the evidence can be found in the systematic review *[106]*.

Certainty of the Evidence

Moderate

The overall certainty of the evidence for the outcomes of interest was considered moderate by the GDG. Although the certainty of evidence, summarized under "Benefits and harms", ranged from low to high, the priority outcomes of clinical malaria and anaemia were assessed as moderate-certainty evidence, while severe malaria was considered low-certainty evidence.

More information on the certainty of evidence assessments can be found in the 'research evidence' tab associated with this recommendation online or in the annex of the pdf version.

Values and preferences

Preferences and values of the target population were determined by:

- consultation with civil society, which indicated that chemoprevention to prevent malaria disease in children under 5 years was seen as a priority in endemic areas (CS4ME *unpublished evidence*);
- a synthesis of contextual factors from trials and pilots of PMC, predominantly in sub-Saharan Africa, which showed that PMC is generally widely accepted by caregivers (Steinhardt *unpublished evidence (a)*).

The GDG determined that there was probably no important uncertainty or variability in how the outcomes of PMC are valued across contexts.

More information can be found in the summary of contextual factors report (Steinhardt *unpublished evidence (a)*) and civil society consultation report (CS4ME *unpublished evidence*).

Resources

PMC is generally considered cost-effective or highly cost-effective due to its use of the EPI delivery platform to deliver the inexpensive drug SP. The cost per dose delivered in nearly all studies was less than $0.25 for PMC with SP, but more expensive with alternative drugs. PMC becomes less cost-effective in settings with a lower malaria burden, as there is less potential to avert disease, and with the use of more expensive medicines. The GDG considered the overall costs of implementing PMC with SP in children to be moderate and judged that PMC is probably cost-effective compared to no intervention.

More information on the evidence can be found in the evidence profile associated with this recommendation.

Equity

Little information on equity of PMC is available. One study found no association between wealth quintile and coverage of PMC *[112]*.

The GDG considered that PMC probably increases health equity when delivered using the EPI platform, since access to

EPI is generally equitable and coverage tends to be high.

More information on the evidence can be found in the summary of contextual factors report (Steinhardt *unpublished evidence (a)*).

Acceptability

PMC has been widely accepted by caregivers, especially when delivered alongside vaccinations using the EPI platform. EPI has also been generally well accepted and perceived as beneficial. Despite some health workers not liking the process of administering PMC and some complaints that it increased workload, most had positive perceptions of PMC, with some suggesting that it improved EPI attendance.

The GDG considered that PMC was probably acceptable to key stakeholders.

More information on the evidence can be found in the summary of contextual factors report (Steinhardt *unpublished evidence (a)*).

Feasibility

Despite logistical challenges such as access to clean water, crushing the tablets, and occasional drug shortages, PMC implementation appears feasible when it is delivered through the EPI platform. One time-and-motion study in the United Republic of Tanzania found that the median time used for PMC implementation was 12.4 minutes (ranging from 1.6 minutes to 28.9 minutes) per nurse per vaccination session *[113]*.

The GDG considered PMC implementation to be feasible.

More information on the evidence can be found in the summary of contextual factors report (Steinhardt *unpublished evidence (a)*).

Justification

This recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *[103]*.

Sources of information

Recommendation development was informed by a systematic review *[106]*, independently evaluated using the AMSTAR-2 Checklist *[114]* (Steinhardt *et al unpublished evidence (b)*), and a report summarizing evidence from published studies on contextual factors related to PMC implementation (Steinhardt *unpublished evidence (a)*), including cost-effectiveness, feasibility, equity, values and acceptability. These sources of information were supplemented by a cross-cutting review on chemoprevention drug resistance (Plowe *unpublished evidence*), a civil society consultation report on chemoprevention (CS4ME *unpublished evidence*) and contributions from the GDG membership, which included former and current national malaria programme representatives.

The systematic review addressed the GDG's PICO (population, intervention, comparison, outcome) question regarding whether children living in settings with perennial malaria transmission should be given antimalarial medicines as chemoprevention to reduce disease burden. The main outcomes of interest were the impact of PMC on confirmed clinical malaria, severe malaria, and anaemia. Other outcomes of interest included: hospital admissions (all-cause and malaria-specific); all-cause mortality; adverse events; drug–vaccine interactions; parasite prevalence; and blood transfusions. Twelve trials were included in the review, three of which were cluster-randomized controlled trials. All the trials were conducted in sub-Saharan Africa: Gabon, Ghana, Kenya, Mali, Mozambique, Uganda, and the United Republic of Tanzania. SP was evaluated in 10 trials, amodiaquine in one trial, AS-AQ in one trial, DHAP in one trial, and SP+AS in one trial[1]. The systematic review included trials that compared PMC with no intervention in young children (aged eight weeks to 24 months), with length of follow-up ranging from nine to 36 months of age, and most studies delivering 3–4 doses of antimalarial. The AMSTAR-2 Checklist assessment concluded that the systematic review was well conducted and covered most of the outcomes identified by the GDG in the PICO question (Steinhardt *et al unpublished evidence (b)*). Three outcomes of interest to the GDG were not covered by the systematic review, namely malaria-specific hospital admissions, blood transfusions, and potential drug–vaccine interactions.

Summary of judgements

The Evidence-to-Decision table captures the evidence from the systematic review considered by the GDG. The GDG determined that the balance between desirable and undesirable effects favoured PMC; moderate costs were associated with PMC implementation delivered through EPI; PMC was considered probably cost-effective, but the use of alternative delivery strategies to EPI may affect the cost-effectiveness of PMC, as might the use of more expensive antimalarials; and PMC was probably acceptable to key stakeholders and feasible to implement. The GDG concluded that a conditional recommendation should be made for PMC based on its moderate beneficial effect and moderate certainty of evidence.

[1] Three trials evaluated more than one drug for PMC.

Implementation

Please refer to the *Intermittent preventive treatment for infants using sulfadoxine-pyrimethamine (IPTi-SP) for malaria control in Africa: implementation field guide [112].*

Evaluation

The effect of introducing PMC may be evaluated using routine hospital, clinic and/or community health worker data.

The WHO chemoprevention efficacy study (CPES) protocol should be used to monitor the efficacy of medicines when used for chemoprevention. Although the potential effect of chemoprevention on the spread of drug resistance may be monitored by the analysis of molecular markers associated with treatment outcomes, the correlation between molecular markers and the efficacy of antimalarials for chemoprevention is unclear and results should be interpreted with caution.

Research Needs

Several evidence gaps were identified regarding PMC. None should prevent adoption and implementation of PMC. Nevertheless, impact could potentially be enhanced by determining:

- the efficacy of PMC with SP, and alternative PMC regimens, within 28 days of administration;
- updated costs and cost-effectiveness of PMC delivered through the EPI, including in settings with low coverage of routine childhood immunization;
- the effectiveness of different SP dosing schedules for PMC in children aged eight weeks up to 24 months;
- the effect of administering PMC to children >24 months old;
- the safety, efficacy and cost-effectiveness of alternative combination drugs for PMC (e.g. sulfadoxine-pyrimethamine plus amodiaquine [SP+AQ]);
- the costs of and coverage achieved by alternative approaches to delivering PMC;
- the effectiveness of PMC in different antimalarial drug resistance contexts.

4.2.3 Seasonal malaria chemoprevention (SMC)

Seasonal malaria chemoprevention (SMC) is the intermittent administration of a curative dose of antimalarial medicine during the malaria season, regardless of whether the child is infected with malaria. The objective of SMC is to establish antimalarial drug concentrations in the blood that clear existing infections and prevent new ones during the period of greatest malaria risk. SMC is recommended in areas of seasonal malaria transmission.

Strong recommendation for , Moderate certainty evidence

Seasonal malaria chemoprevention (2022)

In areas of seasonal malaria transmission, children belonging to age groups at high risk of severe malaria should be given antimalarial medicines during peak malaria transmission seasons to reduce disease burden.

- *Eligibility for seasonal malaria chemoprevention (SMC) is defined by the seasonality of malaria transmission and age groups at risk of severe malaria. Thresholds for assessing these criteria change over time and location. Malaria programmes should assess the suitability of SMC based on the local malaria epidemiology and available funding (see "Practical info"). The added value of a seasonally targeted intervention is likely to be greatest where transmission is intensely seasonal.*
- *Monthly cycles of sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) have been widely used for SMC in African children under 5 years old and have been shown to be efficacious, safe, well tolerated, available and inexpensive (Thwing et al unpublished evidence).*

Practical Info

Antimalarial medicine

WHO recommends a combination medicine for SMC that is different from that used for first-line malaria treatment. The component medicines should have closely matched pharmacology, such that no component is present in the absence of other components for more than a minimal amount of time in order to reduce the risk of new infections encountering only a single drug. SP+AQ has been evaluated in 12 studies of SMC and has been widely used for SMC in Africa. SP+AQ has been shown to be efficacious, safe, well tolerated, available and inexpensive (Thwing *et al unpublished evidence*). The prevalence of molecular markers of resistance to SP+AQ was low in the general population before and two years after SMC implementation in seven countries in west and central Africa (Bhattarai *et al unpublished evidence*). Safety and efficacy have been evaluated for several other drug combinations, but the lack of widescale implementation means that fewer data are available on the potential risks of cumulative toxicity and impact on drug resistance.

Age group

Most research studies have evaluated SMC in children aged 3–59 months. SMC given to children <5 years old reduced the risk of clinical malaria by almost three quarters (risk ratio: 0.27; 95% CI: 0.25–0.29) during the transmission season (Thwing *et al unpublished evidence*). SMC has also been shown to reduce the incidence of clinical malaria in children <10 years old. Studies conducted in one country comparing the effect of SMC among children <5 years old with that in children 5–9 years old found no difference in the effect size for malaria incidence or prevalence, severe malaria, or anaemia (Thwing *et al unpublished evidence*). The age group targeted for SMC should be informed by the local age pattern of severe malaria admissions. The cost-effectiveness of SMC will become less favourable as programmes expand to age groups at lower risk of severe disease and areas of lower malaria transmission *[116]*.

Dosage

Children in age groups at increased risk of severe disease should be given a complete course of antimalarials, at their recommended treatment dose, as SMC. The drug dosage should be determined by the child's weight wherever possible, with dosing according to age only in situations where the child's weight is unknown.

Frequency

The number of cycles should be informed by the duration of the high-transmission season, based on the local malaria epidemiology, and the length of preventive efficacy of the selected drug combination. SMC should be used to protect children during the entire high-transmission season. Current evidence supports monthly administration of SMC for 3–4 cycles in shorter transmission settings, and up to six cycles have been evaluated in settings with longer transmission seasons (Thwing *et al unpublished evidence*).

Delivery

SMC can be provided through door-to-door or fixed-point delivery. A study in Mali found that door-to-door delivery achieved significantly higher coverage than fixed-point delivery (76.1% versus 62.2%, p = 0.0028) *[117]*. Further studies in Mali and Gambia have supported that door-to-door delivery can achieve high coverage *[118][119]*. Studies found similar SMC coverage in children given directly observed treatment compared to non-directly observed treatment *[117][118]*.

Drug resistance

While some prospective trials and ecological studies of SMC with SP+AQ in West Africa have reported increased prevalence of the *dhfr/dhps* quadruple and quintuple mutants, other studies have found no evidence of selection. No evidence has been reported of SMC being followed by increased prevalence of the higher level resistance mutations that most severely impair curative SP efficacy, nor does SMC appear to select for parasites carrying mutations associated with diminished AQ susceptibility (Plowe *unpublished evidence*).

Contraindications

SMC is not recommended for individuals receiving other forms of malaria chemoprevention (e.g. MDA or PMC). Although PMC and SMC could, in principle, be delivered to different age groups in the same geographical area (e.g. where there is perennial malaria transmission with seasonal peaks), there is no operational experience of the co-delivery of these strategies.

SMC is not recommended for children with severe acute illness or those who are unable to take oral medication, children who during the last 30 days received a dose of any of the drugs being used for SMC, or children with an allergy to any of the drugs being used for SMC. Children should not be given SMC including SP if they are receiving a sulfa-based medication as treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole).

Other considerations

Information about SMC should be fully accessible to caregivers and key stakeholders, such as government officials and

religious leaders. As with all health interventions, consent should be obtained from the caregiver on behalf of the child prior to administration of SMC.

Evidence To Decision

Benefits and harms

- **Clinical malaria**: SMC probably reduces the incidence of confirmed clinical malaria in children (<5 years old: rate ratio: 0.27; 95% CI: 0.25–0.29; moderate-certainty evidence; 5–15 years: rate ratio: 0.27; 95% CI: 0.25–0.30; low-certainty evidence). The effect size was similar when compared according to the number of cycles (3–6 cycles), transmission setting (moderate vs high intensity), or drug regimen used (SP+AQ, AS-AQ or SP+AS). Studies conducted in one country showed no difference in effect size against clinical malaria incidence between children <5 years and those 5–9 years. However, the absolute impact in older age groups will vary according to the age pattern of disease in different settings.
- **Parasite prevalence**: SMC probably reduces the prevalence of malaria infection at the end of the transmission season in children under 5 years old (risk ratio: 0.38; 95% CI: 0.34–0.43; moderate-certainty evidence) and reduces the prevalence of malaria infection at the end of the transmission season in children <10 years old (risk ratio: 0.28; 95% CI: 0.17–0.44; high-certainty evidence). The effect was similar when compared according to the number of cycles (3–6 cycles), transmission setting (moderate vs high), or drug regimen (SP+AQ, AS-AQ or SP+AS).
- **Severe malaria**: 3–4 cycles of SP+AQ as SMC reduces the incidence of severe malaria in children <5 years old (rate ratio: 0.57; 95% CI: 0.37–0.89; high-certainty evidence) and probably reduces severe malaria incidence in children 5–9 years old (rate ratio: 0.44; 95% CI: 0.23–0.84; moderate-certainty evidence).
- **Anaemia**: SMC probably reduces the prevalence of any anaemia (haemoglobin <11 mg/dL) at the end of the transmission season in children <5 years old (risk ratio: 0.84; 95% CI: 0.80–0.88; moderate-certainty evidence). SMC reduces the prevalence of any anaemia (haemoglobin <11 mg/dL) at the end of the transmission season in children 5–9 years old (risk ratio: 0.70; 95% CI: 0.52–0.95; high-certainty evidence).
- **Hospital admissions**: SMC probably reduces the incidence of all-cause hospitalization in children <5 years in high-transmission areas (SP+AQ, high-transmission, 3–4 cycles: rate ratio: 0.54; 95% CI: 0.31–0.94; high-certainty evidence; AS-AQ, 5–6 cycles: rate ratio: 0.42; 95% CI: 0.20–0.87; high-certainty evidence; SP+AQ, 3–4 cycles: rate ratio: 1.38; 95% CI: 0.71–2.67; moderate-certainty evidence).
- **All-cause mortality**: There is little evidence of effect of SMC on all-cause mortality in the community (low-certainty evidence). See notes for further information.
- **Adverse events**: SMC increases mild to moderate adverse events in children up to 15 years (risk ratio: 1.40; 95% CI: 1.31–1.51; high-certainty evidence). The most frequent features reported in children receiving SMC (with SP+AQ or SP+AS) were nausea, vomiting, and abdominal pain.
- **Incidence of infection, blood transfusions, and school attendance** were not reported in any of the eligible studies.

More information can be found in the systematic review (Thwing *et al* *unpublished evidence*).

Notes

Results from non-randomized studies were consistent with those from randomized studies across all reported outcomes (incidence of confirmed clinical malaria; prevalence of infection at end of transmission season; prevalence of moderate anaemia; incidence of severe malaria; hospitalization; and all-cause mortality, all for children <5 years), except for prevalence of moderate anaemia, where no effect was observed. Adverse events were not reported.

There was little evidence of an effect on all-cause mortality. It is plausible that a reduction in severe malaria could translate into an impact on mortality. This was observed in one of the studies that was excluded from the systematic review as it did not use a controlled design *[120]*. However, the evidence is hard to ascertain due to potential risk of bias from the study designs (trials with clinical malaria as the main outcome are likely to minimize mortality) and systems for reporting deaths in the studies. Implementation of SMC was associated with reductions in malaria deaths in hospitals by 42.4% (95% CI: 5.9–40.9) in Burkina Faso and by 56.6% (95% CI: 28.9–73.5) in Gambia *[120]*.

Certainty of the Evidence

Moderate

The overall certainty of the evidence for the outcomes of interest was considered to be moderate. The certainty of evidence, as summarized under “Benefits and harms”, ranged from low to high. The priority outcome of confirmed clinical malaria was assessed as moderate-certainty evidence.

More information on the certainty of evidence assessments can be found in the ‘research evidence’ tab associated with this recommendation online or in the annex of the pdf version.

Values and preferences

Preferences and values of the target population were determined by:

- consultation with civil society, which indicated that chemoprevention to prevent malaria disease in children under 5 years was seen as a priority in endemic areas (CS4ME *unpublished evidence*);
- a synthesis of contextual factors from trials and pilots of SMC (Bhattarai *et al* *unpublished evidence*), but no research was identified that described values and preferences related to SMC.

The GDG determined that there was probably no important uncertainty or variability in how the main outcomes of SMC are valued.

More information can be found in the summary of contextual factors report (Bhattarai *et al* *unpublished evidence*) and the civil society consultation report (CS4ME *unpublished evidence*).

Resources

The GDG considered the overall costs of implementing SMC to be moderate. Important cost drivers of SMC are the drug used and the mode of delivery (e.g. door-to-door vs fixed-point). SMC is considered a cost-effective addition to standard care, with the estimated average total economic cost per malaria case averted ranging from US$ 2.91 to US $67.77, depending, in part, on the choice of drug (Bhattarai *et al* *unpublished evidence*). Expanding SMC to children in age groups beyond those at highest risk of severe disease, areas of lower malaria transmission, and the use of more expensive antimalarials will likely influence the cost-effectiveness of SMC.

More information can be found in the summary of contextual factors report for SMC (Bhattarai *et al* *unpublished evidence*).

Equity

The GDG considered that SMC is likely to enhance equitable service delivery based on similar coverage of the intervention across wealth quintiles in all countries where it is being implemented (Bhattarai *et al* *unpublished evidence*). There was generally no significant difference in SMC coverage by age or gender.

More information can be found in the summary of contextual factors report for SMC (Bhattarai *et al* *unpublished evidence*).

Acceptability

SMC acceptability was generally high, with overall refusal rates <1% in five countries (Bhattarai *et al* *unpublished evidence*). Consequently, the GDG considered SMC to be acceptable to key stakeholders.

More information can be found in the summary of contextual factors report for SMC (Bhattarai *et al* *unpublished evidence*).

Feasibility

SMC delivery approaches and coverage vary across countries. For example, in Mali, SMC coverage was significantly higher in children who received SMC using door-to-door delivery compared to fixed-point delivery (76.1% versus 62.2%, p = 0.0028), while in Gambia, SMC delivery through village health workers achieved a substantially higher coverage level than delivery by reproductive and child health teams (74% versus 48%, a difference of 27%; 95% CI: 16%–38%) *[117]*. Overall, the GDG considered SMC implementation to be feasible.

More information can be found in the summary of contextual factors report for SMC (Bhattarai *et al* *unpublished evidence*).

Justification

This recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *[103]*.

Sources of information

WHO commissioned a systematic review to inform this guidance on SMC (Thwing *et al unpublished evidence)*, and a separate report summarizing evidence from published studies on contextual factors related to SMC implementation (Bhattarai *et al unpublished evidence)*, including cost-effectiveness, feasibility, equity, values and acceptability. These sources of information were supplemented by a cross-cutting review on chemoprevention drug resistance (Plowe *unpublished evidence)*, a civil society consultation report on chemoprevention (CS4ME *unpublished evidence)* and contributions from the GDG membership, which included former and current national malaria programme representatives.

The objectives of the systematic review were to assess the effect of SMC with antimalarial drugs on malaria disease burden among children living in places with seasonal malaria transmission, with a specific focus on the age of the children (3–59 months vs 60–120 months of age), the number of treatment cycles during a season (3–4 cycles vs 5–6 cycles), and the drug regimen; and to summarize contextual information regarding acceptability, feasibility, equity, safety, drug resistance, cost and cost-effectiveness. The primary outcome of interest was incidence of confirmed clinical malaria. Other outcomes included: parasite prevalence; incidence of infection; anaemia prevalence; blood transfusions; hospital admissions; severe malaria; all-cause mortality; adverse reactions; and school attendance. Seventeen studies met the criteria for inclusion (12 randomized and five non-randomized studies) and were included in the review. All studies were conducted in sub-Saharan Africa, including in Burkina Faso, Gambia, Ghana, Mali, Niger, Nigeria and Senegal. Twelve studies used SP+AQ, three studies used AS-AQ, one study used SP+AS, and one study used AL. Trials administering three to four cycles were usually located in the sites with shorter transmission seasons, whereas studies administering five to six cycles were in areas with longer transmission seasons. None of the included studies reported incidence of infection or blood transfusions as outcome measures. One study reported education outcomes but not school attendance.

Summary of judgements

Evidence from the systematic review (Thwing *et al unpublished evidence)* and supporting information (Bhattarai *et al unpublished evidence*; CS4ME *unpublished evidence*; Plowe *unpublished evidence)* was appraised by the GDG in October 2021, a summary of which is provided in the Evidence-to-Decision table. The GDG determined that SMC has a large beneficial effect and that the balance of desirable and undesirable effects favours SMC; the costs of implementing SMC are moderate, although the overall cost would be affected by the drug used and the mode of SMC delivery; SMC is cost-effective, but expanding SMC to age groups beyond those at highest risk of severe disease or areas of lower malaria transmission, and the use of more expensive antimalarials could reduce its cost-effectiveness; SMC is an acceptable intervention; SMC delivery approaches and coverage varied across countries, but were judged to be feasible. In sum, the GDG judged the overall certainty of the evidence as moderate and strongly recommended SMC for age groups at high risk of severe malaria living in areas of seasonal malaria transmission to reduce disease burden.

Implementation

Please refer to the *Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: A field guide [117]*.

Evaluation

The effect of introducing SMC may be evaluated using routine hospital, clinic and/or community health worker data.

The WHO chemoprevention efficacy study (CPES) protocol should be used to monitor the efficacy of medicines when used for chemoprevention. Although the potential effect of chemoprevention on the spread of drug resistance may be monitored by the analysis of molecular markers associated with treatment outcomes, the correlation between molecular markers and the efficacy of antimalarials for chemoprevention is unclear and results should be interpreted with caution.

Research Needs

The GDG highlighted the following evidence gaps requiring further research. These relate to:

- the operational effectiveness of SMC;
- the value of administering SMC to children ≥10 years old;
- the effectiveness of SMC in areas with seasonal but >6 months of malaria transmission;
- the effectiveness of SMC in areas with antimalarial drug resistance;
- better understanding of the pharmacokinetics of drugs used for chemoprevention and concentrations required to prevent parasite growth (as opposed to therapeutic concentrations);
- the efficacy and effectiveness of delivering SMC with other drug combinations and intervals between cycles.

4.2.4 Intermittent preventive treatment of malaria in school-aged children (IPTsc)

Intermittent preventive treatment in school-aged children (IPTsc) is the administration of a full treatment course of an antimalarial medicine at regular intervals to treat and prevent malaria infections in children who are old enough to attend school.

Conditional recommendation for , Low certainty evidence

Intermittent preventive treatment of malaria in school-aged children (2022)

School-aged children living in malaria-endemic settings with moderate to high perennial or seasonal transmission can be given a full therapeutic course of antimalarial medicine at predetermined times as chemoprevention to reduce disease burden.

- *Intermittent preventive treatment in school-aged children (IPTsc) has been evaluated in children aged 5–15 years. The burden of malaria and benefits of IPTsc may vary across this age range, but evidence is limited.*
- *National malaria programmes can consider IPTsc if resources allow for its introduction among school-aged children without compromising chemoprevention interventions for those carrying the highest burden of severe disease, such as children < 5 years old.*
- *Schools may provide a low-cost means to deliver chemoprevention to school-aged children. However seasonal variation in malaria transmission and the timing of school terms, as well as equity concerns, may mean alternative delivery channels are needed to maximize impact.*
- *First- and second-line malaria treatments should not be used for IPTsc if safe and effective alternatives are available (see "Practical info").*
- *The dosing schedule for IPTsc should be informed by the local malaria epidemiology and timed to give protection during the period of greatest malaria risk (see "Practical info").*
- *Moderate to high malaria transmission settings are defined as areas with P. falciparum parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000 [30]. These thresholds are indicative and should not be regarded as absolutes for determining applicability of the IPTsc recommendation.*

Practical Info

Antimalarial medicine

Drug regimens evaluated for IPTsc and found to be effective include SP combined with an aminoquinoline (either AQ or piperaquine), SP+AS, and artemisinin-based combination therapy including an aminoquinoline (AS-AQ or DHAP)[1]. SP+AQ has been widely used for chemoprevention in West Africa and has been shown to be efficacious, safe, well tolerated, available and inexpensive. In order to reduce the risk of drug resistance to life-saving drugs, first- and second-line malaria treatments should not be used for IPTsc if safe and effective alternatives are available.

The possibility of interactions with other drugs delivered as part of school health programmes should be considered.

Age group

The target age group should be identified using local data on the age distribution of malaria admissions and severe disease. As young children (≤ 59 months) are the most vulnerable to severe malaria, chemoprevention interventions to protect this age group should be prioritized over those for school-aged children. If resources allow for introduction of chemoprevention for school-aged children without compromising chemoprevention in younger children, national malaria programmes can consider IPTsc.

The majority of IPTsc studies have evaluated the intervention in children under 15 years old. There is some evidence of a stronger effect on malaria-related anaemia in children younger than 10 years versus those who are 10–15 years. However, the effect of IPTsc on *P. falciparum* infection was similar across these two age groups.

If older age groups are included in IPTsc, particular consideration should be given on how best to include girls with a history of menarche. Certain antimalarials should not be given for chemoprevention without first confirming pregnancy status. There is insufficient information on the safety, efficacy and pharmacokinetics of most antimalarial agents in pregnancy, particularly during the first trimester. In IPTsc studies that have included girls with a history of menarche, pregnancy status has been determined either through self-reporting or the use of pregnancy tests. Further research is needed on how best to safely include girls of reproductive age in IPTsc.

Dosage

School-aged children should be given a complete course of antimalarials at their recommended treatment dose as IPTsc. The drug dosage should be determined by the child's weight wherever possible, with dosing according to age only in situations where the child's weight is unknown or cannot be determined.

Frequency
The IPTsc schedule should be informed by the local malaria epidemiology, particularly transmission intensity and seasonality, the pharmacokinetics of the drug used, and the feasibility of delivering each additional IPTsc course. IPTsc should be timed to give protection during the period of greatest malaria risk. Most trials provided IPTsc monthly or each term. In settings where PMC is being provided, IPTsc may need to be given at regular intervals throughout the year. In perennial transmission settings, the higher the transmission intensity, the greater the expected value of drugs with longer half-lives or more frequent dosing, which will increase the proportion of time-at-risk protected by IPTsc. If IPTsc cannot be maintained throughout the year in perennial transmission settings due to resource constraints, IPTsc may be timed to provide protection during transmission peaks.

Delivery
IPTsc can be delivered either through schools or through community-based approaches. The method of delivery should consider the local epidemiology of malaria and whether school-based delivery will offer protection during the period of greatest malaria risk. All types of schools that cater to children aged up to 15 years in the target area should be included for IPTsc delivery. National malaria programmes may be able to work with existing health programmes targeting school-aged children to facilitate delivery of IPTsc. Children not attending school are likely to be at highest risk of malaria and, if school attendance is not high, special efforts may be needed to target children not attending school. In seasonal transmission areas, delivery in schools may not align with peak malaria transmission and thus it may be more appropriate to utilize existing community-based approaches to reach school-aged children, such as those strategies used for SMC. Care is needed to ensure adequate communication with communities, teachers, caregivers and children to maximize understanding and acceptability in these key stakeholder groups. If older age groups are included in IPTsc administration, communication with key stakeholders should pay attention to the inclusion of girls of reproductive age (see 'Age group' above).

Drug resistance
The impact of drug resistance on the protection provided by IPTsc is currently unclear. A re-analysis of data on resistance markers following monthly IPTsc found no suggestion of an increased prevalence of any resistance markers following DHAP administration[2] (Plowe *unpublished evidence*).

A review of the relationship between the different chemoprevention strategies (IPTp, PMC, SMC, MDA, IPTsc) and drug resistance concluded that malaria chemoprevention as used to date does not inevitably lead to an increase in resistance, and even high rates of resistance may not necessarily impair chemoprevention efficacy (Plowe *unpublished evidence*). However, expanded use of antimalarial medicines may increase resistance and eventually undermine efficacy. Using different drugs for chemoprevention and treatment, and combining drugs with counteracting resistance mechanisms may help to preserve efficacy (Plowe *unpublished evidence*).

Contraindications
IPTsc is not recommended for individuals receiving other forms of malaria chemoprevention (e.g. SMC or MDA). Children with sickle cell disease should be included in IPTsc unless they already receive regular chemoprevention due to sickle cell disease. Co-delivery of IPTsc alongside other school health programmes should consider drug manufacturers' guidance regarding whether IPTsc can be safely given with other medicines and whether there are any additional contraindications as a result. Additionally, there is a need to consider how to include girls of reproductive age who should not be given certain antimalarials for prophylaxis without first confirming that they are not pregnant (see "Age group' above for further information).

IPTsc is not recommended in children with severe acute illness, those unable to take oral medication, children who during the last 30 days received a dose of any drug being used for IPTsc, or those allergic to any of the drugs being used for IPTsc. IPTsc-SP should not be given to individuals receiving a sulfa-based medication as treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole) for HIV.

Other considerations
Information about IPTsc should be fully accessible to school-aged children, their caregivers and key stakeholders, such as teachers. As with all health interventions, consent should be obtained from the caregiver on behalf of the child prior to administration of IPTsc and, depending on age, from the child themselves.

[1] Relative risk for *P. falciparum* infection: SP plus aminoquinoline (0.35; 95% CI: 0.25–0.44); SP+AS (0.04; 95% CI: 0.01–0.07); artemisinin derivative with aminoquinoline (0.18; 95% CI: 0.11–0.24).

[2] The original analysis limited resistance outcomes to the prevalence of pure mutant alleles for each locus of interest among all samples that were positive for *P. falciparum* parasitaemia, irrespective of disease. The re-analysis was conducted to compare the proportion of infections containing any resistant parasites, not just pure mutant alleles, based on the principle that any presence of resistance signals the risk of treatment failure.

Evidence To Decision

Benefits and harms

- **Clinical malaria**: IPTsc may reduce clinical malaria during follow-up (ranging from six to 103 weeks) (adjusted relative risk[1]: 0.5; 95% CI: 0.36–0.60; low-certainty evidence).
- **Anaemia**: IPTsc may reduce anaemia (adjusted relative risk*: 0.85; 95% CI: 0.77–0.92; low-certainty evidence).
- **Parasite prevalence**: IPTsc may reduce *P. falciparum* parasite prevalence (adjusted relative risk[2]: 0.46; 95% CI: 0.40–0.53; low-certainty evidence).
- **Adverse events**: Eleven studies reported adverse events. No deaths were attributed to study drugs. Three studies reported more adverse events in the intervention group *[122][123][124]*. The most common adverse events were dizziness, nausea and vomiting shortly after treatment. One (IPTsc with SP+AQ in 6758 students) of the three studies *[122]* reported 23 serious adverse events (SAEs) – 19 in the IPTsc arm, of which three were judged to be drug-related. The most common serious adverse events were problems with balance, dizziness, feeling faint, nausea or vomiting. Another study with 794 participants reported no SAEs *[123]*, but adverse events included headache, cough, abdominal pain, coryza, skin rash, nausea, vomiting and diarrhoea. SP+AQ was associated with more adverse events and more vomiting in the first three days compared to placebo. There were no differences in cumulative adverse events between arms by day 42. Among 404 children who received IPTsc with either SP or SP + piperaquine compared to control *[124]*, no deaths or SAEs were reported. There was no difference in the proportion of children with adverse events, comparing SP to control; however, there were more children with dizziness in the SP + piperaquine arm compared to control.

None of the studies that met the inclusion criteria for the review systematically collected data on **school attendance, severe malaria, hospital admissions** (all-cause and malaria-specific), or **mortality** (all-cause and malaria-specific)[2].

More information on the evidence can be found in the systematic review *[125]*.

[1] Adjusted for age, sex and transmission intensity.

[2] School achievement was not ranked by the GDG as a critical outcome and therefore was not considered. However, the systematic review found a marginal effect of IPTsc on cognitive function in children 10–15 years (adjusted mean difference in standardized test scores: 0.36; 95% CI: 0.01–0.71; p-value for interaction = 0.004), but no significant effect was identified when data were combined across all ages (adjusted relative risk*: 0.12; 95% CI: -0.20–0.43; p = 0.4564).

Certainty of the Evidence

Low

The evidence for all the critical outcomes was of low certainty because of serious risk of bias and inconsistency between the studies included in the review. Therefore, the GDG considered the overall certainty of the evidence for the outcomes of interest to be low.

More information on the certainty of evidence assessments can be found in the ‘research evidence’ tab associated with this recommendation online or in the annex of the pdf version.

Values and preferences

Preferences and values of the target population were determined by:

- consultation with civil society, which indicated that chemoprevention to prevent malaria disease in children was

seen as important in endemic areas – although children under 5 years old were mentioned as the particular priority (CS4ME *unpublished evidence*);
- a synthesis of contextual factors from trials and pilots of IPTsc in sub-Saharan Africa, which found very little data on values and preferences (Gutman *et al unpublished evidence (b)*). In one study, parents considered chemoprevention to be useful and recommended that chemoprevention be expanded to include older children and even adults *[126]*.

The GDG determined that there was probably no important uncertainty or variability in how the outcomes of IPTsc are valued across contexts.

More information can be found in the summary of contextual factors report (Gutman *et al unpublished evidence (b)*) and the civil society consultation report (CS4ME *unpublished evidence*).

Resources

There are relatively few data on the cost of IPTsc. Key cost drivers were human resources (the provision of training to teachers) and the drug used, with intervention costs varying substantially based on the selected regimen. In Mali, the cost of delivering one course of SP+AS was US$ 2.72 per child, which decreased to US$ 1.00 per child for SP+AQ *[127]*. Modelling of IPTsc costs in Kenya estimated the intervention cost to be US$ 1.88 per child treated per year, with US$ 0.25 per child in set-up costs and US$ 1.63 per child in recurrent costs.

The modelled cost-effectiveness of IPTsc in Kenya was US$ 5.36 per *P. falciparum* infection averted and US$ 29.84 per case of anaemia averted *[128]*. The largest drivers of cost-effectiveness were the effectiveness of the intervention and the prevalence of anaemia.

The GDG determined that the resources required to implement IPTsc varied, and the certainty of the evidence on the resources required was low. The GDG concluded that IPTsc is probably a cost-effective intervention, and if existing health interventions are being delivered through schools, integrating IPTsc could yield some cost savings. The overall effectiveness of IPTsc is likely to be influenced by the local malaria epidemiology and age burden of disease: if school children are at high risk during the school term, then the cost-effectiveness of IPTsc is likely to increase.

More information on the evidence can be found in the summary of contextual factors report (Gutman *et al unpublished evidence (b)*).

Equity

There is very limited data on how a school-based platform for delivery of malaria chemoprevention to children would affect equity and health equality.

The GDG considered the equity of IPTsc to vary, depending on the proportion of children attending school. As those absent from school are more likely to be from lower socioeconomic groups and female, delivering IPTsc solely through schools may affect the equity of the strategy. There is some evidence that the effect of IPTsc on school performance may differ between girls and boys *[129]*.

More information on the evidence can be found in the summary of contextual factors report (Gutman *et al unpublished evidence (b)*).

Acceptability

Few studies directly assessed the acceptability of IPTsc. Community sensitization was identified as important for improving the acceptability of IPTsc. In one study, 93% of children reported that they would be willing or very willing to take the tablets for IPTsc each school term *[123]*. Another study, which evaluated IPTsc among other interventions (iron fortification and anthelmintics), delivered two rounds of IPTsc-SP three months apart. Only one person (0.15%) approached for enrolment refused to participate, and there was high compliance (93.7%) among those who participated, suggesting that treatment was acceptable *[130]*. In a study that added malaria treatment to an existing school-based

MDA programme, 87% of children received IPTsc, suggesting that it might be acceptable to combine the intervention with ongoing health programmes *[131]*. In another study, staff noted issues with acceptance from parents, particularly when there were side effects from the drugs. Consequently, parents would refuse the second and third days of treatment, and acceptance was lower with subsequent rounds *[126]*.

The GDG considered IPTsc to probably be acceptable to key stakeholders.

More information on the evidence can be found in the summary of contextual factors report (Gutman *et al* *unpublished evidence* *(b)*).

Feasibility

The feasibility of IPTsc is influenced by the choice of drug regimen. One study suggested that using a simpler antimalarial regimen would enhance compliance, as single-dose regimens could be administered as DOT. Additionally, feasibility may be adversely impacted in girls of reproductive age, given the need to confirm that they are not pregnant before giving certain antimalarials as IPTsc *[132]*. Poor uptake of IPTsc in one study was attributed to poor community perceptions about IPTsc and the requirement for parental informed consent *[132]*. School-based delivery is likely to be more feasible than community-based delivery of IPTsc, but enrolment rates and absenteeism could pose barriers to reaching children through schools *[132]*. In some countries, schools already provide nutrition services and are sites of targeted insecticide-treated net (ITN) distribution and deworming programmes (Gutman *et al* *unpublished evidence* *(b)*).

The GDG considered IPTsc implementation to probably be feasible.

More information on the evidence can be found in the summary of contextual factors report (Gutman *et al* *unpublished evidence* *(b)*).

Justification

This recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *[103]*.

Sources of information

Recommendation development was informed by a systematic review *[125]*, independently evaluated using the AMSTAR-2 Checklist (Gutman *et al* *unpublished evidence* *(c)*)*[114]*, and a report summarizing evidence from published studies on contextual factors related to IPTsc implementation (Gutman *et al* *unpublished evidence* *(b)*), including cost-effectiveness, feasibility, equity, values and acceptability. These sources of information were supplemented by a cross-cutting review on chemoprevention and drug resistance (Plowe *unpublished evidence*), a civil society consultation report on chemoprevention (CS4ME *unpublished evidence*) and contributions from the GDG membership, which included former and current national malaria programme representatives.

The systematic review addressed the GDG's PICO (population, intervention, comparison, outcome) question regarding whether school-aged children living in settings with malaria transmission should be given antimalarial medicines as chemoprevention to reduce disease burden. The main outcome of interest was the impact of IPTsc on confirmed clinical malaria. Other outcomes of interest included anaemia, school attendance, parasite prevalence, severe malaria, hospital admissions (all-cause and malaria-specific), adverse events, and mortality (all-cause and malaria-specific). Thirteen randomized trials were included in the review, 11 of which contributed data to an individual participant data meta-analysis. All the trials were conducted in sub-Saharan Africa: Côte d'Ivoire, Democratic Republic of the Congo, Ghana, Kenya, Mali, Senegal and Uganda. Drug regimens evaluated in the individual studies included DHAP in three trials, SP in three trials, SP+AQ in three trials, SP+AS in two trials, SP with piperaquine in one trial, AL in two trials, AS+AQ in two trials, doxycycline in one trial, primaquine in one trial, mefloquine plus multivitamin in one trial, and proguanil plus chloroquine in one trial. The systematic review grouped the treatment regimens by drug class and pharmacokinetic features: SP alone, SP combined with an aminoquinoline (either AQ or piperaquine), SP+AS, artemisinin-based combination therapy including an aminoquinoline (AS+AQ or DHAP), and AL. Treatment intervals ranged from daily (with subtherapeutic doses of primaquine and doxycycline) to every four months, with the majority of studies providing IPTsc monthly or each term (i.e. 3-4 month intervals). The systematic review included trials that studied IPTsc in children aged 5 to 15 years old, with the follow-up period ranging from six to 103 weeks and most studies delivering 1–12 courses of antimalarial treatment. The authors of the review estimated the proportion of the follow-up period protected by treatment for each of the individual studies, and this ranged from 2% to 100%. The AMSTAR-2 Checklist assessment concluded that the systematic review was of sufficient quality, and

the inclusion of one new study identified since the systematic review was published did not substantially change the conclusions (Gutman *et al unpublished evidence (c)*). Four outcomes of interest to the GDG were not covered by the systematic review, namely school attendance, severe malaria, hospital admissions (all-cause and malaria-specific) and mortality (all-cause and malaria-specific).

Summary of judgements

The Evidence-to-Decision framework captures the evidence from the systematic review considered by the GDG. The GDG considered the balance between desirable and undesirable effects to probably favour IPTsc; costs associated with IPTsc implementation to vary; and the certainty of the evidence on resources required to be low. In addition, IPTsc was considered probably cost-effective; the equity of IPTsc was judged to vary, depending on the proportion of children attending school; and IPTsc was judged as probably acceptable to key stakeholders and probably feasible to implement. The GDG concluded that a conditional recommendation should be made for IPTsc for school-aged children in moderate to high burden malaria transmission settings given IPTsc's moderate beneficial effects and small undesirable effects.

Implementation

A guide to support implementation of IPTsc will be developed in due course, and a manual for subnational tailoring of malaria interventions is under development and expected for publication in 2022.

Evaluation

The safety and impact of IPTsc programmes should be routinely monitored. The effect of introducing IPTsc may be evaluated using routine hospital, clinic and/or community health worker data. School surveys provide an opportunity to evaluate outcomes related to school attendance and achievement.

The WHO chemoprevention efficacy study (CPES) protocol should be used to monitor the efficacy of medicines used for chemoprevention. Although the potential effect of chemoprevention on the spread of drug resistance may be monitored by the analysis of molecular markers associated with treatment outcomes, the correlation between molecular markers and the efficacy of antimalarials for chemoprevention is unclear and results should be interpreted with caution.

Research Needs

The GDG highlighted the following evidence gaps requiring further research. These relate to:

- the efficacy of alternative (e.g. monthly versus each term) IPTsc drug regimens at different transmission intensities;
- the value of IPTsc in children 10 years and under compared to the value in children over 10 years old;
- the full economic and financial costs (including the cost of engaging communities, parents, school teachers, etc.) of introduction and deployment of IPTsc;
- the cost-effectiveness of combining IPTsc with other school health programmes;
- the costs and feasibility of alternative strategies to deliver malaria chemoprevention to school-aged children;
- the development of drugs suitable for use as chemoprevention in school-aged children;
- the effect of IPTsc on community-level transmission;
- the impact of IPTsc on cognition and school performance;
- the development of drugs for malaria chemoprevention that can be administered as a single dose;
- evaluating approaches to safely include girls of reproductive age in IPTsc, including exploring alternative regimens that are safe through pregnancy.

4.2.5 Post-discharge malaria chemoprevention (PDMC)

Post-discharge malaria chemoprevention (PDMC) is the administration of a full antimalarial treatment course at regular intervals to children admitted with severe anaemia. The purpose of PDMC is to prevent new malaria infections in children admitted with severe anaemia during the period after hospital discharge when they are at high risk of re-admission or death. Severe anaemia is defined by WHO's *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity [133]*. The aetiology of severe anaemia is multifactorial and it is often difficult to identify the main cause of any episode of severe anaemia without further laboratory tests, including a complete blood cell count. PDMC should be given even when the cause(s) of severe anaemia in an individual cannot be identified.

Conditional recommendation for , Moderate certainty evidence

Post-discharge malaria chemoprevention (2022)

Children admitted to hospital with severe anaemia living in settings with moderate to high malaria transmission can be given a full therapeutic course of an antimalarial medicine at predetermined times following discharge from hospital to reduce re-admission and death.

- *Post-discharge malaria chemoprevention (PDMC) should be given to children following admission with severe anaemia [133] that is not due to blood loss following trauma, surgery, malignancy or a bleeding disorder.*
- *PDMC implementation should be tailored to admissions of children with severe anaemia and consider the duration of protection of the selected antimalarial, and the feasibility and affordability of delivering each additional PDMC course (see "Practical info").*
- *Moderate to high perennial malaria transmission settings are defined as areas with a P. falciparum parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000 [30]. These thresholds are indicative and should not be regarded as absolute for determining applicability of the PDMC recommendation.*

Practical Info

Antimalarial medicine
Medicines used for PDMC can be the same as the first-line malaria treatment, but an alternative medicine is preferred. SP, AL and DHAP were used in three trials and all regimens were found to be effective for PDMC (Phiri *et al* *unpublished evidence*).

Age group
Local data on the age distribution of severe anaemia should be referenced when determining the target age group for PDMC. Two studies evaluated PDMC doses in children under 59 months *[134][135]*, and one study evaluated doses in children aged 3 months to 9 years *[136]*.

Dosage
Children on PDMC should receive a complete course of antimalarials at the recommended treatment dose. The drug dosage should be determined by the child's weight wherever possible, with dosing according to age only in situations where the child's weight is unknown or cannot be determined.

Frequency
The frequency of PDMC administration should be informed by the length of protective efficacy of the selected drug, the duration of the transmission season, and the feasibility of delivering each additional PDMC treatment. Two of the three trials providing evidence for this recommendation provided three PDMC treatments. One trial administered SP monthly starting seven days post-discharge until the end of the transmission season *[136]*; another trial administered AL at discharge then twice at four and eight weeks post-discharge *[134]*; and the third trial administered AL at discharge and then DHAP three times starting 14 days post-discharge and then monthly *[135]*.

Delivery
Two delivery approaches for PDMC were evaluated in one effectiveness study: community-based and facility-based delivery strategies. For community-based delivery, caregivers received all courses of PDMC on discharge, whereas for facility-based delivery, the caregiver had to collect the PDMC drugs from a health facility each month. Community-based delivery was preferred by caregivers and associated with increased adherence compared to facility-based strategies (community:70.6% vs. facility: 52.0%, p = 0.006) *[137]*. Caregivers felt that the instructions on PDMC administration written on the child's health card were sufficient without reminders via text message or from community health workers (CHWs). There was no statistical evidence that SMS reminders resulted in greater adherence (incidence rate ratio: 1.03; 95% CI: 0.88–1.21; p = 0.68) *[138]*.

Drug resistance
The impact of drug resistance on the protection provided by PDMC is currently unclear. A relatively small proportion of the population is eligible for PDMC compared to other malaria chemoprevention interventions such as SMC, PMC or IPTp. Hence, the selective pressure exerted by PDMC on the parasite population, and consequent risk of PDMC increasing resistance to antimalarials across the population, is likely to be small.

Contraindications

Individuals should not receive both PDMC and other forms of malaria chemoprevention (e.g. SMC, PMC or MDA). If other malaria chemoprevention programmes are unable to effectively screen and exclude individuals receiving PDMC, then PDMC should not be administered during periods when SMC, PMC or MDA are being provided. Children with sickle cell disease should be included in PDMC, unless they are already receiving regular chemoprevention due to sickle cell disease.

PDMC is not recommended in children who develop severe acute illness following discharge, those who are unable to take oral medication, children who during the last 30 days received a dose of any of the drugs being used for PDMC, or those allergic to any of the drugs being used for PDMC. PDMC-SP should not be given to individuals receiving a sulfa-based medication as treatment or prophylaxis, including co-trimoxazole (trimethoprim–sulfamethoxazole) for HIV.

Other considerations
Information about PDMC should be fully accessible to caregivers. As with all health interventions, consent should be obtained from the caregiver on behalf of the child prior to administration of PDMC.

Evidence To Decision

Benefits and harms

Study outcomes were considered during the period of intervention and in the period immediately following the intervention. The intervention period began at the first dose of the first course of PDMC and ended four weeks after the first dose of the last course of PDMC. The post-intervention period began on the day after completion of the intervention period and continued for up to 26 weeks (six months).

- **Re-admission (all-cause and severe anaemia)**: PDMC probably reduces all-cause re-admission during the intervention period (risk ratio: 0.42; 95% CI: 0.34–0.52; moderate-certainty evidence). In the post-intervention period, the effect of PDMC varies and may result in little to no difference in all-cause re-admission (hazard ratio: 1.04; 95% CI: 0.83–1.30; moderate-certainty evidence). PDMC probably reduces re-admission for severe anaemia during the intervention period (hazard ratio: 0.38; 95% CI: 0.26–0.56; moderate-certainty evidence) and during the post-intervention period (hazard ratio: 0.74; 95% CI: 0.52–1.05; moderate-certainty evidence). PDMC probably reduces re-admission for severe malaria during the intervention period (hazard ratio: 0.32; 95% CI: 0.22–0.48; moderate-certainty evidence), but may have little effect during the post-intervention period (hazard ratio: 1.06; 95% CI: 0.81–1.39; moderate-certainty evidence).
- **Death (all-cause)**: PDMC reduces all-cause mortality during the intervention period (risk ratio: 0.23; 95% CI: 0.08–0.70; high-certainty evidence). The effect in the post-intervention period varies and may result in little or no difference in all-cause mortality (risk ratio: 1.61; 95% CI: 0.81–3.19; moderate-certainty evidence). Overall, PDMC probably reduces all-cause mortality (risk ratio: 0.77; 95% CI: 0.47–1.28; moderate-certainty evidence).
- **Clinical malaria**: PDMC probably reduces clinical malaria (hazard ratio: 0.64; 95% CI: 0.58–0.72; moderate-certainty evidence), with most of the benefit accruing during the intervention period (hazard ratio: 0.43; 95% CI: 0.36–0.50; versus 0.96; 95% CI: 0.83–1.11 during the post-intervention period; both moderate-certainty evidence).
- **Adverse events**: The three randomized controlled studies provided moderate-certainty evidence on adverse events associated with using different antimalarials: SP, AL, and DHAP. Minor symptoms recorded for those in the SP arm 30 days after the administration of each treatment were similar to those seen in the placebo arm *[136]*. DHAP administration was associated with vomiting within 60 minutes after drug intake (12.4%, compared to placebo 3.8%) *[135]*. No drug-related serious adverse events were reported in the study arm receiving monthly AL *[134]*. DHAP was associated with an 18.6 ms (95% CI: 15.6–21.8; moderate-certainty evidence) increase of the QTc interval (Fridericia correction) after the third dose of each course. All events of QTc interval prolongation were asymptomatic and none of the children in the DHAP group had QTc interval values of more than 500 ms (Fridericia-corrected).

No information was provided in the systematic review on **severe malaria, anaemia** or **severe anaemia not associated with re-admission, blood transfusion** or **parasite prevalence outcomes**.

More information on the evidence can be found in the systematic review (Phiri *et al* *unpublished evidence*).

Certainty of the Evidence

Moderate

The certainty of the evidence across all critical outcomes ranged from moderate to high. Only the evidence on the effect

of PDMC on all-cause mortality during the 2–14-week intervention period was of high certainty. The GDG consequently considered the certainty of the evidence overall to be moderate.

More information on the certainty of evidence assessments can be found in the 'research evidence' tab associated with this recommendation online or in the annex of the pdf version.

Values and preferences

Preferences and values of the target population were determined by:

- consultation with civil society, which indicated that chemoprevention to prevent malaria disease in children under 5 years was seen as a priority in endemic areas, although there was no specific mention of the need during the post-discharge period (CS4ME *unpublished evidence*);
- a synthesis of contextual factors from trials of PDMC in sub-Saharan Africa (Lange *et al* *unpublished evidence*). The report showed that caregivers had generally positive views of PDMC. Caregivers understood the value of giving preventive malaria medicines during the post-discharge period, given that their children had recently been in hospital *[139]*. CHWs also viewed PDMC as an important and beneficial intervention *[137]*.

The GDG determined that there was probably no important uncertainty or variability in how the outcomes of PDMC are valued across contexts.

More information can be found in the summary of contextual factors report (Lange *et al* *unpublished evidence*) and the civil society consultation report (CS4ME *unpublished evidence*).

Resources

The mean estimated cost of implementing community-based PDMC was between US$ 22.91 and US$ 28.33 per child treated in the three countries where the studies were conducted. Implementation costs for community-based PDMC were outweighed by cost savings for re-admission compared to standard care, with a mean expected saving per child between US$ 22.08 and US$ 45.24. Health care providers' net cost saving per child receiving PDMC, including health care (especially blood transfusion) and societal costs, was between US$ 19.12 and US$ 25.71. Two approaches for delivering PDMC were evaluated: (i) facility-based, in which children had to be brought to a health facility to receive subsequent doses of PDMC, and (ii) community-based, in which the caregiver received all doses for PDMC on discharge with instructions and dates for administration written on the child's health card, and with CHWs reminding caregivers when to administer doses, SMS reminders, or no reminders. Community-delivered PDMC was found to be more cost-saving compared to health facility-based delivery due to costs from repeated travel for drug collection, which also posed a disincentive to adherence.

The GDG judged that PDMC probably results in moderate savings and is therefore probably cost-effective, but the certainty of the evidence regarding the resources required was low.

More information on the evidence can be found in the report on PDMC cost-effectiveness (Kühl *et al* *unpublished evidence*).

Equity

None of the studies included in the PDMC contextual factors report were designed to capture issues related to equity. However, caregivers whose children received PDMC from the health facility reported that repeated travel to the hospital to collect medicines was costly and time-consuming. Caregiver literacy was identified as a potential challenge for equitable PDMC delivery among participants who received all medicines when their child was discharged (community-based delivery), as some caregivers may not be able to read the PDMC administration dates recorded on their child's health card. SMS reminders (see "Feasibility" below) may also raise concerns over equity.

The GDG considered that PDMC has a variable effect on health equity and noted that PDMC likely reinforces existing

health inequities, given that it is administered to children who have already accessed a hospital. Nevertheless, among those who have already accessed a hospital, the intervention is likely to be equitable; however, this may be dependent on how PDMC is administered, with community-based delivery being potentially more equitable than facility-based delivery.

More information on the evidence can be found in the summary of contextual factors report (Lange *et al* *unpublished evidence*).

Acceptability

One study showed that community-based PDMC resulted in higher self-reported adherence than facility-based PDMC (71% vs 52% adherence to the full three courses). Community-based adherence may have been influenced by the anticipation of study staff visits for pill counts after each treatment course. Potential stigma from repeated CHW visits may be a potential issue for community-based adherence.

The GDG considered PDMC to probably be acceptable to key stakeholders.

More information on the evidence can be found in the summary of contextual factors report (Lange *et al* *unpublished evidence*).

Feasibility

For community-based delivery of PDMC, CHWs reported a high level of intrinsic motivation to conduct home visits to remind caregivers to administer PDMC doses. Nevertheless, adherence to the required number of home visits was poor, with less than half of the CHWs conducting the required home visit reminders. Positive factors that encouraged CHWs to conduct home visits were the knowledge and perception of PDMC effectiveness, and recognition from the community and the health system. Reported barriers to CHWs conducting home visits included poor training, lack of supervision, and high workload.

Written reminders of PDMC treatment dates on children's health cards were positively viewed by participants. Most caregivers preferred SMS reminders over CHW visits, but those who didn't own a phone had to receive reminders through neighbours and/or family members, which caused delays. Although PDMC adherence was higher among SMS recipients (66.2%) compared to non-SMS participants (56.9%), there was no statistical evidence that SMS reminders resulted in greater adherence (incidence rate ratio: 1.03; 95% CI: 0.88–1.21; p = 0.68).

The GDG concluded that it was unclear whether PDMC implementation was broadly feasible, given that there is currently only evidence from three trials, including one implementation study. The optimal approach to PDMC implementation may vary in different places and, where CHWs are involved, may benefit from a direct link between health facilities and community-based care.

More information on the evidence can be found in the summary of contextual factors report (Lange *et al* *unpublished evidence*).

Justification

This recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *[103]*.

Sources of information

Recommendation development was informed by a systematic review (Phiri *et al* *unpublished evidence*), independently evaluated using the AMSTAR-2 Checklist *[114]*(Gutman *et al* *unpublished evidence (d)*), and a report summarizing evidence from published studies on contextual factors related to PDMC implementation (Lange *et al* *unpublished evidence*), including feasibility, equity, values and acceptability, as well as a cost-effectiveness analysis (Kühl *et al* *unpublished evidence*). These sources of information were supplemented by a cross-cutting review on chemoprevention and drug resistance (Plowe *unpublished evidence)*, a civil society consultation report on chemoprevention (CS4ME *unpublished evidence)* and contributions from the GDG membership, which included former and current national malaria programme representatives.

The systematic review addressed the GDG's PICO (population, intervention, comparison, outcome) question regarding

whether children hospitalized with severe anaemia in malaria-endemic settings should be given antimalarial medicines as chemoprevention post-discharge. The main outcomes of interest were the impact of PDMC on re-admission (all-cause and severe anaemia), mortality (all-cause), severe anaemia, and blood transfusion. Other outcomes of interest included confirmed clinical malaria, severe malaria, anaemia, adverse events, and parasite prevalence. Three randomized double-blind placebo-controlled trials were included in the review. All the trials were conducted in sub-Saharan Africa: Gambia, Kenya, Malawi and Uganda. One trial evaluated monthly SP until the end of the malaria transmission season; another trial evaluated monthly AL at four and eight weeks post-discharge; and the third trial evaluated monthly DHAP at 14, 42 and 70 days post-discharge. The systematic review included trials that compared PDMC with no intervention in children aged < 9 years with anaemia, defined as haemoglobin < 7 g/dL (one trial), or severe anaemia, defined as haemoglobin < 5 g/dL. The intervention period started from the first dose of the first course of PDMC and continued until four weeks after the first dose of the last course of PDMC, a follow-up period of 2–14 weeks. The post-intervention period started the day after the completion of the intervention period and continued up to 26 weeks. The AMSTAR-2 Checklist assessment concluded that the systematic review was good quality overall (Gutman *et al* *unpublished evidence (d)*). Five outcomes of interest were not covered by the systematic review, namely severe malaria, anaemia, severe anaemia, blood transfusion and parasite prevalence.

Summary of judgements

The Evidence-to-Decision framework captures the evidence from the systematic review considered by the GDG. The GDG determined that the balance between desirable and undesirable effects favoured PDMC; moderate cost savings were probably associated with PDMC implementation; PDMC is therefore probably cost-effective, although the certainty of evidence regarding required resources was low; and PDMC is probably acceptable to key stakeholders, but the feasibility of implementing PDMC at scale is not known. The GDG concluded that a conditional recommendation should be made for PDMC based on the moderate- to high-certainty evidence of large beneficial effects and likely low costs.

Implementation

A guide to support implementation of PDMC will be developed in due course, and a manual for subnational tailoring of malaria interventions is under development and expected for publication in 2022.

Evaluation

PDMC programmes should be routinely monitored for safety, efficacy, drug resistance and effectiveness. The impact of introducing PDMC may be evaluated using routine hospital, clinic and/or CHW data.

The potential effect of PDMC on the spread of drug resistance is likely to be modest, given the small proportion of the population receiving the intervention. Resistance may be monitored by the analysis of molecular markers associated with treatment outcomes, although the correlation between molecular markers and the efficacy of antimalarials for chemoprevention is unclear and should be interpreted with caution.

Further guidance will be made available in the PDMC implementation guide, which will be developed in due course.

Research Needs

The GDG identified the following evidence gaps as requiring further research. These relate to:

- the optimal duration for PDMC in different geographical and transmission settings, and understanding of the short-, medium- and long-term benefits of PDMC of different durations; these evaluations should recognize the underlying pattern of post-discharge death and/or re-admission, and the higher risk of some groups dying soon after discharge; to minimize bias, the overall impact during the whole intervention and follow-up period should be considered;
- a better understanding of risk factors (including age) for adverse outcomes following discharge with severe anaemia, and potential differential effects of PDMC in different risk groups;
- patient adherence to PDMC when deployed at scale;
- costs of and coverage achieved by alternative approaches to delivering PDMC;
- feasibility of different coordination mechanisms between hospital and outpatient/community settings for PDMC;
- feasibility of implementing PDMC in parallel with other malaria chemoprevention interventions (e.g. SMC and PMC);
- the long-term (e.g. 12 months and longer) impact of PDMC on child survival;
- the effectiveness of PDMC on severe anaemia of different etiologies;
- the effectiveness of PDMC for children diagnosed with severe anaemia and malaria in low transmission settings;
- the feasibility, costs and effects of combining PDMC with additional interventions (e.g. ITNs) to reduce the household's risk of further infection and adverse health outcomes.

4.2.6 Mass drug administration (MDA)

Mass drug administration (MDA) for malaria is the administration of a full therapeutic course of an antimalarial

medicine at approximately the same time, and often at repeated intervals, to all age groups of a population in a defined geographical area. Antimalarial medicines are administered without prior malaria testing and therefore regardless of the malaria infection status of individuals. Consequently, any existing infections are treated and new infections are prevented for the duration of the drug's prophylactic period. MDA has been an important component of malaria control and elimination programmes for decades *[140]*. Some earlier WHO documents referred to "age-targeted MDA": however, such use cases are no longer considered MDA and recommendations for such targeted use are presented separately – see recommendations for perennial malaria chemoprevention (PMC) (section 4.2.2) and seasonal malaria chemoprevention (SMC) (section 4.2.3). The use of chemoprevention in occupationally vulnerable groups, such as forest workers, is considered targeted drug administration (TDA) and not MDA. Similarly, use of chemoprevention around a confirmed case in areas approaching elimination or post-elimination preventing re-establishment is known as reactive drug administration (RDA). Although not called MDA, all of these strategies share a common underlying principle – that the provision of a treatment dose of antimalarial medicine will cure existing infections and prevent new ones.

Historically, MDA has been given either to reduce malaria disease burden or to reduce malaria transmission. The distinction between the two MDA use cases for *P. falciparum* is to some extent artificial, as any intervention that reduces transmission will also reduce disease burden, and burden-reducing interventions that reach a sufficient proportion of the population will also reduce transmission. Nevertheless, the evidence on the use of MDA for disease burden and transmission reduction was considered separately by two Guideline Development Groups (GDGs). The two GDGs broadly recommended that programmes may consider MDA to reduce *P. falciparum* transmission in very low to low transmission settings, and to reduce disease burden in moderate to high transmission settings. A *P. falciparum* prevalence (*Pf*$PR_{2\text{-}10}$) of around 10% (or incidence of infection around 250 per 1000 population per year) may be used to differentiate areas of low to very low transmission from areas of moderate to high transmission. These thresholds should not be considered absolute cut-offs and it is biologically plausible that MDA in settings near the 10% threshold may reduce both disease burden and transmission intensity. However, the relative effects of burden reduction versus transmission reduction differ along the transmission spectrum. Malaria programmes should therefore review the MDA recommendations and practical information for both burden and transmission reduction and decide whether or not an MDA intervention is likely to lead to a successful outcome in their setting.

The use of MDA for *P. vivax* is more complicated, as *P. vivax* infections may relapse within a few months unless treated with an antimalarial medicine that includes an 8-aminoquinoline to clear hypnozoites. An 8-aminoquinoline medicine has the potential to cause severe haemolysis in persons deficient for the glucose-6-phosphate dehydrogenase (G6PD) enzyme. Safe administration of an 8-aminoquinoline requires G6PD testing, an effective pharmacovigilance system and emergency access to blood transfusion services. The two GDGs that reviewed evidence for the impact of MDA on *P. vivax* prioritized different outcome measures and arrived at different recommendations. Whereas the evidence was considered insufficient to recommend MDA for the reduction of *P. vivax* disease, it was recognized that, in some situations, MDA may usefully contribute to the reduction of *P. vivax* transmission. Malaria programmes should, therefore, review the MDA recommendations for *P. vivax* and decide whether or not an MDA intervention is likely to lead to a successful outcome in their setting.

A chemoprevention strategy related to MDA that is intended to reduce transmission of *P. vivax* is mass relapse prevention (MRP). MRP is similar to MDA in that the entire population of a delimited geographical area is provided with an antimalarial medicine at approximately the same time. In the case of MRP, however, only an 8-aminoquinoline drug is provided. In the past, the strategy used primaquine and was referred to as "mass primaquine prophylactic treatment". However, the name of this strategy has since been expanded to include the potential for new drugs with similar anti-relapse properties. Generally deployed in areas with cold winters and highly seasonal transmission of *P. vivax*, the medicine is provided to the population in early spring, when there is no or very low transmission of the parasite, to treat hypnozoites and prevent relapses that could infect a new population of mosquitoes in the summer months.

WHO recommends that malaria programmes tailor intervention packages to their local context. The MDA recommendations are subject to considerations, identified by the GDGs, which will influence the likelihood of successful outcomes. These contextual considerations are outlined in remarks under the recommendations and in the "Practical info" sections.

- Recommendations regarding the use of MDA for burden reduction are presented in section *4.2.6.1 MDA for burden reduction*; and recommendations for burden reduction in emergency settings are presented in section *4.2.6.2 MDA for burden reduction in emergency settings*;
- Recommendations for transmission reduction are found in section *4.2.6.3 MDA to reduce transmission of* P. falciparum *in very low to low transmission settings*; section *4.2.6.4 MDA to reduce transmission of* P. falciparum *in moderate to high transmission settings*; and section *4.2.6.5 MDA to reduce transmission of* P. vivax.
- The recommendation for MRP is found in section *4.2.6.6 MRP to reduce transmission of* P. vivax.

4.2.6.1 MDA for burden reduction

Conditional recommendation for , Low certainty evidence

MDA for burden reduction (2022)

Antimalarial medicine can be given as chemoprevention through mass drug administration (MDA) in areas of moderate to high transmission of *P. falciparum* to provide short-term reductions in disease burden.

- *MDA may quickly reduce clinical malaria incidence in settings with moderate to high P. falciparum transmission, but the effect wanes within 1–3 months. Therefore, if MDA is implemented, it should be one of several components of a robust malaria control programme (including good coverage of effective case management and appropriate prevention tools and strategies).*
- *Malaria programmes should judge the suitability of using MDA in their context based on the desired impact, level of endemicity, and resources required. MDA for burden reduction should be targeted at moderate to high transmission settings, regardless of seasonality (see "Practical info").*
- *Moderate to high malaria transmission settings are defined as areas with P. falciparum parasite prevalence greater than 10%, or incidence greater than 250 P. falciparum cases per 1000 population per year [30]. These thresholds should not be regarded as absolutes for determining applicability of MDA implementation. It is biologically plausible that MDA in intermediate transmission settings may reduce both disease burden and transmission intensity.*

Practical Info

Transmission setting

The impact of MDA on disease burden varies between high and low malaria transmission settings. In high transmission settings, the impact of MDA on disease is likely to be large and may be cost-effective due to the high background disease burden. However, as transmission intensity and the corresponding disease burden decrease, the impact of MDA also decreases and MDA becomes less cost-effective for disease burden reduction. The effect on other outcomes, parasite incidence and prevalence, and incidence of severe disease also appears to vary by transmission intensity. There are no studies directly comparing the impact of MDA for burden reduction with the impact of more targeted approaches to chemoprevention (e.g. SMC) (Schneider *et al* unpublished evidence *(a)*). MDA for burden reduction should be targeted at moderate to high transmission settings, regardless of seasonality.

Antimalarial medicine

WHO recommends the use of a combination medicine for MDA that is different from that used as first-line malaria treatment. The component medicines should have closely matched pharmacology, such that no component is present in the absence of other components for more than a minimal amount of time in order to reduce the risk of new infections encountering only a single drug. A drug regimen that can be administered as a directly observed single dose is preferable to a multi-day regimen. Data were insufficient to discern a specific effect of single-dose primaquine. Available evidence suggests that maximum benefits are seen within 1–3 months after the last round of the intervention (Schneider *et al* unpublished evidence *(a)*).

Dosage

A complete therapeutic course of antimalarials, at doses recommended by the manufacturer, should be given to all eligible adults and children within a defined geographical area. Drug dosage should be determined by weight wherever possible, with dosing according to age only in situations where the person's weight is unknown.

Frequency

The frequency of MDA rounds should take into account the local malaria epidemiology, the half-life of the antimalarial used, and the feasibility and cost of delivering each additional round. Consistent with trial data, mathematical models predict that a single round of MDA would lead to an initial decrease in infections, but that the duration of effect would be short-lived. Application of additional rounds is predicted to substantially improve the impact and duration of effect. MDA should not be given to individuals receiving other forms of malaria chemoprevention (e.g. SMC, PMC, or IPTp) (Schneider *et al* unpublished evidence *(a)*).

Drug resistance

There is limited evidence to date on whether MDA accelerates the development and spread of antimalarial drug resistance. However, where data were collected, MDA had little to no effect on drug resistance markers (*PfKelch13* and *Pfplasmepsin2/3* copy number) among *P. falciparum* infections (Schneider *et al* unpublished evidence *(a)*; Plowe unpublished evidence).

Contraindications
Depending on the medicine chosen, certain population groups may need to be excluded from MDA. These include pregnant women in their first trimester; infants <6 months of age or weighing <5kg; people recently treated with the same medicine; people with a known allergy to the medicine; anyone with severe acute illness or who is unable to take oral medication; people taking medicine known to interact with the medicine used for MDA; and people with specific contraindications to the medicine used *[141]*.

Other considerations
Information about MDA should be fully accessible to caregivers, health workers and key stakeholders, such as government officials and religious leaders. As with all health interventions, consent should be obtained, including from the carers of children, prior to administration of MDA.

Evidence To Decision

Benefits and harms

Moderate to high transmission areas

- **Clinical malaria**: MDA may reduce clinical malaria incidence 1–3 months post-MDA[1] (rate ratio: 0.41; 95% CI: 0.04–4.42; low-certainty evidence). There was limited evidence available on the effect on malaria burden 4–12 months post-MDA or 12–24 months post-MDA.
- **All-cause mortality**: It is very uncertain whether MDA affects mortality within the first month post-MDA (risk ratio: 0.68; 95% CI: 0.57–0.81; very low-certainty evidence) or 1–3 months post-MDA (odds ratio: 1.77; 95% CI: 1.54–2.04; very low-certainty evidence). No evidence was available from randomized trials and the certainty of evidence from non-randomized trials was graded very low.
- **Parasitaemia**: MDA probably reduces the incidence of *P. falciparum* infection 1–3 months post-MDA (rate ratio: 0.61; 95% CI: 0.40–0.92; moderate-certainty evidence), but may have little to no effect on incidence 4–12 months post-MDA as the evidence is very uncertain (rate ratio: 0.91; 95% CI: 0.55–1.50; very low-certainty evidence). MDA may result in little to no difference in *P. falciparum* prevalence 1–3 months (risk ratio: 1.76; 95% CI: 0.58–5.36; low-certainty evidence) or 4–12 months post-MDA (risk ratio: 1.18; 95% CI: 0.89–1.56; low-certainty evidence). Evidence from non-randomized trials suggests: MDA may reduce parasite prevalence 12–24 months post-MDA (risk ratio: 0.77; 95% CI: 0.70–0.84; low-certainty evidence), 1–3 months post-MDA (risk ratio: 0.85; 95% CI: 0.78–0.93; very low-certainty evidence) and 4–12 months post-MDA (risk ratio: 0.60; 95% CI: 0.55–0.67; very low-certainty evidence), but the evidence is very uncertain.
- **Adverse events**: We are uncertain whether MDA increases or decreases adverse events 1–3 months post-MDA (odds ratio: 3.25; 95% CI: 0.68–15.53; very low-certainty evidence). No data were available to assess the effect of MDA on serious adverse events in moderate to high transmission settings, but the absolute risk is very low (0.01 per 1000 doses).
- **Anaemia, drug resistance, hospitalization, severe malaria, or blood transfusions**: In the studies that met the inclusion criteria, none systematically collected data on these outcomes for moderate to high transmission areas, beyond what was reported as severe adverse events.

Very low to low transmission areas

- **Clinical malaria**: MDA may reduce the incidence of clinical malaria due to *P. falciparum* 1–3 months post-MDA (rate ratio: 0.58; 95% CI: 0.12–2.73; low-certainty evidence) and 12–24 months post-MDA (rate ratio: 0.77; 95% CI: 0.2–3.03; low-certainty evidence). It is uncertain whether MDA reduces clinical malaria 4–12 months post-MDA, as the evidence is very uncertain (rate ratio: 0.47; 95% CI: 0.21–1.03; very low-certainty evidence).
- **Anaemia**: MDA increases mean haemoglobin (mean difference: 0.53; 95% CI: 0.27–0.79; high-certainty evidence).
- **Parasitaemia**: MDA probably reduces the incidence of *P. falciparum* infection 1–3 months post-MDA (rate ratio: 0.37; 95% CI: 0.21–0.66; moderate-certainty evidence). MDA may reduce *P. falciparum* prevalence 0–1 month post-MDA (risk ratio: 0.12; 95% CI: 0.03–0.52; moderate-certainty evidence) and probably reduces *P. falciparum* prevalence 1–3 months post-MDA (risk ratio: 0.25; 95% CI: 0.15–0.41; moderate-certainty evidence). MDA may reduce *P. falciparum* prevalence 4–12 months post-MDA (risk ratio: 0.82; 95% CI: 0.56–1.22; low-certainty evidence). MDA may reduce *P. falciparum* prevalence 12–24 months post-MDA, but the evidence is very uncertain (risk ratio: 0.34; 95% CI: 0.06–1.97; very low-certainty evidence).
- **Drug resistance**: There was no evidence of an effect on *Pfkelch13* or on multi-copy *Pfplasmepsin2/3* drug

resistance markers among those who received three rounds of MDA over three months, compared to the control.
- **Adverse events**: MDA may increase the number of serious adverse events within three months (odds ratio: 3.61; 95% CI: 0.43–30.03; moderate-certainty evidence) and 4–12 months post-MDA (odds ratio: 1.47; 95% CI: 0.68–3.20; moderate-certainty evidence). However, the absolute event rate is very low (0.03 per 1000). Four studies only presented narrative summaries of adverse events. No data were available to assess the effect of MDA on adverse events in very low to low transmission settings.
- **All-cause mortality, hospitalization, severe malaria, or blood transfusions**: In the studies that met the inclusion criteria, none systematically collected data on these outcomes for very low to low transmission areas, beyond what was reported as severe adverse events.

P. vivax

- **Clinical malaria**: It is uncertain whether MDA increases or reduces *P. vivax* malaria 4–12 months post-MDA, as the evidence is very uncertain (rate ratio: 1.38; 95% CI: 0.97–1.95; very low-certainty evidence). Non-randomized trials showed that MDA may reduce the incidence of *P. vivax* malaria at <1 month (rate ratio: 0.23; 95% CI: 0.21–0.25; very low-certainty evidence), 1–3 months (rate ratio: 0.29; 95% CI: 0.26–0.31; very low-certainty evidence), 4–12 months (rate ratio: 0.72; 95% CI: 0.68–0.76; very low-certainty evidence) or 12–24 months post-MDA (rate ratio: 0.04; 95% CI: 0.02–0.07; very low-certainty evidence), but the evidence is very uncertain.
- **Parasitaemia**: MDA probably reduces *P. vivax* prevalence 0–1 month post-MDA (risk ratio: 0.18; 95% CI: 0.08–0.40; moderate-certainty evidence), and may reduce *P. vivax* prevalence 1–3 months (risk ratio: 0.15; 95% CI: 0.10–0.24; low-certainty evidence) and 12–24 months post-MDA (risk ratio: 0.81; 95% CI: 0.44–1.48; low-certainty evidence). However, MDA may result in little or no difference 4–12 months post-MDA (risk ratio: 1.01; 95% CI: 0.87–1.18; low-certainty evidence). Evidence from non-randomized trials for incidence of *P. vivax* infection show that MDA may reduce incidence <1 month after MDA (rate ratio: 0.15; 95% CI: 0.12–0.19; low-certainty evidence). MDA may reduce *P. vivax* incidence at 1–3 months (rate ratio: 0.37; 95% CI: 0.32–0.43; very low-certainty evidence) and 4–12 months post-MDA (rate ratio: 0.15; 95% CI: 0.07–0.34; very low-certainty evidence), but the evidence is very uncertain.
- **Adverse events**: With the drugs used in the studies included in the review, MDA probably increases the frequency of serious adverse events post-MDA (0–3 months post-MDA: odds ratio: 3.61; 95% CI: 0.43–30.03; moderate-certainty evidence; 4–12 months post-MDA: odds ratio: 1.47; 95% CI: 0.68–3.20; moderate-certainty evidence).
- **Anaemia, all-cause mortality, drug resistance, hospitalization, severe malaria, or blood transfusions**: In the studies that met the inclusion criteria, none systematically collected data on these outcomes for *P. vivax* transmission areas, beyond what was reported as severe adverse events.

More information on the evidence can be found in the systematic review (Schneider *et al* *unpublished evidence* *(a)*).

[1] In studies with multiple rounds, “post-MDA” refers to after the last round of MDA in a given transmission season or year.

Certainty of the Evidence

Low

The GDG considered the overall certainty of the evidence for the outcomes of interest to be low. The certainty of evidence, as summarized under “Benefits and harms”, ranged from very low to high. The priority outcome of confirmed clinical malaria was assessed as having predominantly low-certainty evidence for *P. falciparum* transmission settings and very low-certainty evidence for *P. vivax* transmission settings. Most studies reported on outcomes after the last round of MDA, rather than during the intervention period. Studies with multiple rounds of MDA may not have captured important effects that occurred between the first and last rounds of MDA, and outcomes may reflect a cumulative effect for MDA. There is a lack of evidence on clinical outcomes during the 0–1 months post-intervention, when impact may be expected to be the greatest. There is no information on

effectiveness if rounds of MDA continue for >1 year.

More information on the certainty of evidence assessments can be found in the 'research evidence' tab associated with this recommendation online or in the annex of the pdf version.

Values and preferences

Preferences and values of the target population were determined by:

- consultation with civil society, which indicated that chemoprevention to prevent malaria disease is broadly considered a priority, especially in children under 5 years and women in pregnancy;
- synthesis of contextual factors from trials and pilots of MDA. One study that surveyed participants' values found that the most common explanation for the uptake of MDA was the desire to protect their family or community from future malaria infections.

The GDG determined that there was possibly important uncertainty or variability in how the main outcomes are valued across contexts, dependent on the transmission setting and burden of disease.

More information on the evidence can be found in the systematic review (Schneider *et al* *unpublished evidence (a))* and the civil society consultation report (CS4ME *unpublished evidence*).

Resources

The estimated costs per person per round varied from approximately US$ 1.04 to US$ 19.40; one study estimated that drugs accounted for 70% of the cost of MDA (Schneider *et al* *unpublished evidence (a)).* The costs associated with MDA are likely to vary depending on the extent to which the intervention could leverage existing campaigns and platforms.

Moderate to high transmission areas
Data on the cost-effectiveness of MDA are sparse. However, the GDG judged that MDA is likely to be cost-effective in moderate to high transmission settings due to the greater number of cases averted in these settings.

Very low to low transmission areas
Given that fewer malaria cases will be averted, the GDG judged MDA as probably not cost-effective for disease burden reduction in low transmission settings.

More information can be found in the systematic review (Schneider *et al* *unpublished evidence (a)).*

Equity

There was no evidence of a direct impact of MDA on health equity, although the GDG judged that it would likely increase health equity by enhancing access to medicines for those at risk of malaria. Specific effort may be needed to reach high-risk communities, among whom uptake tends to be lower, and ethnic minority communities that may suffer geographical isolation.

More information can be found in the systematic review (Schneider *et al* *unpublished evidence (a)).*

Acceptability

MDA is probably acceptable to key stakeholders. Studies have shown that sensitization, education, and inclusion of local leaders, such as government figures, religious leaders and health authorities, are very important in improving acceptability. The most common barrier to acceptability is fear of perceived adverse events. Two studies found that participants were concerned that adverse events may inhibit their economic productivity, although, in another study,

respondents felt that malaria infection was more likely to limit their economic activity than adverse events.

Previous experience reinforced initial perceptions of MDA: individuals who had been part of previous MDA trials shared stories in their communities; if those experiences were poor, community members had negative impressions of MDA. In areas where other malaria interventions had been implemented effectively, MDA for malaria was viewed more positively.

More information can be found in the systematic review (Schneider *et al* *unpublished evidence (a)*).

Feasibility

The feasibility of implementing MDA varies and is highly context-specific, with more remote or mobile populations being harder to reach.

More information can be found in the systematic review (Schneider *et al* *unpublished evidence (a)*).

Justification

This recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *[103]*.

Sources of information

A systematic review of existing evidence was commissioned to inform this guidance on the use of MDA to reduce the burden of malaria disease (Schneider *et al* *unpublished evidence (a)*). The review team produced a separate report to address the needs of the GDG developing the MDA recommendation for transmission reduction. The main objective of the review was to synthesize evidence on the efficacy and safety of giving a full therapeutic course of antimalarial medicine at approximately the same time to people residing in defined geographical areas with ongoing human malaria transmission to reduce the burden of clinical disease from *P. falciparum* and *P. vivax*. Secondary objectives included summarizing evidence on contextual factors that affect the implementation of MDA and findings from mathematical modelling studies with respect to the impact of different operational factors on MDA efficacy. The primary outcome of interest was confirmed clinical malaria at 0–1 months, 1–3 months, 4–12 months, and 12–24 months post-MDA. Secondary outcomes of interest included: hospital admissions (all-cause and malaria-specific); all-cause mortality; parasite prevalence; adverse events; anaemia; drug resistance; severe malaria; and blood transfusions. The systematic review was supplemented by a cross-cutting review on chemoprevention drug resistance (Plowe *unpublished evidence*), a civil society consultation report on chemoprevention (CS4ME *unpublished evidence*) and contributions from the GDG membership, which included national malaria programme representatives.

The systematic review identified 20 studies: eight provided data on *P. falciparum* (five cluster-randomized controlled studies and three non-randomized studies); five cluster-randomized controlled trials provided data on both *P. falciparum* and *P. vivax*; and an additional seven studies provided data on *P. vivax* only (all non-randomized, before-after studies) (Schneider *et al* *unpublished evidence (a)*). The drugs used for MDA in studies evaluating an effect on *P. falciparum* included: amodiaquine (1); AS-AQ (1); chloroquine (1); DHAP (8); pyronaridine-artesunate (1); sufalene-pyrimethamine (1); and SP+AS (2). The drugs used for MDA in studies evaluating an effect on *P. vivax* included: atebrin (1); chloroquine (2); chloroquine plus pyrimethamine (1); DHAP (5); and pyrimethamine (3). Seven of the 13 studies evaluating an effect on *P. falciparum* included an 8-aminoquinoline, such as low-dose primaquine, as did seven of the 12 studies evaluating an effect on *P. vivax*. *P. falciparum* gametocytes and *P. vivax* hypnozoites are eliminated by 8-aminoquinolines, but these drugs may cause haemolysis in people with G6PD deficiency. None of the *P. vivax* studies included anti-relapse treatment. Follow-up ranged from 0 to 24 months post-MDA for studies investigating *P. falciparum* and studies looking at both *P. falciparum* and *P. vivax*, whereas for *P. vivax* studies, follow-up ranged from 0 to 12 months post-MDA. Studies that reported data on *P. falciparum* were stratified into areas of moderate to high (>10% prevalence of *P. falciparum* infection) versus low to very low (≤10% prevalence of *P. falciparum* infection) transmission due to heterogeneity in the outcomes. Three studies were not included in the review due to an imbalance of background interventions. In addition, large-scale operational experience of MDA in Central Asia, China and Russian Federation, among others, was not captured, although MDA has been a prominent feature of control and elimination efforts in those settings.

Summary of judgements

Evidence from the systematic review (Schneider *et al* *unpublished evidence (a)*) and supporting information (CS4ME *unpublished evidence*; Plowe *unpublished evidence*) was appraised by the GDG in October 2021. The evidence and their

judgements are captured in the Evidence-to-Decision table. Where the GDG felt there were differences in moderate to high versus very low to low transmission areas, a separate assessment was made for each transmission setting. The GDG determined that the balance of effects favoured MDA for short-term disease burden reduction in moderate to high *P. falciparum* transmission settings, given the moderate-certainty evidence that MDA reduces the incidence of *P. falciparum* infection 1–3 months post-MDA and has a consistent-sized effect on clinical outcomes. The GDG also considered it plausible that a reduction in the incidence of infection would translate into an impact on disease. The balance of effects with regard to burden reduction thus favoured implementation of MDA in moderate to high transmission *P. falciparum* settings for short-term reduction of disease burden. There was insufficient evidence from field trials on the impact of MDA as a long-term (e.g. >1 year) intervention on disease burden in moderate to high transmission areas. In very low to low *P. falciparum* transmission settings, the GDG favoured standard care over MDA for malaria disease burden reduction, given the low certainty of evidence of desirable effects and the low disease burden in low *P. falciparum* transmission settings: burden reduction alone was not considered adequate justification for implementing MDA in such settings due to the small gains in burden reduction from MDA. The overall balance of effects for MDA for burden reduction in *P. vivax* transmission settings was not considered by the GDG, given the weak and conflicting available evidence. The GDG considered that implementation of MDA was associated with moderate costs and that MDA was considered cost-effective to reduce disease burden in moderate to high transmission settings; however, it was not considered cost-effective for burden reduction in very low to low transmission settings due to the fewer cases averted in these contexts. MDA was probably acceptable to key stakeholders, and the feasibility of MDA implementation was deemed variable, as this is highly context-specific.

Studies evaluating MDA have generally explored the potential of MDA to reduce transmission. Such studies prioritize infection end-points and this may limit their ability to detect clinical outcomes. The certainty of evidence on clinical outcomes was considered low, and confidence intervals crossed the null. However, the GDG considered it biologically plausible that a reduction in the incidence of infection would translate into impact on disease, and recognized that the point estimates of effect sizes against these end-points were consistent with each other. The GDG concluded that a conditional recommendation should be made for MDA for short-term burden reduction in moderate to high transmission settings, given the large impact on burden reduction, low risk of adverse events, moderate costs, likelihood of increasing equity in terms of access to health interventions, and likely acceptability of short-term MDA in most settings. However, the feasibility of delivering the intervention could vary and warrants careful consideration in each setting. The GDG determined that the recommendation should apply to areas with mainly *P. falciparum* transmission, as there was little and contradictory evidence for *P. vivax*.

Implementation

Please refer to the *Mass drug administration for falciparum malaria: a practical field manual [137]*.

Evaluation

Mass drug administration for falciparum malaria: a practical field manual [137] should be used to monitor MDA programmes for burden reduction. Programmes should include monitoring of efficacy, drug safety and adverse events, drug resistance and the impact of MDA on morbidity and mortality. Malaria programmes are also encouraged to evaluate the operational effectiveness and costs of implementation of MDA within their contexts.

Research Needs

Evidence gaps requiring further research include:

- the comparative value of age-targeted chemoprevention (e.g. SMC) vs MDA in terms of disease burden reduction;
- the relative cost-effectiveness of MDA vs targeted chemoprevention (e.g. SMC) for burden reduction;
- the effectiveness of MDA based on different dosing schedules and duration;
- MDA drug choice options for young infants;
- MDA drug choice options for women in their first trimester of pregnancy.

4.2.6.2 MDA for burden reduction in emergency settings

Conditional recommendation for , Low certainty evidence

MDA for burden reduction in emergency settings (2022)

During emergencies or periods of health service disruption, antimalarial medicine can be used for mass drug administration (MDA) in defined geographical areas to provide short-term reductions in the burden of disease caused by *P. falciparum*.

- *MDA may quickly reduce clinical malaria incidence in settings with moderate to high P. falciparum transmission, but the effect wanes within 1–3 months. As far as possible, MDA should be implemented as part of a package of malaria control measures (including effective case management and appropriate prevention tools and strategies).*
- *Malaria programmes should judge the suitability of using MDA in their context based on the desired impact, level of endemicity, and resources required (see "Practical info").*
- *There is very limited evidence on the impact of MDA on disease in emergency settings. However, the biological effects of MDA on disease in non-emergency settings are likely to translate to MDA recipients in emergency settings. The size of effect will vary according to the type of emergency and level of disruption to health services, as well as underlying transmission intensity, choice of drug, delivery method and other factors.*

Practical Info

See section 4.2.6.1 for the recommendation on MDA for burden reduction for further practical considerations.

Evidence To Decision

Benefits and harms

- **All-cause mortality**: The evidence is very uncertain about the effect of MDA in emergency settings on all-cause mortality <1 month (risk ratio: 0.68; 95% CI: 0.57–0.81; very low-certainty evidence) and 1–3 months (odds ratio: 1.77; 95% CI: 1.54–2.04; very low-certainty evidence) post-MDA, among all ages.
- **Hospitalization**: MDA in emergency settings may reduce all-cause and malaria-specific hospitalization 0–1 month post-MDA, but the evidence is very uncertain.
- **Confirmed clinical malaria**: MDA in emergency settings may reduce parasitologically confirmed malaria 0–1 month post-MDA, but the evidence is very uncertain.
- **Parasitaemia, adverse events, anaemia, drug resistance, severe malaria, or blood transfusions**: In the studies that met the inclusion criteria, there was no available evidence for assessment of these outcomes.

More information on the evidence can be found in the systematic review (Sayre *et al unpublished evidence*).

Certainty of the Evidence

Low

The GDG judged the overall certainty of evidence for all critical outcomes to be low.

More information on the certainty of evidence assessments can be found in the 'research evidence' tab associated with this recommendation online or in the annex of the pdf version.

Values and preferences

There was no available evidence for assessing preferences or values. The GDG determined that there was probably no important uncertainty or variability in how the main outcomes assessed for MDA are valued across contexts.

Resources

There was limited evidence on the cost-effectiveness of MDA in emergency settings. One study estimated that

MDA in an emergency setting cost US$ 46 per malaria case averted.

More information on the evidence can be found in the systematic review (Sayre *et al unpublished evidence*).

Equity

No evidence was available to assess equity.

Acceptability

Acceptability of MDA was high, despite challenges to implementation in emergency settings.

More information on the evidence can be found in the systematic review (Sayre *et al unpublished evidence*).

Feasibility

Accurate estimation of the target population, supervision of field staff, and inconsistencies in drug supply were among the challenges cited in reports of MDA use in emergency settings.

More information on the evidence can be found in the systematic review (Sayre *et al unpublished evidence*).

Justification

This recommendation was developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework *[103]*.

Sources of information

WHO commissioned a systematic review to inform this recommendation on MDA in emergencies or periods of health service disruption. The systematic review aimed to determine whether people residing in malaria-endemic settings during an emergency, in a period of health service disruption, or during a febrile illness epidemic should be given an antimalarial for chemoprevention through MDA. Secondary objectives included summarizing evidence on contextual factors that affect the implementation of MDA in emergencies. Two studies were included in the quantitative assessment – neither of which was a randomized controlled trial. These studies were conducted in Sierra Leone and the Democratic Republic of the Congo with, respectively, two rounds of artesunate-amodiaquine (AS-AQ) given five weeks apart and two rounds of AS-AQ followed by one round of pyronaridine-artesunate 4–7 weeks apart (Sayre *et al unpublished evidence*). The evidence was reviewed by the GDG using the Evidence-to-Decision framework in October 2021.

The overall certainty of the evidence regarding the use of MDA in emergency settings was low and the complexity of conducting research in emergency settings was noted by the GDG. Despite the limited evidence of MDA impact on disease in emergency settings, the GDG considered that the biological effects of MDA on disease in non-emergency settings would likely translate to MDA recipients in emergency settings. The size of effect will likely vary according to the type of emergency and level of disruption to health services, as well as factors affecting MDA impact such as underlying transmission intensity, delivery method, and other factors.

Summary of judgements

The GDG determined that the balance between desirable and undesirable effects favoured MDA in emergency settings, and resource requirements would likely vary depending on the nature of the emergency and the setting. In addition, the GDG judged that MDA in emergency settings is probably cost-effective; can be feasible, although this will vary depending on the context; would increase health equity; and is probably acceptable to key stakeholders. Consequently, the GDG concluded that a conditional recommendation should be made for MDA in emergency settings, highlighting the strong ethical and moral imperative for malaria prevention in these contexts.

Evaluation

It is acknowledged that the monitoring and evaluation of MDA in emergencies is particularly challenging. However, programmes should actively consider including systems for monitoring and evaluation to provide evidence for future

reviews of this recommendation.

4.2.6.3 MDA to reduce transmission of *P. falciparum* in very low to low transmission settings

Conditional recommendation for , Low certainty evidence

MDA to reduce transmission of *P. falciparum* in very low to low transmission settings (2022)

In areas with very low to low levels of *P. falciparum* transmission, antimalarial medicine can be given as chemoprevention through mass drug administration (MDA) to reduce transmission.

- *MDA may quickly reduce transmission of P. falciparum in very low to low transmission areas, but the effect wanes within 1–3 months. Therefore, if MDA is implemented, it should be one of several components of a robust malaria elimination programme (including, at minimum, good coverage of case-based surveillance with parasitological diagnosis, effective antimalarial treatment, and appropriate prevention tools and strategies) in order to reduce the risk of resurgence after the MDA programme has ended.*
- *MDA should be considered only for geographical areas where there is limited risk of importation of malaria either from adjacent communities or through travel of the population to endemic areas.*
- *Malaria programmes should consider whether sufficient resources are available to implement MDA without affecting other components of a robust malaria elimination programme.*
- *Very low to low transmission settings are defined as areas with P. falciparum parasite prevalence less than 10%, or P. falciparum incidence less than 250 cases per 1000 population per year [30]. These thresholds should not be regarded as absolutes for determining applicability of MDA implementation for transmission reduction. MDA implemented in areas with levels of transmission near these cut-offs may reduce both disease burden and transmission intensity.*

Practical Info

The WHO guidance document, *Mass drug administration for falciparum malaria: a practical field manual* provides technical and operational guidance on the practical aspects of organizing a successful MDA program *[141]*.

MDA has been found to have a short-term (1–3 months) impact on *P. falciparum* transmission in very low to low transmission areas. For MDA to contribute meaningfully towards achievement of malaria elimination, activities must already be in place to capitalize on the reduction in transmission achieved through the strategy. For that reason, if MDA is implemented, it should be as one component of a robust malaria elimination programme that includes, at minimum, good coverage of case-based surveillance, quality-assured parasitological diagnosis, effective antimalarial treatment and additional prevention strategies such as vector control. MDA will have maximal benefit to an elimination programme if the aim is to reduce transmission to the level that intensive surveillance and follow-up of every case can begin.

MDA is likely to be most effective at reducing transmission in geographical areas where there is limited risk of importation of malaria either from adjacent communities or through travel of the population to endemic areas. Additionally, MDA rounds should be scheduled for time periods when populations exhibit low levels of movement in and out of the area in order to increase coverage of the intervention and reduce risk of importation. The impact of MDA will be greater, and last longer, if a large proportion of the population present in the area benefits from the treatment and prophylaxis provided by the medicine and if the rate of parasite importation is low.

The frequency of rounds and duration of the MDA programme should take into account the local malaria epidemiology, the length of the prophylactic period provided by the antimalarial used, and the feasibility and cost of delivering each additional round. Consistent with trial data, mathematical models predicted that a single round of MDA would lead to an initial decrease in infections, but that the duration of effect would be short lived. Application of additional rounds is predicted to substantially improve the impact and duration of effect, but attempts should be made in later rounds to reach individuals who did not participate in earlier rounds.

Achieving high coverage of the population and good adherence to the antimalarial medicine are critical aspects of MDA programmes. MDA programmes ask many asymptomatic, healthy people to take a medicine when they do not feel ill, with the potential for adverse reactions to occur. Improving coverage and adherence requires development of understanding and trust in the institutions implementing the programme. Community engagement is thus a key factor in

determining the success of MDA in order to improve participation rates and adherence to the full treatment course of the medicine.

A complete therapeutic course of antimalarial medicine, at doses recommended by the manufacturer, should be given to all eligible adults and children within the defined geographic area. Drug dosage should be determined by weight wherever possible, with dosing according to age only in situations where the person's weight is unknown. The antimalarial medicines chosen for use in MDA should: a) be WHO recommended and prequalified; b) be efficacious against local parasites; c) be different from the medicine used as first-line treatment, where possible c) have a superior safety and tolerability profile; d) provide a longer duration of post-treatment prophylaxis with component medicines that have closely matched pharmacology to reduce the risk of new infections encountering only a single drug; e) have a positive public reputation and acceptability and f) be available and low-cost. Programmes may consider including a single, low-dose of primaquine in MDA programmes in order to increase the gametocytocidal effect, although the evidence was insufficient to discern an additional benefit of single low-dose primaquine. A drug regimen that can be administered as a directly-observed single dose is preferred to multi-day regimens.

Depending on the medicine chosen, certain population groups may need to be excluded from MDA, such as: pregnant women in their first trimester; infants < 6 months of age or weighing < 5kgs; people recently treated with the same medicine; people with a known allergy to the medicine; anyone with severe acute illness or unable to take oral medication; people taking medication known to interact with the medicine used for MDA; and people with specific contraindications to the medicine used *[141]*. MDA should not be given to individuals receiving other forms of malaria chemoprevention (e.g. seasonal malaria chemoprevention, perennial malaria chemoprevention, or intermittent preventive treatment during pregnancy).

Evidence To Decision

Benefits and harms

The systematic review identified eight community-randomized controlled trials (cRCTs) in very low to low transmission settings in six countries (Cambodia, Lao People's Democratic Republic, Myanmar, United Republic of Tanzania, Viet Nam, and Zambia) assessing the impact of MDA on *P. falciparum* to no MDA (Schneider *et al* *unpublished evidence* (*b*)). The time periods for results were grouped as 1–3, 4–12 and 12–24 months after the last round of MDA. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available under Research evidence.

Immediate-to-short-term benefit 1–3 months after the last round of MDA

- MDA probably reduces *P. falciparum* prevalence (risk difference [RD]: -18 cases per 1000 persons; 95% CI: -20 to -14 per 1000 persons; eight cRCTs; moderate-certainty evidence).
- MDA probably reduces the incidence of *P. falciparum* (RD: -8 cases per 1000 p-y; 95% CI: -10 to -4 per 1000 p-y; one cRCT; moderate-certainty evidence).
- MDA may result in little to no difference in the incidence of *P. falciparum* clinical malaria (RD: -3 cases per 1000 p-y; 95% CI: -5 to 11 per 1000 p-y; two cRCTs; low-certainty evidence).

Medium-term benefit 4–12 months after the last round of MDA

- MDA may result in little to no difference in *P. falciparum* prevalence (RD: -3 per 1000 persons; 95% CI: -8 to 4 per 1000 persons; six cRCTs; low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on the incidence of *P. falciparum* clinical malaria (RD: -6 per 1000 p-y; 95% CI: -9 to 0 per 1000 p-y; four cRCTs; very low-certainty evidence).

Long-term benefit 12–24 months after the last round of MDA

- The evidence is very uncertain about the effect of MDA on the prevalence of *P. falciparum* (RD: -21 per 1000 persons; 95% CI: -30 to 31 per 1000 persons; one cRCT; very low-certainty evidence).
- MDA may reduce the incidence of *P. falciparum* clinical malaria (RD: -4 per 1000 p-y; 95% CI: 14 to 34 per 1000 p-y; one cRCT; low-certainty evidence).

Serious adverse events

- At 0–3 months, MDA probably has little to no effect on serious adverse events (RD: 1 per 1000 persons; 95% CI: 0 to 11 per 1000 persons; one cRCT; moderate-certainty evidence).
- At 4–12 months, MDA may increase serious adverse events slightly (RD: 2 per 1000 persons; 95% CI: -1 to 8 per 1000 persons; one cRCT; moderate-certainty evidence).
- Among people who participated in MDA, the rate of serious adverse events was 0.03 per 1000 doses of antimalarial medicine (four cRCTs; not GRADEd because no information was available from the comparator arm).

Adverse events

- At 1–3 months, the evidence is very uncertain about the effect of MDA on adverse events (RD: 300 per 1000 persons; 95% CI: -43 to 1 937 per 1000 persons; one cRCT; very low-certainty evidence).
- Among people who participated in MDA, the rate of adverse events was 4.6 per 1000 doses of antimalarial medicine (four cRCTs; not GRADEd because no information was available from the comparator arm).

Artemisinin resistance markers (PfKelch13)

- At 1–3 months after the last round, the evidence is very uncertain about the effect of MDA on artemisinin resistance markers (PfKelch13) among *P. falciparum* infections (RD: -109 per 1000 persons; 95% CI: -334 to 310 per 1000 persons; one cRCT very low-certainty evidence).
- At 1–3 months after the last round MDA may reduce the proportion of artemisinin resistance markers (PfKelch13) among all participants (RD: -56 per 1000 persons; 95% CI: -61 to -45 per 1000 persons; one cRCT; low-certainty evidence).
- At 4–12 months after the last round, the evidence is very uncertain about the effect of MDA on the proportion of infections with artemisinin resistance markers (PfKelch13) among all *P. falciparum* infections (RD: 98 per 1000 persons; 95% CI: -104 to 372 per 1000 persons; one cRCT; very low-certainty evidence).
- At 4–12 months after the last round, MDA may reduce the proportion of artemisinin resistance markers (PfKelch13) among all participants (RD: -15 per 1000 persons; 95% CI: -21 to -4 per 1000 persons; one cRCT; low-certainty evidence).
- At 12–24 months after the last round, the evidence is very uncertain about the effect of MDA on the proportion of infections with artemisinin resistance markers (PfKelch13) among all *P. falciparum* infections (RD: 50 per 1000 persons; 95% CI: -129 to 286 per 1000 persons; one cRCT; very low-certainty evidence).
- At 12–24 months after the last round, MDA may reduce the proportion of artemisinin resistance markers (PfKelch13) among all participants (RD: -9 per 1000 persons; 95% CI: -15 to 3 per 1000 persons; one cRCT; low-certainty evidence).

Judgement of the panel

The GDG noted the difficulty in judging the effect of MDA on *P. falciparum* in very low to low transmission settings given the small number of studies identified by the systematic review with outcomes of interest and the overall low certainty of the evidence. The GDG assessed the size of the desirable effects to be moderate and the undesirable effects to be small. The GDG judged the balance of effects to probably favour MDA for *P. falciparum* in areas of very low to low transmission, although there was concern about the sustainability of impact if only one or two rounds are conducted.

Certainty of the Evidence

Low

The overall certainty of the evidence was judged to be low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in the preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified four studies with information on resource needs for MDA (Schneider *et al* *unpublished evidence (b)*). The cost of MDA varied from ~US$ 1.04 to US$ 19.40 per person per round; one study estimated that drugs accounted for 70% of the cost of MDA. Compared to reactive drug administration (RDA), MDA was superior in all cost-effectiveness measures, including cost per infection averted, cost per case averted, cost per death averted, and cost per disability-adjusted life year (DALY) averted. Furthermore, the cost of MDA per person reached was substantially lower in an operational setting (US$ 2.90) than in a research setting (US$ 4.71).

The GDG judged the resources required to implement MDA to be large. The GDG found it difficult to judge the cost-effectiveness of MDA as the evidence of an effect was of low certainty, and both the effectiveness and cost of the intervention are likely to vary depending on the time period over which outcomes are measured and whether elimination is achieved. However, the GDG concluded that cost-effectiveness in very low to low transmission areas probably favoured the intervention.

Equity

No studies were identified that addressed the issue of whether MDA increased or decreased health equity.

The GDG judged that the impact of MDA on equity is likely to vary. While MDA has the potential to reach people who might have difficulty accessing other malaria prevention and treatment services, MDA might also expose many people to antimalarials who were not infected. The GDG felt that MDA could exacerbate inequity if not implemented appropriately or if implementation resulted in only a small, temporary effect. However, if implementation of MDA contributed to elimination of *P. falciparum*, then the intervention would likely improve equity.

Acceptability

The systematic review identified 18 studies with information on acceptability (Schneider *et al* *unpublished evidence (b)*). The most common barrier to acceptability of MDA reported in the literature was fear of adverse events. Two studies found that participants were concerned that adverse events from MDA might inhibit their economic productivity, although in another study respondents felt that malaria infection was more likely to limit economic activity than adverse events from MDA.

One study found that, in addition to sensitization on the benefits of MDA, providing healthcare to communities participating in MDA helped to reduce concerns about adverse effects; however, another study found that the presence of expatriate physicians, an ambulance, and the unfamiliar informed consent process elevated rather than reduced concerns. Previous experience reinforced initial perceptions of MDA: individuals who had been part of previous MDA trials shared stories in their communities; if those experiences were poor, community members had negative impressions of MDA. In areas where other malaria interventions had been implemented effectively, MDA for malaria was viewed more positively. One study found that reported acceptability of MDA increased from 62% before the intervention to 98% after, while the proportion of respondents who answered that MDA could cause side effects decreased from 30% to 20% in the same timeframe.

Common themes in analyses of drivers of acceptance were sensitization or education about the intervention, support from a range of local authority figures, and additional health support. One study reported that “Respondents who felt that they have received enough information… were more likely to participate in all rounds of MDA,” a theme that was reiterated in five other studies.

One study found that a lack of engagement with local healthcare providers limited adherence due to conflicting messages around the efficacy of MDA.

The GDG judged the acceptability of MDA for *P. falciparum* in very low to low transmission settings to vary depending on whether factors that affect community and individual acceptability have been appropriately addressed in the design of the intervention. The GDG considered that a country's previous experience with MDA, whether positive or negative, was likely to affect their level of acceptance of the intervention. The GDG suggested that a key consideration was whether malaria programme staff find MDA to be an acceptable intervention, but no surveys of this key stakeholder were identified.

Feasibility

The systematic review identified 13 studies providing information on the feasibility of implementation of MDA (Schneider *et al unpublished evidence (b)*). Ten studies described barriers to implementing MDA due to residents' absence. Of these, three studies noted that absenteeism was one of the major driving forces of non-adherence to medicine. One study noted that determining participants' seasonal mobility prior to the MDA campaign had contributed to the success of the campaign. Three studies noted difficulties related to determining the optimal timing of the MDA campaign: weather-related challenges, agricultural activities, overlaps with religious events, especially those involving fasting, unpredictable policy changes at the national level and the school year. Feasibility concerns related to participants' religion were further noted in one study that attempted to implement directly observed drug administration but found that some women were unwilling to remove their face coverings in front of strangers. This issue was resolved by creating sequestered administration sites staffed by accepted local staff.

The GDG judged the feasibility of implementing MDA to vary depending on the size of the population, with improved feasibility in smaller populations and island communities.

Justification

The systematic review of the impact of MDA on *P. falciparum* identified significant heterogeneity in the meta-analysis of a key outcome (prevalence of infection 1–3 months after the last round of MDA) (Schneider *et al unpublished evidence (b)*). A subgroup analysis found that the heterogeneity between studies could be explained by differences between higher and lower transmission settings. In the systematic review, a cut-off of 10% prevalence of *P. falciparum* infection and incidence of 250 *P. falciparum* cases per 1000 population per year was used to differentiate between areas of very low to low transmission and areas of moderate to high transmission. As higher transmission settings have a larger parasite reservoir, higher rate of new infections and often greater vectorial capacity than lower transmission settings, it is biologically plausible for MDA to have a differential impact on transmission reduction depending on the transmission setting. As a result, the systematic review stratified all analyses by transmission setting, and separate recommendations were developed on the use of MDA for reducing transmission of *P. falciparum* in very low to low and moderate to high transmission areas.

The GDG concluded that the balance of effects probably favoured implementation of MDA to reduce *P. falciparum* transmission in very low to low transmission settings although there were concerns about the sustainability of impact if only one or two rounds are implemented. The GDG judged that the resources required for implementation of MDA were large and could impact negatively on the implementation of other recommended malaria prevention strategies. While there were limited data on cost-effectiveness, the GDG judged that cost-effectiveness probably favoured MDA but would depend on the time period over which outcomes were measured; if elimination were achieved, in part, through MDA, the cost-effectiveness would be very high. The GDG judged that the acceptability of the intervention was likely to vary depending on the stakeholder group and the population's previous experience with MDA. The feasibility of implementing the intervention was judged to vary depending on the size of the population to be covered. The GDG concluded that a conditional recommendation for MDA for *P. falciparum* in very low to low transmission settings should be issued given the moderate-certainty evidence for a short-term benefit, variability around issues such as acceptability and feasibility and large resource requirements.

Research Needs

- Further evidence is needed on the impact (incidence or prevalence of malaria infection at the community level) and potential harms/unintended consequences of MDA for *P. falciparum* in very low to low transmission areas, including resistance to antimalarial medicines. Evidence of impact disaggregated by sex, age and socioeconomic status is needed to understand whether there are any equity considerations.
- Determine the optimal timing and number of MDA rounds to maximize the impact (incidence or prevalence of

malaria infection at the community level) of MDA on *P. falciparum* in very low to low transmission areas.
- Determine the minimum effective coverage of MDA in the population to maximize the impact (incidence or prevalence of malaria infection at the community level) of MDA on *P. falciparum* in very low to low transmission areas.
- Determine whether multiple years of effective coverage of MDA as part of an elimination programme is feasible and acceptable and whether it can contribute to interrupting *P. falciparum* transmission in very low to low transmission areas.
- Investigate approaches to improving the acceptability of MDA and adherence to antimalarial medicines in very low to low transmission areas.
- Determine whether the addition of single, low-dose primaquine modifies the impact (incidence or prevalence of malaria infection at the community level) of MDA on *P. falciparum* in very low to low transmission areas.

4.2.6.4 MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings

Conditional recommendation against , Very low certainty evidence

MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings (2022)

In areas with moderate to high levels of *P. falciparum* transmission, providing antimalarial medicine through mass drug administration (MDA) to reduce transmission is not recommended.

- *The studies included in the systematic review did not demonstrate evidence that MDA has either a short- or long-term effect on P. falciparum transmission in moderate to high transmission settings.*
- *Recommendations on MDA to reduce the burden of malaria in moderate to high transmission settings can be found in section 4.2.4.1 MDA for burden reduction. Moderate to high transmission settings are defined as areas with P. falciparum parasite prevalence greater than 10%, or P. falciparum incidence above 250 cases per 1000 population per year [30]. These thresholds should not be regarded as absolutes for determining applicability of MDA.*

Evidence To Decision

Benefits and harms

The systematic review identified two cRCTs and two nonrandomised studies (NRSs) in moderate to high transmission settings in four countries (Burkina Faso, Gambia, Nigeria and Zambia) assessing the impact of MDA on *P. falciparum* compared to no MDA (Schneider *et al* *unpublished evidence* *(b)*). The time periods for results were grouped as 1–3, 4–12 and 12–24 months after the last round of MDA; cRCTs and NRS were analysed and GRADEd separately. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Immediate-to-short-term benefits 1–3 months after the last round of MDA

- MDA may result in little to no difference in *P. falciparum* prevalence (RD: 38 cases per 1000 persons; 95% CI: -21 to 219 per 1000 persons; one cRCT; low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on *P. falciparum* prevalence (RD: -108 per 1000 persons; 95% CI: -159 to -51 per 1000 persons; one NRS; very low-certainty evidence).
- MDA probably reduces the incidence of *P. falciparum* parasitaemia (RD: -22 per 1000 p-y; 95% CI: -34 to -5 per 1000 p-y; one cRCT; moderate-certainty evidence).
- MDA may result in little to no difference in the incidence of *P. falciparum* clinical malaria (RD: -1 per 1000 p-y; 95% CI: -2 to 8 per 1000 p-y; one cRCT; low-certainty evidence).

Medium-term benefit 4–12 months after the last round of MDA

- MDA may result in little to no difference in *P. falciparum* prevalence (RD: -87 per 1000 persons; 95% CI: -53 to 271 per 1000 persons; one cRCT; low-certainty evidence).

- MDA may reduce *P. falciparum* prevalence (RD: -167 per 1000 persons; 95% CI: -188 to -138 per 1000 persons; one NRS; low-certainty evidence)
- The evidence is very uncertain about the effect of MDA on the incidence of *P. falciparum* parasitaemia (RD: -10 per 1000 p-y; 95% CI: -49 to 54 per 1000 p-y; one cRCT; very low-certainty evidence).

Long-term benefit 12–24 months after the last round of MDA

- MDA may reduce *P. falciparum* prevalence (RD: -99 per 1000 p-y; 95% CI: -129 to -69 per 1000 p-y; one NRS; low-certainty evidence).

Serious adverse events

- Among people who participated in MDA, the rate of serious adverse events was 0.01 per 1000 doses of antimalarial medicine (one cRCT; not GRADEd because no information was available from the comparator arm).

Adverse events

- The evidence is very uncertain about the effect of MDA on adverse events (RD: 200 per 1000 persons; 95% CI: -39 to 572 per 1000 persons; one cRCT; very low-certainty evidence).
- Among people who participated in MDA, the rate of adverse events was 2.0 per 1000 doses of antimalarial medicine (one cRCT; not GRADEd because no information was available from the comparator arm).

Judgement of the panel
The GDG noted the difficulty in judging the effect of MDA on *P. falciparum* in moderate to high transmission settings given how few studies with the outcomes of interest were identified by the systematic review and the overall very low certainty of evidence. The GDG judged that the sizes of both the desirable and undesirable effects were small, and the balance of effects probably did not favour MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings. In addition, the GDG was concerned that any impact of MDA would be very short-lived in a moderate to high transmission setting.

Certainty of the Evidence

Very low

The overall certainty of evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified four studies with information on resource needs for MDA (Schneider *et al* *unpublished evidence* (*b*)). The cost of MDA varied from ~US$ 1.04 to US$ 19.40 per person per round; one study estimated that drugs accounted for 70% of the cost of MDA. Compared to reactive drug administration (RDA), MDA was superior in all cost-effectiveness measures, including cost per infection averted, cost per case averted, cost per death averted, and cost per disability-adjusted life year (DALY) averted. Furthermore, the cost of MDA per person reached was substantially lower in an operational setting (US$ 2.90) than in a research setting (US$ 4.71).

The GDG judged the resources required to implement MDA to be large. The GDG judged that cost-effectiveness

probably favoured no MDA but found it difficult to judge the cost-effectiveness of MDA as the evidence for an effect was of very low certainty and both the effectiveness and cost of the intervention are likely to vary depending on the time period over which they are measured.

Equity

The systematic review did not identify any research that addressed the issue of how MDA affects health equity.

The GDG judged the impact of implementing MDA on equity to vary. While MDA had the potential to reach people who might have difficulty accessing other malaria prevention and treatment services, it also exposes uninfected people to the potential adverse effects of antimalarials. The GDG felt that MDA could exacerbate inequity if not implemented appropriately or if implementation resulted only in a small, temporary effect.

Acceptability

The systematic review identified 18 studies with information on acceptability (Schneider *et al* *unpublished evidence (b)*). The most common barrier to acceptability of MDA reported in the literature was fear of adverse events. Two studies found that participants were concerned that adverse events from MDA might inhibit their economic productivity, although in another study respondents felt that malaria infection was more likely to limit economic activity than adverse events.

One study found that, in addition to sensitization on the benefits of MDA, providing healthcare to communities participating in MDA helped to reduce concerns about adverse effects; however, another study found that the presence of expatriate physicians, an ambulance, and the unfamiliar informed consent process elevated rather than reduced concerns. Previous experience reinforced initial perceptions of MDA: individuals who had been part of previous MDA trials shared stories in their communities; if those experiences were poor, community members had negative impressions of MDA. In areas where other malaria interventions had been implemented effectively, MDA for malaria was viewed more positively. One study found that reported acceptability of MDA increased from 62% before the intervention to 98% after, while the proportion of respondents who answered that MDA could cause side effects decreased from 30% to 20% in the same timeframe.

Common themes in analyses of drivers of acceptance were sensitization or education about the intervention, support from a range of local authority figures, and additional health support. One study reported that “Respondents who felt that they have received enough information… were more likely to participate in all rounds of MDA,” a theme that was reiterated in five other studies.

One study found that a lack of engagement with local healthcare providers limited adherence due to conflicting messages around the efficacy of MDA.

The GDG judged the acceptability of MDA for *P. falciparum* in moderate to high transmission settings to depend on whether factors that affect community and individual acceptability have been appropriately addressed in the design of the intervention. The GDG considered that a country’s previous experience with MDA, whether positive or negative, was likely to affect their level of acceptance of the intervention. The GDG suggested that a key consideration was whether malaria programme staff find MDA to be an acceptable intervention, but no surveys of this key stakeholder were identified.

Feasibility

The systematic review identified 13 studies providing information on the feasibility of implementation of MDA (Schneider *et al* *unpublished evidence (b)*). Ten studies described barriers to implementing MDA due to residents’ absence. Of these, three studies noted that absenteeism was one of the major driving forces of non-adherence to medicine. One study noted that determining participants’ seasonal mobility prior to the MDA campaign had contributed to the success of the campaign. Three studies noted difficulties related to determining the optimal timing of the MDA campaign: weather-related challenges, agricultural activities, overlaps with religious events,

especially those involving fasting, unpredictable policy changes at the national level and the school year. Feasibility concerns related to participants' religion were further noted in one study that attempted to implement directly observed drug administration but found that some women were unwilling to remove their face coverings in front of strangers. This issue was resolved by creating sequestered administration sites staffed by accepted local staff.

The GDG judged the feasibility of implementing MDA to vary depending on the size of the population, with improved feasibility in smaller populations and island communities.

Justification

The GDG judged that the balance of effects probably favoured not implementing MDA to reduce *P. falciparum* transmission in moderate to high transmission settings. The GDG judged that the resources required for implementation of MDA were large and could impact negatively on the implementation of other recommended malaria prevention strategies. While cost-effectiveness data were limited, the GDG judged that cost-effectiveness probably did not favour MDA in moderate to high transmission settings. The GDG judged that the acceptability of the intervention was likely to vary depending on the stakeholder group and previous experience of the population with MDA. The feasibility of implementing the intervention was judged to vary depending on the size of the population to be covered. The GDG concluded that there should be a conditional recommendation against the implementation of MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings given the lack of evidence for either a short- or long-term benefit, variability around issues such as acceptability and feasibility and large resource requirements.

4.2.6.5 MDA to reduce transmission of *P. vivax*

Conditional recommendation for , Very low certainty evidence

MDA to reduce transmission of *P. vivax* (2022)

In areas with *P. vivax* transmission, antimalarial medicine can be given as chemoprevention through mass drug administration (MDA) to reduce transmission.

- *MDA may quickly reduce transmission of P. vivax, but the effect wanes within 1–3 months. Therefore, if MDA is implemented, it should be one of several components of a robust malaria elimination programme (including, at minimum, good coverage of case-based surveillance with parasitological diagnosis, effective antimalarial treatment including treatment for hypnozoites, and appropriate prevention tools and strategies) in order to reduce the risk of resurgence after the MDA programme has ended.*
- *MDA should be considered only for geographical areas where there is limited risk of importation of malaria either from adjacent communities or through travel of the population to endemic areas.*
- *Malaria programmes should consider whether sufficient resources are available to implement MDA without affecting other components of a robust malaria elimination programme.*
- *Programmes considering implementing MDA for P. vivax should carefully reflect on how to safely and feasibly administer treatment to prevent relapses.*

Practical Info

MDA without an 8-aminoquinoline medicine may have a short-term (1–3 months) impact on *P. vivax* transmission. For MDA to contribute meaningfully towards achievement of malaria elimination, activities must already be in place to capitalize on the reduction in transmission achieved through the strategy. For that reason, MDA should be implemented as a component of a robust malaria elimination programme that includes, at minimum, good coverage of case-based surveillance, quality-assured parasitological diagnosis, effective antimalarial treatment and additional prevention strategies such as vector control. MDA will have maximal benefit to an elimination programme if the aim is to reduce transmission to the level that intensive surveillance and follow-up of every case can begin.

MDA is likely to be most effective at reducing transmission in geographical areas where there is limited risk of importation of malaria either from adjacent communities or through travel of the population to endemic areas. Additionally, MDA rounds should be scheduled for time periods when populations exhibit low levels of movement in and

out of the area in order to increase coverage of the intervention and reduce risk of importation. The impact of MDA will be greater, and last longer, if a large proportion of the population present in the area benefits from the treatment and prophylaxis provided by the medicine and if the rate of parasite importation is low.

The frequency of rounds and duration of the MDA programme should take into account the local malaria epidemiology, the half-life of the antimalarial used, and the feasibility and cost of delivering each additional round. Consistent with trial data, mathematical models predicted that a single round of MDA would lead to an initial decrease in infections, but that the duration of effect would be short lived. Application of additional rounds is predicted to substantially improve the impact and duration of effect.

Achieving high coverage of the population and good adherence to the antimalarial medicine are critical aspects of MDA programmes. MDA programmes ask many asymptomatic, healthy people to take a medicine when they do not feel ill, with the potential for adverse reactions to occur. Improving coverage and adherence requires development of understanding and trust in the institutions implementing the programme. Community engagement is thus a key factor in determining the success of MDA, to improve participation rates and adherence to the full treatment course of the medicine.

A complete therapeutic course of antimalarial medicine, at doses recommended by the manufacturer, should be given to all eligible adults and children within the defined geographic area. Drug dosage should be determined by weight wherever possible, with dosing according to age only in situations where the person's weight is unknown. The antimalarial medicines chosen for use in MDA should: a) be WHO recommended and prequalified; b) be efficacious against local parasites; c) be different from the medicine used as first-line treatment, where possible c) have a superior safety and tolerability profile; d) provide a longer duration of post-treatment prophylaxis with component medicines that have closely matched pharmacology to reduce the risk of new infections encountering only a single drug; e) have a positive public reputation and acceptability and f) be available and low-cost. A drug regimen that can be administered as a directly-observed single dose is preferred to multi-day regimens.

Depending on the medicine chosen, certain population groups may need to be excluded from MDA, such as: pregnant women in their first trimester; infants < 6 months of age or weighing <5kgs; people recently treated with the same medicine; people with a known allergy to the medicine; anyone with severe acute illness or unable to take oral medication; people taking medication known to interact with the medicine used for MDA; and people with specific contraindications to the medicine used *[141]*. MDA should not be given to individuals receiving other forms of malaria chemoprevention (e.g. seasonal malaria chemoprevention, perennial malaria chemoprevention, or intermittent preventive treatment during pregnancy).

MDA for *P. vivax* is complicated because many *P. vivax* infections are likely to be dormant stages (hypnozoites) in the liver that will not be cured unless an 8-amnoquinoline, the only type of medicine that treats hypnozoites, is administered. Without provision of an 8-aminoquinoline, a large proportion of *P. vivax* cases treated in the MDA programme will relapse within a few months. However, programmes contemplating providing medicine for radical cure of *P. vivax* as part of MDA should carefully consider whether it is feasible to administer this treatment regimen safely, i.e. with testing for G6PD deficiency prior to treatment, an effective pharmacovigilance system and emergency access to blood transfusion services. Programmes should also consider whether sufficient coverage and adherence to the full course of radical cure can be achieved.

Evidence To Decision

Benefits and harms

The systematic review identified five cRCTs and six NRSs in eight countries (Cambodia, India, Lao People's Democratic Republic, Myanmar, Panama, Solomon Islands, Venezuela [Bolivarian Republic of] and Viet Nam) assessing the impact of MDA on *P. vivax* transmission to no MDA (Schneider *et al unpublished evidence (b)*). None of the cRCTs and only one of the NRSs used sufficient dosage of an 8-aminoquinoline to achieve radical cure of *P. vivax* hypnozoites[1]. The time periods for results were grouped as 1–3, 4–12 and 12–24 months after the last round of MDA. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Immediate-to-short-term benefits 1–3 months after the last round of MDA

- MDA may reduce *P. vivax* prevalence (RD: -113 per 1000 persons; 95% CI: -119 to -101 per 1000 persons; five

cRCTs; low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on *P. vivax* prevalence (RD: -189 per 1000 persons; 95% CI: -208 to -155 per 1000 persons; two NRSs; very low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on the incidence of *P. vivax* parasitaemia (risk difference [RD] low transmission: -3 per 1000 p-y; 95% CI: -3 to -3 per 1000. RD high transmission: -113 per 1000 p-y; 95% CI: -122 to -103 per 1000 p-y. two NRSs; very low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on the incidence of *P. vivax* clinical malaria (RD low transmission: -16 per 1000 p-y; 95% CI: -16 to -15 per 1000 p-y. RD high transmission: -111 per 1000 p-y; 95% CI: -115 to -108 per 1000 p-y. two NRSs; very low-certainty evidence).

Medium-term benefit 4–12 months after the last round of MDA

- MDA may result in little to no difference in *P. vivax* prevalence (RD: 1 per 1000 persons; 95% CI: -12 to 17 per 1000 persons; five cRCTs; low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on the prevalence of *P. vivax* (RD: -47 per 1000 persons;95% CI: -60 to -16 per 1000 persons; one NRS; very low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on the incidence of *P. vivax* clinical malaria (RD: -4 per 1000 p-y; 95% CI: -4 to -3 per 100 p-y; one NRS; very low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on the incidence of *P. vivax* clinical malaria (RD: -44 per 1000 p-y; 95% CI: -50 to -37 per 1000 p-y; one cRCT; very low-certainty evidence).

Long-term benefit 12–24 months after the last round of MDA

- MDA may result in little to no difference in *P. vivax* prevalence (RD: -33 per 1000 persons; 95% CI: -98 to 84 per 1000 persons; one cRCT; low-certainty evidence).
- The evidence is very uncertain about the effect of MDA on the incidence of *P. vivax* clinical malaria (RD: -150 per 1000 p-y; -153 to -145 per 1000 p-y; one NRS; very low-certainty evidence).

Serious adverse events

- MDA probably results in little to no difference in serious adverse events within 0–3 months of the last round of MDA (RD: 1 per 1000 persons; 95% CI: 0 to 11 per 1000 persons; one cRCT; moderate-certainty evidence).
- MDA probably results in little to no difference in serious adverse events 4–12 months after the last round of MDA (RD: 2 per 1000 persons; 95% CI: -1 to 8 per 1000 persons; one cRCT; moderate-certainty evidence).
- Among people who participated in MDA, the rates of adverse events and serious adverse events were 19.9 per 1000 and 0.3 per 1000 doses of antimalarial medicine, respectively (two cRCTs; not GRADEd because no information was available from the comparator arm).

Judgement of the panel

The GDG noted that there were important differences between the few studies included in the systematic review in terms of the background level of malaria transmission and other factors, which complicated the assessment of the balance of benefits and harms. Only one of the NRSs and none of the cRCTs identified by the systematic review used sufficient dosage of an 8-aminoquinoline for radical cure of the *P. vivax* hypnozoite reservoir. The GDG noted that the balance of effects could be different if radical cure of *P. vivax* was attempted as part of MDA. While a greater impact of MDA on *P. vivax* would be expected if relapses were prevented through treatment of hypnozoites, potential harms might increase from exposure of G6PD deficient individuals to an 8-aminoquinoline. Levels of acceptability and feasibility might decrease given the need to test for G6PD deficiency, establish or maintain an effective pharmacovigilance system and provide emergency access to blood transfusion services. Therefore, the GDG noted that there was limited evidence on the benefits and harms of including radical cure as part of MDA for *P. vivax* to inform the recommendation.

Cognizant of the limitations of the available evidence, the GDG judged that the sizes of both the desirable and

undesirable effects were small, and the balance of effects did not favour either MDA or no MDA for *P. vivax*.

[1]The systematic review considered the following as the minimum adult dosage of 8-aminoquinoline medicines to achieve radical cure: 210 mg of primaquine over eight weeks; 1.25 g of plasmochin over 14 days. One study considered its primaquine adult dosage regimen (40 mg of primaquine every two weeks for two years) to be radical cure, but as the total dose for an eight-week period (i.e. 160 mg) was less than 210 mg, the systematic review did not consider this to be radical cure (Schneider et al *unpublished evidence (b)*).

Certainty of the Evidence

Very low

The overall certainty of the evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in the preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified four studies with information on resource needs for MDA (Schneider *et al unpublished evidence (b)*). The cost of MDA varied from ~US$ 1.04 to US$ 19.40 per person per round; one study estimated that drugs accounted for 70% of the cost of MDA. Compared to reactive drug administration (RDA), MDA was superior in all cost-effectiveness measures, including cost per infection averted, cost per case averted, cost per death averted, and cost per disability-adjusted life year (DALY) averted. Furthermore, the cost of MDA per person reached was substantially lower in an operational setting (US$ 2.90) than in a research setting (US$ 4.71).

The GDG judged the resources required to implement MDA to be large. The GDG found it difficult to judge the cost-effectiveness of MDA as there were no data on cost or cost-effectiveness identified in the studies of *P. vivax*. The GDG judged that the effectiveness and cost of MDA are likely to vary depending on the time period over which they are measured and whether elimination is achieved.

Equity

The systematic review did not identify any research that addressed the issue of how MDA affects health equity.

The GDG judged the impact of implementing MDA on equity to vary. While MDA had the potential to reach people who might have difficulty accessing other malaria prevention and treatment services, it also exposes uninfected people to the potential adverse effects of antimalarials. The GDG felt that MDA could exacerbate inequity if not implemented appropriately or if implementation resulted only in a small, temporary effect.

Acceptability

The systematic review identified 18 studies with information on acceptability (Schneider *et al unpublished evidence (b)*). The most common barrier to acceptability of MDA reported in the literature was fear of adverse events. Two studies found that participants were concerned that adverse events from MDA might inhibit their economic productivity, although in another study respondents felt that malaria infection was more likely to limit economic activity than adverse events.

One study found that, in addition to sensitization on the benefits of MDA, providing healthcare to communities participating in MDA helped to reduce concerns about adverse effects; however, another study found that the

presence of expatriate physicians, an ambulance, and the unfamiliar informed consent process elevated rather than reduced concerns. Previous experience reinforced initial perceptions of MDA: individuals who had been part of previous MDA trials shared stories in their communities; if those experiences were poor, community members had negative impressions of MDA. In areas where other malaria interventions had been implemented effectively, MDA for malaria was viewed more positively. One study found that reported acceptability of MDA increased from 62% before the intervention to 98% after, while the proportion of respondents who answered that MDA could cause side effects decreased from 30% to 20% in the same timeframe.

Common themes in analyses of drivers of acceptance were sensitization or education about the intervention, support from a range of local authority figures, and additional health support. One study reported that "Respondents who felt that they have received enough information… were more likely to participate in all rounds of MDA," a theme that was reiterated in five other studies.

One study found that a lack of engagement with local healthcare providers limited adherence due to conflicting messages around the efficacy of MDA.

The GDG judged that the acceptability of MDA for *P. vivax* would vary depending on whether factors that affect community and individual acceptability have been appropriately addressed in the design of the intervention.

The GDG considered that a country's previous experience with MDA, whether positive or negative, was likely to affect their level of acceptance of the intervention. The GDG suggested that a key consideration is whether malaria programme staff find MDA to be an acceptable intervention, but no surveys of this key stakeholder were identified. The GDG felt that the inclusion of an 8-aminoquinoline in MDA for radical cure would likely have a negative effect on the acceptability of the intervention due to safety concerns and the long treatment period.

Feasibility

The systematic review identified 13 studies providing information on the feasibility of implementation of MDA (Schneider *et al unpublished evidence (b)*). Ten studies described barriers to implementing MDA due to residents' absence. Of these, three studies noted that absenteeism was one of the major driving forces of non-adherence to medicine. One study noted that determining participants' seasonal mobility prior to the MDA campaign had contributed to the success of the campaign. Three studies noted difficulties related to determining the optimal timing of the MDA campaign: weather-related challenges, agricultural activities, overlaps with religious events, especially those involving fasting, unpredictable policy changes at the national level and the school year. Feasibility concerns related to participants' religion were further noted in one study that attempted to implement directly observed drug administration but found that some women were unwilling to remove their face coverings in front of strangers. This issue was resolved by creating sequestered administration sites staffed by accepted local staff.

The GDG judged the feasibility of implementing MDA for *P. vivax* to vary depending on the size of the population, with improved feasibility in smaller populations and island communities. Feasibility would also vary depending on whether radical cure using an 8-aminoquinoline medicine was part of the MDA strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

Justification

The GDG concluded that the balance of effects did not favour either MDA or no MDA to reduce *P. vivax* transmission. There was a lack of studies evaluating the efficacy and safety of MDA drug regimens that included an 8-aminoquinoline for radical cure of *P. vivax*; the GDG expressed concern both for the likely decreased long-term effectiveness of MDA for *P. vivax* without use of an 8-aminoquinoline and the increased complexity of safely administering 8-aminoquinolines. The GDG judged that the resources required for implementation of MDA were large and could impact negatively on the implementation of other recommended malaria strategies. While cost-effectiveness data were limited, the GDG judged that cost-effectiveness probably favoured MDA to reduce *P. vivax* transmission but would depend on the time period over which it was measured and whether elimination was achieved. The GDG judged that the acceptability of the intervention was likely to vary depending on the stakeholder group, the population's previous experience with MDA and whether radical cure with an 8-aminoquinoline was included. The feasibility of implementing the intervention was judged to vary depending on the size of the population to be covered and whether radical cure, with the need for G6PD deficiency testing, an effective pharmacovigilance system and emergency access to blood transfusion services, was

included in the MDA programme.

The GDG concluded that MDA could be a useful intervention if it reduced *P. vivax* transmission quickly to enable the initiation of intensive surveillance activities. The GDG therefore proposed a conditional recommendation for the use of MDA for *P. vivax*.

Research Needs

- Further evidence is needed on the impact (incidence or prevalence of malaria infection at the community level) and potential harms/ unintended consequences of MDA for *P. vivax*.
- Evidence is needed on the acceptability, feasibility, impact (incidence or prevalence of malaria infection at the community level) and potential harms/unintended consequences (death, hospital admission, severe anaemia or any severe adverse event) of safe provision (including testing for G6PD deficiency and, additionally, an effective pharmacovigilance system and emergency access to blood transfusion services) of an 8-aminoquinoline as part of MDA for radical cure of *P. vivax*.
- Determine the optimal timing and number of MDA rounds to maximize the impact (incidence or prevalence of malaria infection at the community level) of MDA on *P. vivax*.
- Determine the minimum effective coverage of MDA in the population to maximize the impact (incidence or prevalence of malaria infection at the community level) of MDA on *P. vivax*.
- Determine whether the degree of geographical isolation of communities or mobility of the population modifies the impact (incidence or prevalence of malaria infection at the community level) of MDA on *P. vivax*.

4.2.6.6 Mass relapse prevention (MRP) to reduce transmission of *P. vivax*

Conditional recommendation against , Very low certainty evidence

Mass relapse prevention (MRP) to reduce transmission of *P. vivax* (2022)

Mass treatment with an 8-aminoquinoline medicine alone to reduce the transmission of *P. vivax* is not recommended.

- *Without testing for G6PD deficiency, the GDG noted the potential for severe harm from the use of a therapeutic dose of an 8-aminoquinoline for radical cure of P. vivax hypnozoites. However, conducting G6PD testing for a large population would significantly add to the complexity and cost of the intervention.*
- *The GDG noted that there may be highly exceptional circumstances under which mass relapse prevention (MRP) may be appropriate, such as during a small focal outbreak of P. vivax in a temperate area. However, under such circumstances the GDG considered that an MDA programme providing a schizonticide in addition to an 8-aminoquinoline would likely be a better strategy.*

Evidence To Decision

Benefits and harms

The systematic review identified two NRSs that provided data on MRP for *P. vivax* (Shah *et al* *unpublished evidence*). Studies were conducted in the Democratic People's Republic of Korea in 2002 and in the Republic of Azerbaijan in 1970–1971. Both studies provided primaquine for 14 days at 0.25 mg/kg per day, administered in a single round prior to the peak transmission season. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Immediate-to-short-term benefit 1–3 months after the last round of MRP

- The evidence is very uncertain about the effect of MRP on the incidence of *P. vivax* infection. (RD: -102 per 1000 p-y; 95% CI: -103 to -102 per 1000 p-y; two NRSs; very low-certainty evidence).

Medium-term benefit 4–12 months after the last round of MRP

- The evidence is very uncertain about the effect of MRP on the prevalence of *P. vivax* infection (RD: -3 per 1000 persons; 95% CI: -4 to -2 per 1000 persons; one NRS; very low-certainty evidence).
- The evidence is very uncertain about the effect of MRP on the incidence of *P. vivax* infection (RD: -11 per 1000 p-y; 95% CI: -11 to -10 per 1000 p-y; two NRSs; very low-certainty evidence).

Adverse events

- The evidence is very uncertain about the effect of MRP on adverse events (one NRS; very low-certainty evidence).

Judgement of the panel
The GDG could not judge the size of the beneficial effects given the very low certainty of the evidence. However, the GDG was clear that there was the potential for large undesirable effects, given the possibility of severe haemolysis among people with G6PD deficiency who take an 8-aminoquinoline. Overall, the GDG judged the balance of effects to probably favour no MRP.

Certainty of the Evidence

Very low

The overall certainty of the evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

No studies were identified on the costs of implementing MRP.

The GDG judged the costs were likely to be large.

Equity

No studies were identified addressing the issue of whether MRP increased or decreased health equity.

The GDG judged that equity might be reduced by MRP, given that the undesirable effects were likely to be focalized in a healthy subgroup of the population with G6PD deficiency.

Acceptability

No studies were identified on the acceptability of MRP.

The GDG was unable to judge whether or not the intervention was acceptable.

Feasibility

The systematic review identified one study on the feasibility of implementing MRP, which provided information on the size and composition of implementation teams and how adverse events were identified and managed (Shah *et al*

unpublished evidence).

The GDG judged that population screening for G6PD deficiency, along with an effective pharmacovigilance system and emergency access to blood transfusion services, would be needed to implement MRP safely, which would significantly increase the complexity and cost of the intervention.

Justification

The GDG was disappointed in the very low quality of evidence to judge the impact of MRP on *P. vivax* transmission. The GDG judged that the balance of effects probably favoured no MRP while the feasibility of implementing an MRP programme was very low given the complexity of safely administering radical cure for *P. vivax* hypnozoites, which would entail a high cost. Additionally, the GDG was concerned that the MRP strategy does not include an antimalarial medicine that targets blood-stage parasites (i.e. schizonticide), given evidence for improved efficacy of primaquine against relapses when co-administered with a schizonticide. The GDG concluded that there should be a conditional recommendation against implementation of the strategy but considered that there may be highly exceptional circumstances, such as a small focal outbreak of *P. vivax* in a temperate area, under which an MRP intervention might be appropriate.

Research Needs

The GDG suggested that the strategy could be reconsidered if a new drug to treat hypnozoites was developed that could be administered without the need for G6PD testing.

4.3 Vaccine

The use of vaccines for the prevention of malaria

Immunization is a success story for global health and development, saving millions of lives every year. Between 2010 and 2018, 23 million deaths were averted with the measles vaccine alone. The number of infants vaccinated annually – more than 116 million, or 86% of all infants born – has reached the highest level ever reported. More than 20 life-threatening diseases can now be prevented through immunization. Since 2010, 116 countries have introduced vaccines that they did not previously use, including those against major killers such as pneumococcal pneumonia, diarrhoea, cervical cancer, typhoid, cholera and meningitis *[142]*.

A vaccine has the potential to increase the proportion of children with access to one or more approaches to malaria prevention tools (e.g. ITNs). Introduction of the RTS,S/AS01 vaccine in the Malaria Vaccine Implementation Programme extended the reach of malaria prevention tools; across the three pilot countries more than two thirds of children who reportedly did not sleep under an ITN received at least the first dose of RTS,S/AS01. Overall, vaccine introduction increased to over 90% the proportion of children in each of the three countries with access to one or more malaria prevention tool (ITN or RTS,S/AS01). Vaccine uptake was equitable by sex and socioeconomic status and had no negative effects on the uptake of other childhood vaccinations, ITN use, or health-seeking behaviour for febrile illness (*unpublished evidence*).

Malaria vaccine pipeline

The RTS,S/AS01 vaccine is the first and currently the only malaria vaccine to be recommended for use by WHO. RTS,S/AS01 is the result of decades of public–private scientific partnership, with origins dating back to 1983. Although there are a handful of *P. falciparum* malaria vaccine candidates in the clinical stages of evaluation, RTS,S/AS01 is the first vaccine to have completed Phase 3 evaluations *[143]* and the first to be provided to children through routine immunization services as part of phased pilot introductions. In 2015, RTS,S/AS01 received a positive scientific opinion from the European Medicines Agency *[144]* and in 2019, it received national regulatory authorization for use in the pilot areas of Ghana, Kenya and Malawi for the Malaria Vaccine Implementation Programme. A separate trial of RTS,S/AS01 took advantage of the vaccine's high initial efficacy by administering a primary series of three doses at monthly intervals and subsequent annual single doses just prior to the intense, 4–5 month-long high transmission season. The vaccine was non-inferior to seasonal malaria chemoprevention (SMC); the combination of the vaccine and SMC was significantly better than either SMC alone or RTS,S/AS01 alone *[145]*.

Two vaccine candidates are approaching late-stage clinical evaluation: the R21/MatrixM vaccine candidate targeting *PfCSP* protein *[146]* and the attenuated whole sporozoite vaccine *Pf*SPZ *[147]*. Additional candidates targeting other malaria life-cycle stages include the Rh5 blood-stage vaccine candidate *[148]* and *Pfs*25 and *Pfs230* vaccine candidates targeting sexual-stage antigens to prevent human-to-mosquito transmission (NCT02942277). New technologies, such as DNA- and mRNA-based vaccines *[149]*, the ongoing development of adjuvants *[150]*, and delivery platforms such as virus-like particles (VLPs; the delivery platform used for RTS,S/AS01) and vesicle-based technologies are being explored for use in malaria vaccines. WHO has developed guidelines on the quality, safety, and efficacy of the recombinant malaria vaccines targeting pre-

erythrocytic and blood stages of *P. falciparum [151]* and a set of preferred product characteristics (PPCs). The PPCs include attributes ranging from safety and efficacy to route of administration, product stability and storage, in order to help support the ongoing development of new malaria vaccines. These PPCs *[152]* are currently being updated to reflect recent advances in malaria vaccine research and development.

National programmes for immunization and malaria

The RTS,S/AS01 malaria vaccine should be provided as part of a comprehensive malaria control strategy. All malaria control interventions provide partial protection and the highest impact is achieved when multiple interventions are used concomitantly. Appropriate mixes of interventions should be identified for different subnational strata. These are defined by national malaria programmes (NMPs) on the basis of the local malaria epidemiology (e.g. transmission intensity, age pattern of severe disease, vector species, insecticide resistance patterns) and contextual factors (e.g. structure and function of the formal health system).

Where applicable, the malaria vaccine should be integrated into relevant immunization guidelines and malaria control strategies, including national strategic plans to define the package of interventions needed to optimize malaria control and elimination in a country. WHO is developing operational guidance on principles for the subnational tailoring of malaria interventions.

Country considerations and planning for malaria vaccine introduction should rely on data-driven decision-making in which NMP and Expanded Programme on Immunization (EPI) staff consider parasite prevalence, disease burden, existing malaria interventions, vaccine delivery, the logistics, strength and support of the immunization programme, and the availability of funding support, among other factors. Decision making on whether to adopt and implement the malaria vaccine should be in close collaboration between the NMP and the EPI and other relevant ministry of health departments. In pilot countries, the NMP actively participated in the vaccine introduction and implementation activities in order to ensure that malaria control perspectives were incorporated and to maximize opportunities for integration. Malaria vaccine technical working groups were established with joint participation from the EPI and NMP to provide technical guidance on decision-making and a forum for alignment. The EPI leads the logistics of vaccine roll-out and delivery to relevant health facilities. The EPI manages the planning and activities required for vaccine introduction and programme implementation, such as vaccine and supplies procurement; advocacy; communications and social mobilization; training and supervision of health personnel; logistics and cold chain for vaccine storage; service delivery; and monitoring and evaluation. Both fixed sites for vaccination at health care facilities and opportunities for mobile vaccination delivery or outreach services should be considered. To increase uptake, periodic mass vaccination campaigns or periodic intensified routine immunization activities can be deployed. Monitoring of coverage levels occurs through routine health facility data; the malaria vaccine can be integrated into the District Health Information Software 2 (DHIS2) platform alongside NMP and EPI indicators.

Please refer to the WHO malaria vaccine position paper for more information on the malaria vaccine *[153]*.

Please refer to WHO Immunization, Vaccines and Biologicals for more resources and published guidance, including the forthcoming “Guide for introducing a malaria vaccine."

Strong recommendation for , High certainty evidence

Malaria vaccine (2021)

The RTS,S/AS01 malaria vaccine should be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO.

- *The RTS,S/AS01 malaria vaccine should be provided in a four-dose schedule in children from 5 months of age.*
- *Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy, in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks.*
- *Countries that choose to introduce the vaccine in a five-dose seasonal strategy are encouraged to document their experiences, including adverse events following immunization.*
- *RTS,S/AS01 malaria vaccine should be provided as part of a comprehensive malaria control strategy.*

Practical Info

Vaccine characteristics, content, dosage, administration and storage

RTS,S/AS01 is a pre-erythrocytic recombinant protein vaccine, based on the RTS,S recombinant antigen. It comprises the hybrid polypeptide RTS, in which regions of the *P. falciparum* circumsporozoite protein known to induce humoral (R region) and cellular (T region) immune responses are covalently bound to the hepatitis B virus surface antigen (S). The vaccine is currently produced as a two-dose RTS,S powder to be reconstituted with a two-dose AS01 adjuvant system suspension. After reconstitution, the total volume is 1ml (two doses of 0.5 ml). No preservative is included in either the RTS,S formulation or the AS01 adjuvant system. The vials should therefore be discarded at the end of the vaccination session, or within six hours after

opening, whichever comes first. The reconstituted 0.5ml vaccine should be administered by injection into the deltoid muscle in children aged 5 months or older. The shelf life of the RTS,S/AS01 vaccine is three years. A vaccine vial monitor is on the AS01 vial *[144]*.

Schedule
WHO recommends that the first dose of vaccine be administered from 5 months of age. There should be a minimum interval of four weeks between doses. The vaccine should be administered in a three-dose primary schedule, with a fourth dose provided 12–18 months after the third dose to prolong the duration of protection. However, there can be flexibility in the schedule to optimize delivery, for example, to align the fourth dose with other vaccines given in the second year of life. Children who begin their vaccination series should complete the four-dose schedule *[153]*.

Optional schedule for settings with highly seasonal malaria or perennial malaria with seasonal peaks
Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a five-dose strategy in areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks. This strategy seeks to maximize vaccine impact by ensuring that the period of highest vaccine efficacy (just after vaccination) coincides with the period of highest malaria transmission. The primary series of three doses should be provided at monthly intervals, with additional doses provided annually prior to the peak transmission season. Countries that choose seasonal deployment of the RTS,S/AS01 vaccine are strongly encouraged to document their experiences, including the vaccine's effectiveness, feasibility and occurrence of any adverse events following immunization—as additional input for future updates to the guidance. WHO also encourages international and national funders to support relevant learning opportunities *[153]*.

Co-administration
RTS,S/AS01 given in conjunction with routine childhood vaccines has been evaluated in several trials *[158][159]*. Non-inferiority criteria were met for all vaccines given with RTS,S/AS01, in comparison with the same vaccines given without RTS,S/AS01. RTS,S/AS01 can be given concomitantly with any of the following monovalent or combination vaccines: diphtheria, tetanus, whole cell pertussis, acellular pertussis, hepatitis B, *Haemophilus influenzae* type b, oral poliovirus, measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines *[144]*. No co-administration studies have been conducted with RTS,S/AS01 and meningococcus A, typhoid conjugate, cholera, Japanese encephalitis, Tick-borne encephalitis, rabies, mumps, influenza or varicella vaccines *[153]*.

Identifying areas for vaccine introduction
Decisions about where to introduce the malaria vaccine should be made in the context of national planning of mixes of malaria interventions and strategies and considering the need for subnational tailoring of packages of interventions. Subnational tailoring considers variations in malaria epidemiology, health system structure and function, and broader contextual considerations.

Current WHO guidance defines moderate or high transmission settings as those with an annual incidence greater than about 250 cases per 1000 population or a prevalence of *P. falciparum* infection in children aged 2—10 years (*Pf*$PR_{2\text{-}10}$) of approximately 10% or more. These are indicative values and should not be used as strict thresholds.

Vaccine safety
The RTS,S/AS01 vaccine is safe and well tolerated. There is a small risk of febrile seizures within seven days (mainly within 2—3 days) of vaccination. As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand.

The only contraindication to use of RTS,S/AS01 vaccine is severe hypersensitivity to any of the vaccine components *[144]*.

Vaccination of special populations
Malnourished or HIV-positive infants may be vaccinated with the RTS,S/AS01 vaccine using a standard schedule. These children may be at particular risk from malaria infection and the vaccine has been shown to be safe in these groups.

The vaccine should be provided to infants and young children aged 5—17 months of age who relocate to an area of moderate to high transmission, including during emergency situations.

The vaccine has been developed for use in young children living in malaria-endemic settings, and has not undergone full clinical testing in adults, nor is it recommended for adults. The vaccine is not indicated for travellers, who should use chemoprophylaxis and vector control methods to prevent malaria when traveling to endemic settings.

Surveillance
As for all new vaccines, the effectiveness and safety of the RTS,S/AS01 vaccine should be monitored post-introduction. Countries that choose to introduce the vaccine in a five-dose seasonal strategy are encouraged to document their experience,

including adverse events following immunization.

Research priorities
The WHO-coordinated Malaria Vaccine Implementation Programme will continue through 2023, with continued monitoring of data on safety, impact, coverage achieved and the added benefit of the fourth dose. In areas with highly seasonal malaria or with perennial malaria transmission with seasonal peaks, operational research is needed specifically related to the seasonal delivery of vaccine doses, including annual preseason dosing after a primary series given through the routine health clinics. Further evaluation will be required to determine how best to deliver the combination of SMC and seasonal malaria vaccination in areas. Data should be collected on safety, immunogenicity, and effectiveness of annual doses beyond the fifth dose.

Considerations for immunization and health systems
The additional visits needed for RTS,S/AS01 are opportunities to provide other integrated and preventive health services. Efforts should be made to take advantage of these visits to catch up on missed vaccinations, administer Vitamin A, carry out deworming and other preventive interventions, and remind parents of the importance of continuing to use an ITN every night and seeking prompt diagnosis and treatment for fever.

A framework for allocation of limited supply
Supplies of the RTS,S/AS01 vaccine are expected to be limited in the short to medium term, and demand is expected to be high. WHO is working with partners to develop a framework to guide the allocation of the initial limited doses of malaria vaccine, using a transparent process that incorporates input from key parties, with appropriate representation and consultation. This framework will include dimensions of market dynamics, learning from experience, scientific evidence for high impact, implementation considerations and social values, including fairness and equity.

Evidence To Decision

Benefits and harms

The RTS,S/AS01 vaccine, provided in a four-dose schedule, has been demonstrated in clinical trials and the pilot implementation studies to have meaningful impact, with a substantial reduction in hospitalization for life-threatening severe malaria, which is considered to be a surrogate indicator for the impact on mortality.

- There were significant reductions in clinical malaria (51%); and severe malaria (45%), demonstrated after 12 months' follow-up of the first three doses in the Phase 3 trial *[143]*.
- There were significant reductions in clinical malaria (39%); severe malaria (29%); severe malaria anaemia (61%); malaria-related hospitalization (37%); and the need for blood transfusions (30%), demonstrated over 46 months' follow-up after the first three doses in the Phase 3 trial in children who received a fourth dose 18 months after the third dose *[143]*.
- There were 1774 clinical malaria cases averted per 1000 children vaccinated with four RTS,S/AS01 doses over 46 months' follow-up in the Phase 3 trial *[143]*.
- There were significant reductions in clinical malaria (24%) demonstrated after 7 years' follow-up after vaccination among a subset of children in the Phase 3 trial living in areas of moderate to high transmission; they did not have an excess risk of clinical or severe malaria *[154]*.
- There were significant reductions in hospitalization with severe malaria (29%) and hospitalization with malarial parasitemia or antigenemia (21%), demonstrated among children who were age-eligible for three doses of vaccine delivered through routine systems by the ministries of health in parts of Ghana, Kenya, and Malawi (Milligan et al. *unpublished evidence*).
- Median estimates ranged from 200 to 700 deaths averted per 100 000 children vaccinated with a 4-dose schedule in areas of moderate to high transmission *[156]*.
- There were substantially greater reductions in uncomplicated malaria (63%), hospital admissions with severe malaria (70%), and death from malaria (73%) among children who received the combination of RTS,S/AS01 seasonal vaccination and SMC when compared to SMC alone. Seasonal vaccination with RTS,S/AS01 before the peak transmission season was non-inferior to SMC in preventing clinical malaria *[145]*.

The RTS,S/AS01 vaccine is safe and well tolerated *[153]*.

- There is a small risk of febrile seizures within seven days (mainly within 2–3 days) of vaccination *[144]*.
- As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand *[153]*.

- As for all new vaccines, the effectiveness and safety of the RTS,S/AS01 vaccine should be monitored post-introduction *[153]*.

More information can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper (*unpublished evidence*) sections 5.3.2 and 6.1 (MVIP safety, methods and results); sections 5.3.3 and 6.2 (MVIP impact, methods and results); sections 7.2 (Phase 3 results); section 8 (Additional data since Phase 3 completion); section 9 (Modelled public health impact and cost-effectiveness estimates).

Further details on "Benefits and harms" are also included in the SAGE/MPAG Evidence-to-Recommendations framework (*unpublished evidence*).

Certainty of the Evidence

High

The overall rating of the evidence on RTS,S/AS01 malaria vaccine is considered to be HIGH. The certainty of evidence ranged from very low to high.

Critical outcomes related to effectiveness of RTS,S/AS01 were mostly rated HIGH in the large-scale Phase 3 clinical trial and MODERATE (due to large confidence intervals [CIs]) in the pilot implementation study.

Overall the certainty of evidence for the safety outcomes was rated MODERATE. Three safety signals, thought to be chance findings, were identified in the Phase 3 trial; these rare, unexplained events were graded with LOW and VERY LOW certainty of evidence:

- An excess of meningitis and cerebral malaria (in the context of overall reduction in severe malaria).
- An excess of deaths among girls who had received RTS,S/AS01 (shown in a post hoc analysis compared to boys).

The Malaria Vaccine Pilot Evaluations were designed to answer the outstanding questions related to safety. Evidence on the safety outcomes of meningitis, cerebral malaria, and gender-specific mortality is now graded MODERATE certainty reflecting the wide CIs related to relatively rare events. Multiple WHO advisory committees reviewed the data from the pilot implementation study and concluded that there was no evidence that the Phase 3 safety signals were causally related to RTS,S/AS01. Additionally these safety signals were not seen in the Phase 2 trials *[157]* or subsequent Phase 3 trials *[154][145]*.

More information can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper (*unpublished evidence*) Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Evidence summary table by the Cochrane Response and the SAGE/MPAG Evidence-to-Recommendations framework (*unpublished evidence*).

Values and preferences

No substantial variability expected

Malaria remains a primary cause of childhood illness and mortality in much of sub-Saharan Africa.

Preferences and values of the target population have been assessed in several ways:

- Qualitative interviews with caregivers and health providers revealed the perceived value of the vaccine in reducing the severity and frequency of malaria. Positive attitudes and trust among caregivers increased substantially over time, driven mainly by their perception of the vaccine's health benefits in their own children and the broader community.
- Malaria vaccine coverage from cross-sectional household surveys and from routine facility-based administrative data indicated that the vaccine was acceptable to the target population with relatively rapid scale–up for a new vaccine with a unique schedule and dropout between doses comparable to other vaccines (see "Feasibility" section).
- Coverage of other interventions from household survey and routine administrative data in areas where the vaccine has been introduced indicated that the vaccine had no negative effects on the uptake of other childhood vaccinations, on ITN use, or health–seeking behaviour for febrile illness.

Note: Midline surveys and the second round of the qualitative study were conducted between the provision of the third dose and the provision of the fourth dose and thus did not capture data on the uptake/coverage/acceptability of the fourth dose.

More information can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper (*unpublished evidence*) sections 5.3.4.2 and 6.3.1 (routine data, methods and results); sections 5.3.4.3 and 6.3.2 (household survey methods and results), and sections 5.3.4.5 and 6.3.4 (qualitative health utilization study methods and results, *unpublished evidence*).

Further details on “Values and Preferences" are also included in the SAGE/MPAG Evidence-to-Recommendations framework (*unpublished evidence*).

Resources

The resources required are likely to be comparable to other new vaccine introductions.

Mathematical models examined the addition of the vaccine to existing malaria control interventions and treatment *[156]*.

- At an assumed vaccine price of US$5 per dose and $PfPR_{2\text{-}10}$ of 10-65%, the models predicted a median ICER compared with no vaccine of $25 (95%CI 16–222) per clinical case averted and $87 (95%CI 48–224) per DALY averted for the four-dose schedule.
- Public health impact and cost-effectiveness tended to be greater at higher levels of transmission.
- Overall, the model estimated that ICERs were only marginally lower for the seasonal vaccination strategies (i.e. more cost-effective) despite the higher number of overall doses delivered.
- Caution is required in the comparison of cost-effectiveness estimates for different interventions evaluated with different methods, outcome measures, time intervals and context (e.g. with different concurrent health interventions and standards of care). Nevertheless, the predictions of RTS,S/AS01 cost per DALY averted are broadly positive and comparable with other new vaccines, based on mathematical models, and other malaria interventions.

Table 1 is based on the evidence reviewed by the RTS,S/AS01 SAGE/MPAG Working Group on the incremental cost estimates of introducing and delivering the RTS,S/AS01 malaria vaccine within routine immunization programmes in subnational areas of the malaria vaccine pilot countries: Ghana, Kenya and Malawi. The line items account for the activities conducted in the first 1–2 years of vaccine implementation (through December 2020).

More information on the evidence can be found in the Full evidence review on the RTS,S/AS01 malaria vaccine background paper (*unpublished evidence*) sections 5.3.4.6 and 6.3.5 (cost of introduction and delivery study methods and results) and section 9 (*unpublished evidence*). Further details on “Resource use” and “Cost-effectiveness” (*unpublished evidence*) are also included in the SAGE/MPAG Evidence-to-recommendations framework (*unpublished evidence*).

Table 1: Line items from RTS,S/AS01 cost of delivery and vaccine introduction study

Line item (Resource)	Resource description
Staff	• EPI and NMP, among other ministry of health staff including vaccinators at health facilities • District malaria and health information management coordinators for DHIS2 data analysis
Training	• Training materials development • Readiness assessment for national-level facilitators (orientation) • Training of national-level trainers, regional or sub county-level trainers, health workers (facility-level) • Follow-up training for health workers and supportive supervision • Training of health workers for periodic intensification of routine immunization
Transport	• Distribution of vaccine between cold stores (national to regional to district/

	county levels)
Supplies	• RTS,S two-dose vials • 2 mL reconstitution syringes • 0.5 mL auto-destruct injection syringes • Safety boxes (100-syringe capacity) • Printing of training kit books (decks) • Office support supplies
Equipment	• Cold chain equipment (fridges, cold boxes) • Office support supplies like printers, cartridges/ toners, tablets, monitors, projectors, laptops • Vehicles and motorcycles
Monitoring and evaluation	• Development of recording and reporting materials • Printing of monitoring charts, tally books, reporting forms, under-2 registers, defaulter tracing registers, and other tools • Distribution of monitoring tools • Pre-introduction assessments at national, regional, and district/county levels • Post-introduction supportive supervision • Review meetings at health facility level to validate and reconcile EPI data • Supportive supervision by national, regional, and district/county levels • Mapping of unimmunized and under-immunized children
Communication	• Message and information, education, communications material development, validation, pre-testing and translation • Printing of communications materials and field guides • Press release in newspapers, public address system, airing of messages at radio stations, community centres and mobile vans • Spokesperson trainings • Planning meetings • Social mobilization activities including peer education, orientation sessions, social announcements, periodic intensification of routine immunization • Sensitization of district health management teams, community leaders, religious leaders, community health assistants and volunteers, and communities via a house-to-house approach • National and/or regional-level launch events for first vaccination • Stakeholder engagements at national, regional and district/county levels
Governance/programme management	• Meetings for national coordination, subcommittees, technical working groups • Joint meetings between EPI and NMP • Planning and budgeting meetings • Microplanning at district level

Equity

Vaccine uptake was equitable by sex and socioeconomic status.

- Vaccine uptake had no negative effect on the uptake of other childhood vaccinations, ITN use or health-seeking behaviour for febrile illness.
- Introduction of RTS,S/AS01 extended the reach of malaria prevention tools; across the three pilot countries, more than two thirds of the children who reportedly did not sleep under an ITN received at least their first dose of the malaria vaccine.
- Overall, vaccine introduction increased to over 90% the proportion of children in each of the three pilot countries with access to one or more malaria prevention tools (ITN or RTS,S/AS01).

More information on the evidence can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper (*unpublished evidence*) section 10 (Equity considerations). Further details on "Equity" are also included in the SAGE/MPAG Evidence-to-Recommendations framework (*unpublished evidence*).

Acceptability

RTS,S/AS01 malaria vaccine considered acceptable to the following groups:

- **Target population (including eligible children and their caregivers):** This is based on administrative data and household surveys that indicate good uptake and coverage, and modest drop-out rates. Continued increases in uptake suggest that the additional visits needed to receive the vaccine are acceptable to the target populations. Qualitative data indicate high acceptance and desirability of the vaccine.
- **Key stakeholders (including ministries of health and immunization programme managers):** This is based on post-introduction evaluations, the good uptake and coverage of the malaria vaccine, and qualitative study interviews with health providers. Chief concerns from health providers were around the operational challenges faced in introducing and delivering RTS,S/AS01 (i.e. increased workload, training, eligibility).

Household surveys found no impact on the use of ITNs in intervention areas following the introduction of RTS,S/AS01, indicating that both interventions are acceptable and the vaccine has not displaced ITN use. Overall health-seeking behaviour for febrile illness was also similar between the implementing and comparison groups as well as between the baseline and midline surveys.

More information on the evidence can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper (*unpublished evidence*) sections 5.3.4.2 and 6.3.1 (routine data, methods and results); sections 5.3.4.3 and 6.3.2 (household survey methods and results), sections 5.3.4.4 and 6.3.3 (post-introduction evaluation methods and results) and sections 5.3.4.5 and 6.3.4 (qualitative health utilization study methods and results). Further details on "Acceptability" (*unpublished evidence*) are also included in the SAGE/MPAG Evidence-to-Recommendations framework (*unpublished evidence*).

Feasibility

Vaccine introduction is feasible with good and equitable coverage of RTS,S/AS01 seen through routine immunization systems even in the context of the COVID-19 pandemic.

Administrative data from the start of pilot programme vaccinations in 2019 and April 2021 (24 months in Ghana and Malawi, and 18 months in Kenya) showed that:

- More than 1.7 million RTS,S/AS01 vaccine doses were administered across the three pilot countries and more than 650 000 children received their first dose.
- All three countries reached more than 70% of their target populations with the first RTS,S/AS01 dose and at least 62% with the third RTS,S/AS01 dose (*unpublished evidence*).

More information on the evidence can be found in the Full evidence report on the RTS,S/AS01 malaria vaccine background paper (*unpublished evidence*) sections 5.3.4.2 and 6.3.1 (routine data, methods and results). Further details on "Feasibility" are also included in the SAGE/MPAG Evidence-to-Recommendations framework (*unpublished evidence*).

Justification

A Framework for WHO recommendation on RTS,S/AS01 malaria vaccine (*unpublished evidence*), endorsed by SAGE and MPAG in 2019, provided guidance on how data from the MVIP should inform WHO recommendations, with the aim of ensuring that a recommendation could be made as soon as the risk–benefit of the vaccine was established with the necessary level of confidence, such that the vaccine would not be unnecessarily withheld from countries in need if it was found to be safe and beneficial.

The Framework stated that a WHO recommendation could be made if and when concerns regarding the safety signals were satisfactorily resolved, and evidence on severe malaria or mortality was assessed as consistent with a beneficial impact of the vaccine.

The Framework clarified that a recommendation should not be predicated on attaining high coverage, including high coverage with the fourth vaccine dose, based on: (1) data from the Phase 3 long-term follow up study showing that children living in areas of perennial moderate to high malaria transmission benefit from three or four doses of the vaccine; and (2) experience that it usually takes time for new vaccines to attain high coverage, particularly when administered in the second year of life.

The RTS,S/AS01 vaccine is considered safe and well tolerated. There is a small risk of febrile seizures within seven days (mainly within 2–3 days) of vaccination. As with any vaccine introduction, proper planning and training of staff to conduct appropriate pharmacovigilance should take place beforehand.

RTS,S/AS01 has a demonstrated ability to quickly achieve high coverage and high impact when delivered through routine immunization systems, with a 30% reduction in severe malaria observed after the vaccine was introduced in areas where ITNs are widely used and there is good access to diagnosis and treatment. Modelling shows that the vaccine is cost–effective in areas of moderate to high malaria transmission.

RTS,S/AS01 increases access to malaria prevention with no negative effect on the uptake other childhood vaccinations, ITN use, or health–seeking behaviour for febrile illness.

5. CASE MANAGEMENT

Background

Malaria case management, consisting of early diagnosis and prompt effective treatment, remains a vital component of malaria control and elimination strategies. The WHO Guidelines for the treatment of malaria were first developed in 2006 and have been revised periodically, with the most recent edition published in 2015. WHO guidelines contain recommendations on clinical practice or public health policy intended to guide end-users as to the individual or collective actions that can or should be taken in specific situations to achieve the best possible health outcomes. Such recommendations are also designed to help the user to select and prioritize interventions from a range of potential alternatives. The third edition of the WHO Guidelines for the treatment of malaria consolidated here contains updated recommendations based on new evidence particularly related to dosing in children, and also includes recommendations on the use of drugs to prevent malaria in groups at high risk.

Since publication of the first edition of the *Guidelines for the treatment of malaria* in 2006 and the second edition in 2010, all countries in which *P. falciparum* malaria is endemic have progressively updated their treatment policy from use of monotherapy with drugs such as chloroquine, amodiaquine and sulfadoxine–pyrimethamine (SP) to the currently recommended artemisinin-based combination therapies (ACT). The ACTs are generally highly effective and well tolerated. This has contributed substantially to reductions in global morbidity and mortality from malaria. Unfortunately, resistance to artemisinins has arisen recently in *P. falciparum* in South-East Asia, which threatens these gains.

Core principles

The following core principles were used by the Guidelines Development Group that drew up the Guidelines for the Treatment of Malaria.

1. Early diagnosis and prompt, effective treatment of malaria

Uncomplicated falciparum malaria can progress rapidly to severe forms of the disease, especially in people with no or low immunity, and severe falciparum malaria is almost always fatal without treatment. Therefore, programmes should ensure access to early diagnosis and prompt, effective treatment within 24–48 h of the onset of malaria symptoms.

2. Rational use of antimalarial agents

To reduce the spread of drug resistance, limit unnecessary use of antimalarial drugs and better identify other febrile illnesses in the context of changing malaria epidemiology, antimalarial medicines should be administered only to patients who truly have malaria. Adherence to a full treatment course must be promoted. Universal access to parasitological diagnosis of malaria is now possible with the use of quality-assured rapid diagnostic tests (RDTs), which are also appropriate for use in primary health care and community settings.

3. Combination therapy

Preventing or delaying resistance is essential for the success of both national and global strategies for control and eventual elimination of malaria. To help protect current and future antimalarial medicines, all episodes of malaria should be treated with at least two effective antimalarial medicines with different mechanisms of action (combination therapy).

4. Appropriate weight-based dosing

To prolong their useful therapeutic life and ensure that all patients have an equal chance of being cured, the quality of antimalarial drugs must be ensured, and antimalarial drugs must be given at optimal dosages. Treatment should maximize the likelihood of rapid clinical and parasitological cure and minimize transmission from the treated infection. To achieve this, dosage regimens should be based on the patient's weight and should provide effective concentrations of antimalarial drugs for a sufficient time

to eliminate the infection in all target populations.

Please refer to *Malaria case management: operations manual [162]*.

5.1 Diagnosing malaria

Suspected malaria

The signs and symptoms of malaria are non-specific. Malaria is suspected clinically primarily on the basis of fever or a history of fever. There is no combination of signs or symptoms that reliably distinguishes malaria from other causes of fever; diagnosis based only on clinical features has very low specificity and results in overtreatment. Other possible causes of fever and whether alternative or additional treatment is required must always be carefully considered. The focus of malaria diagnosis should be to identify patients who truly have malaria, to guide rational use of antimalarial medicines.

In malaria-endemic areas, malaria should be suspected in any patient presenting with a history of fever or temperature ≥ 37.5 °C and no other obvious cause. In areas in which malaria transmission is stable (or during the high-transmission period of seasonal malaria), malaria should also be suspected in children with palmar pallor or a haemoglobin concentration of < 8 g/dL. High-transmission settings include many parts of sub-Saharan Africa and some parts of Oceania.

In settings where the incidence of malaria is very low, parasitological diagnosis of all cases of fever may result in considerable expenditure to detect only a few patients with malaria. In these settings, health workers should be trained to identify patients who may have been exposed to malaria (e.g. recent travel to a malaria-endemic area without protective measures) and have fever or a history of fever with no other obvious cause, before they conduct a parasitological test.

In all settings, suspected malaria should be confirmed with a parasitological test. The results of parasitological diagnosis should be available within a short time (< 2 h) of the patient presenting. In settings where parasitological diagnosis is not possible, a decision to provide antimalarial treatment must be based on the probability that the illness is malaria.

In children < 5 years, the practical algorithms for management of the sick child provided by the WHO–United Nations Children's Fund (UNICEF) strategy for Integrated Management of Childhood Illness *[163]* should be used to ensure full assessment and appropriate case management at first-level health facilities and at the community level.

Parasitological diagnosis

The benefit of parasitological diagnosis relies entirely on an appropriate management response of health care providers. The two methods used routinely for parasitological diagnosis of malaria are light microscopy and immunochromatographic RDTs. The latter detect parasite-specific antigens or enzymes that are either genus or species specific.

Both microscopy and RDTs must be supported by a quality assurance programme. Antimalarial treatment should be limited to cases with positive tests, and patients with negative results should be reassessed for other common causes of fever and treated appropriately.

In nearly all cases of symptomatic malaria, examination of thick and thin blood films by a competent microscopist will reveal malaria parasites. Malaria RDTs should be used if quality-assured malaria microscopy is not readily available. RDTs for detecting PfHRP2 can be useful for patients who have received incomplete antimalarial treatment, in whom blood films can be negative. This is particularly likely if the patient received a recent dose of an artemisinin derivative. If the initial blood film examination is negative in patients with manifestations compatible with severe malaria, a series of blood films should be examined at 6–12 h intervals, or an RDT (preferably one detecting PfHRP2) should be performed. If both the slide examination and the RDT results are negative, malaria is extremely unlikely, and other causes of the illness should be sought and treated.

This document does not include recommendations for use of specific RDTs or for interpreting test results. For guidance, see the WHO manual *Universal access to malaria diagnostic testing [164]*.

Diagnosis of malaria

In patients with suspected severe malaria and in other high-risk groups, such as patients living with HIV/AIDS, absence or delay of parasitological diagnosis should not delay an immediate start of antimalarial treatment.

At present, molecular diagnostic tools based on nucleic-acid amplification techniques (e.g. loop-mediated isothermal amplification or polymerase chain reaction [PCR]) do not have a role in the clinical management of malaria.

Where *P. vivax* malaria is common and microscopy is not available, it is recommended that a combination RDT be used that allows detection of P. vivax (pLDH antigen from *P. vivax*) or pan-malarial antigens (Pan-pLDH or aldolase).

Light microscopy

Microscopy not only provides a highly sensitive, specific diagnosis of malaria when performed well but also allows quantification of malaria parasites and identification of the infecting species. Light microscopy involves relatively high costs for training and supervision, and the accuracy of diagnosis is strongly dependent on the competence of the microscopist. Microscopy technicians may also contribute to the diagnosis of non-malarial diseases.

Although nucleic acid amplification-based tests are more sensitive, light microscopy is still considered the "field standard" against which the sensitivity and specificity of other methods

must be assessed. A skilled microscopist can detect asexual parasites at a density of < 10 per µL of blood, but under typical field conditions, the limit of sensitivity is approximately 100 parasites per µL *[165]*. This limit of detection approximates the lower end of the pyrogenic density range. Thus, microscopy provides good specificity for diagnosing malaria as the cause of a presenting febrile illness. More sensitive methods allow detection of an increasing proportion of cases of incidental parasitaemia in endemic areas, thus reducing the specificity of a positive test. Light microscopy has other important advantages:

- low direct costs, if laboratory infrastructure to maintain the service is available;
- high sensitivity, if the performance of microscopy is high;
- differentiation of Plasmodia species;
- determination of parasite densities – notably identification of hyperparasitaemia;
- detection of gametocytaemia;
- allows monitoring of responses to therapy and
- can be used to diagnose many other conditions.

Good performance of microscopy can be difficult to maintain, because of the requirements for adequate training and supervision of laboratory staff to ensure competence in malaria diagnosis, electricity, good quality slides and stains, provision and maintenance of good microscopes and maintenance of quality assurance *[166]* and control of laboratory services.

Numerous attempts have been made to improve malaria microscopy, but none has proven to be superior to the classical method of Giemsa staining and oil-immersion microscopy for performance in typical health care settings *[167]*.

Rapid diagnostic tests

Rapid diagnostic tests (RDTs) are immuno-chromatographic tests for detecting parasite-specific antigens in a finger-prick blood sample. Some tests allow detection of only one species (*P. falciparum*); others allow detection of one or more of the other species of human malaria parasites (*P. vivax*, *P. malariae* and *P. ovale*) *[168][169][170]*. They are available commercially in various formats, e.g. dipsticks, cassettes and cards. Cassettes and cards are easier to use in difficult conditions outside health facilities. RDTs are relatively simple to perform and to interpret, and they do not require electricity or special equipment *[171]*.

Since 2012, WHO has recommended that RDTs should be selected in accordance with the following criteria, based on the results of the assessments of the *WHO Malaria RDT Product Testing programme* *[172]*:

- For detection of *P. falciparum* in all transmission settings, the panel detection score against *P. falciparum* samples should be at least 75% at 200 parasites/µL.
- For detection of *P. vivax* in all transmission settings the panel detection score against *P. vivax* samples should be at least 75% at 200 parasites/µL.
- The false positive rate should be less than 10%.
- The invalid rate should be less than 5%.

Current tests are based on the detection of histidine-rich protein 2 (HRP2), which is specific for *P. falciparum*, pan-specific or species-specific *Plasmodium* lactate dehydrogenase (*p*LDH) or pan-specific aldolase. The different characteristics of these antigens may affect their suitability for use in different situations, and these should be taken into account in programmes for RDT implementation. The tests have many potential advantages, including:

- rapid provision of results and extension of diagnostic services to the lowest-level health facilities and communities;
- fewer requirements for training and skilled personnel (for instance, a general health worker can be trained in 1 day); and
- reinforcement of patient confidence in the diagnosis and in the health service in general.

They also have potential disadvantages, including:

- inability, in the case of *Pf*HRP2-based RDTs, to distinguish new infections from recently and effectively treated infections, due to the persistence of *Pf*HRP2 in the blood for 1–5 weeks after effective treatment;
- the presence in countries in the Amazon region of variable frequencies of HRP2 deletions in *P. falciparum* parasites, making HRP2-based tests not suitable in this region *[173]*;
- poor sensitivity for detecting *P. malariae* and *P. ovale*; and
- the heterogeneous quality of commercially available products and the existence of lot-to-lot variation.

In a systematic review *[174]*, the sensitivity and specificity of RDTs in detecting *P. falciparum* in blood samples from patients in endemic areas attending ambulatory health facilities with symptoms suggestive of malaria were compared with the sensitivity and specificity of microscopy or polymerase chain reaction. The average sensitivity of *Pf*HRP2-detecting RDTs was 95.0% (95% confidence interval [CI], 93.5–96.2%), and the specificity was 95.2% (93.4–99.4%). RDTs for detecting *p*LDH from *P. falciparum* are generally less sensitive and more specific than those for detecting HRP2, with an average sensitivity (95% CI) of 93.2% (88.0–96.2%) and a specificity of 98.5% (96.7–99.4%). Several studies have shown that health workers, volunteers and private sector providers can, with adequate training and supervision, use RDTs correctly and provide accurate malaria diagnoses. The criteria for selecting and procuring RDTs can be found on the WHO website.

Diagnosis with either microscopy or RDTs is expected to reduce overuse of antimalarial medicines by ensuring that treatment is given only to patients with confirmed malaria infection, as opposed to treating all patients with fever *[175]*. Although providers of care may be willing to perform diagnostic tests, they do not, however, always respond appropriately to the results. This is especially true when they are negative. It is therefore important to ensure the accuracy of parasite- based diagnosis and also to demonstrate this to users and to provide them with the resources to manage both positive and negative results adequately *[164]*.

Immunodiagnosis and nucleic acid amplification test methods
Detection of antibodies to parasites, which may be useful for epidemiological studies, is neither sensitive nor specific enough to be of use in the management of patients suspected of having malaria *[176]*.

Techniques to detect parasite nucleic acid, e.g. polymerase chain reaction and loop-mediated isothermal amplification, are highly sensitive and very useful for detecting mixed infections, in particular at low parasite densities that are not detectable by conventional microscopy or with RDTs. They are also useful for studies of drug resistance and other specialized epidemiological investigations *[177]*; however, they are not generally available for large-scale field use in malaria- endemic areas, nor are they appropriate for routine diagnosis in endemic areas where a large proportion of the population may have low-density parasitaemia.

These techniques may be useful for population surveys and focus investigation in malaria elimination programmes.

At present, nucleic acid-based amplification techniques have no role in the clinical management of malaria or in routine surveillance systems *[178]*.

Good practice statement

Diagnosing malaria (2015)

All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.

Justification

Prompt, accurate diagnosis of malaria is part of effective disease management. All patients with suspected malaria should be treated on the basis of a confirmed diagnosis by microscopy examination or RDT testing of a blood sample. Correct diagnosis in malaria-endemic areas is particularly important for the most vulnerable population groups, such as young children and non-immune populations, in whom falciparum malaria can be rapidly fatal. High specificity will reduce unnecessary treatment with antimalarial drugs and improve the diagnosis of other febrile illnesses in all settings.

WHO strongly advocates a policy of “test, treat and track” to improve the quality of care and surveillance.

5.2 Treating malaria

5.2.1 Treating uncomplicated malaria

Definition of uncomplicated malaria
A patient who presents with symptoms of malaria and a positive parasitological test (microscopy or RDT) but with no features of severe malaria is defined as having uncomplicated malaria (see section 9.1 for definition of severe falciparum malaria).

Therapeutic objectives
The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. “Cure” is defined as elimination of all parasites from the body. The public health objectives of treatment are to prevent onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

Incorrect approaches to treatment

Use of monotherapy
The continued use of artemisinins or any of the partner medicines alone will compromise the value of ACT by selecting for drug resistance.

As certain patient groups, such as pregnant women, may need specifically tailored combination regimens, single artemisinin derivatives will still be used in selected referral facilities in the public sector, but they should be withdrawn entirely from the private and informal sectors and from peripheral public health care facilities.

Similarly, continued availability of amodiaquine, mefloquine and SP as monotherapies in many countries is expected to shorten their useful therapeutic life as partner drugs of ACT, and they should be withdrawn wherever possible.

Incomplete dosing
In endemic regions, some semi-immune malaria patients are cured by an incomplete course of antimalarial drugs or by a treatment regimen that would be ineffective in patients with no immunity. In the past, this led to different recommendations for patients considered semi-immune and those considered non-immune. As individual immunity can vary considerably, even in areas of moderate-to-high transmission intensity, this practice is no longer recommended. A full treatment course

with a highly effective ACT is required whether or not the patient is considered to be semi-immune.

Another potentially dangerous practice is to give only the first dose of a treatment course to patients with suspected but unconfirmed malaria, with the intention of giving the full treatment if the diagnosis is confirmed. This practice is unsafe, could engender resistance, and is not recommended.

Additional considerations for clinical management

Can the patient take oral medication?
Some patients cannot tolerate oral treatment and will require parenteral or rectal administration for 1–2 days, until they can swallow and retain oral medication reliably. Although such patients do not show other signs of severity, they should receive the same initial antimalarial treatments recommended for severe malaria. Initial rectal or parenteral treatment must always be followed by a full 3-day course of ACT.

Use of antipyretics
In young children, high fevers are often associated with vomiting, regurgitation of medication and seizures. They are thus treated with antipyretics and, if necessary, fanning and tepid sponging. Antipyretics should be used if the core temperature is > 38.5 °C. Paracetamol (acetaminophen) at a dose of 15 mg/kg bw every 4 h is widely used; it is safe and well tolerated and can be given orally or as a suppository. Ibuprofen (5 mg/kg bw) has been used successfully as an alternative in the treatment of malaria and other childhood fevers, but, like aspirin and other non-steroidal anti-inflammatory drugs, it is *no longer recommended* because of the risks of gastrointestinal bleeding, renal impairment and Reye's syndrome.

Use of anti-emetics
Vomiting is common in acute malaria and may be severe. Parenteral antimalarial treatment may therefore be required until oral administration is tolerated. Then a full 3-day course of ACT should be given. Anti-emetics are potentially sedative and may have neuropsychiatric adverse effects, which could mask or confound the diagnosis of severe malaria. They should therefore be used with caution.

Management of seizures
Generalized seizures are more common in children with *P. falciparum* malaria than in those with malaria due to other species. This suggests an overlap between the cerebral pathology resulting from falciparum malaria and febrile convulsions. As seizures may be a prodrome of cerebral malaria, patients who have more than two seizures within a 24 h period should be treated as for severe malaria. If the seizures continue, the airways should be maintained and anticonvulsants given (parenteral or rectal benzodiazepines or intramuscular paraldehyde). When the seizure has stopped, the child should be treated as indicated in section 7.10.5, if his or her core temperature is > 38.5 °C. There is no evidence that prophylactic anticonvulsants are beneficial in otherwise uncomplicated malaria, and they are not recommended.

5.2.1.1 Artemisinin-based combination therapy

Strong recommendation for , High certainty evidence

Artemisinin-based combination therapy (2015)

Children and adults with uncomplicated *P. falciparum* malaria should be treated with one of the following ACTs*:

- artemether-lumefantrine (AL)
- artesunate-amodiaquine (AS+AQ)
- artesunate-mefloquine (ASMQ)
- dihydroartemisinin-piperaquine (DHAP)
- artesunate + sulfadoxine-pyrimethamine (AS+SP)
- artesunate-pyronaridine (ASPY) (2022)

*Artesunate + sulfadoxine-pyrimethamine and artesunate-pyronaridine are not recommended for use in the first trimester of pregnancy. For details of treatment using ACTs in the first trimester of pregnancy, see 5.2.1.4.1 below.

Artesunate-pyronaridine is now included in the list of options for the treatment of uncomplicated malaria (2022). See the full recommendation and supporting evidence below.

Practical Info

The pipeline for new antimalarial drugs is healthier than ever before, and several new compounds are in various stages of development. Some novel antimalarial agents are already registered in some countries. The decision to recommend

antimalarial drugs for general use depends on the strength of the evidence for safety and efficacy and the context of use. In general, when there are no satisfactory alternatives, newly registered drugs may be recommended; however, for global or unrestricted recommendations, considerably more evidence than that submitted for registration is usually required, to provide sufficient confidence for their safety, efficacy and relative merits as compared with currently recommended treatments.

Several new antimalarial drugs or new combinations have been introduced recently. Some are still in the pre-registration phase and are not discussed here. Arterolane + piperaquine, artemisinin + piperaquine base and artemisinin + napththoquine are new ACTs, which are registered and used in some countries. In addition, there are several new generic formulations of existing drugs. None of these yet has a sufficient evidence base for general recommendation (i.e. unrestricted use).

Arterolane + piperaquine is a combination of a synthetic ozonide and piperaquine phosphate that is registered in India. There are currently insufficient data to make general recommendations.

Artemisinin + piperaquine base combines two well-established, well-tolerated compounds. It differs from previous treatments in that the piperaquine is in the base form, the artemisinin dose is relatively low, and the current recommendation is for only a 2-day regimen. There are insufficient data from clinical trials for a general recommendation, and there is concern that the artemisinin dose regimen provides insufficient protection against resistance to the piperaquine component.

Artemisinin + naphthoquine is also a combination of two relatively old compounds that is currently being promoted as a single-dose regimen, contrary to WHO advice for 3 days of the artemisinin derivative. There are currently insufficient data from rigorously conducted randomized controlled trials to make general recommendations.

Many ACTs are generics. The bioavailability of generics of currently recommended drugs must be comparable to that of the established, originally registered product, and the satisfactory pharmaceutical quality of the product must be maintained.

Please refer to *Good procurement practices for artemisinin-based antimalaria medicines [179]*.

Evidence To Decision

Benefits and harms

Recommendation: Treat adults and children with uncomplicated *P. falciparum* malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) with an ACT.

Desirable effects

- Studies have consistently demonstrated that the six WHO-recommended ACTs result in < 5% PCR-adjusted treatment failures in settings with no resistance to the partner drug (high- quality evidence).

Undesirable effects

- Increased cost.

Recommendation: Dihydroartemisinin + piperaquine is recommended for general use.

Desirable effects:

- A PCR-adjusted treatment failure rate of < 5% has been seen consistently in trials of dihydroartemisinin + piperaquine (high-quality evidence).
- Dihydroartemisinin + piperaquine has a longer half-life than artemether + lumefantrine, and fewer new infections occur within 9 weeks of treatment with dihydroartemisinin + piperaquine (high-quality evidence).
- Dihydroartemisinin + piperaquine and artesunate + mefloquine have similar half-lives, and a similar frequency of new infections is seen within 9 weeks of treatment (moderate-quality evidence).

Undesirable effects:

- A few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine had a prolonged QT interval (low-quality evidence)
- A few more patients receiving dihydroartemisinin + piperaquine than those given artesunate + mefloquine or artemether + lumefantrine had borderline QT prolongation.

Certainty of the Evidence High

For all critical outcomes: High.

Justification

GRADE

In the absence of resistance to the partner drug, the five recommended ACTs have all been shown to achieve a PCR-adjusted treatment failure rate of 5% in many trials in several settings in both adults and children (high-quality evidence) *[180][181]*.

Other considerations

The guideline development group decided to recommend a menu of approved combinations, from which countries can select first- and second-line treatment.

Remarks

Recommendation: Treat adults and children with uncomplicated *P. falciparum* malaria (including infants, pregnant women in their second and third trimesters and breastfeeding women) with ACT.

The WHO-approved first-line ACT options are: artemether + lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, dihydroartemisinin + piperaquine and artesunate + sulfadoxine–pyrimethamine.

These options are recommended for adults and children, including infants, lactating women and pregnant women in their second and third trimester.

In deciding which ACTs to adopt in national treatment policies, national policy- makers should take into account: the pattern of resistance to antimalarial drugs in the country, the relative efficacy and safety of the combinations, their cost, the availability of paediatric formulations and the availability of co-formulated products.

Fixed-dose combinations are preferred to loose tablets or co-blistered products.

The Guideline Development Group decided to recommend a “menu” of approved combinations from which countries can select first- and second- line therapies. Modelling studies suggest that having multiple first-line ACTs available for use may help to prevent or delay the development of resistance.

Recommendation: Dihydroartemisinin + piperaquine is recommended for general use.

A systematic review showed that the dosing regimen of dihydroartemisinin + piperaquine currently recommended by the manufacturers leads to sub-optimal dosing in young children. The group plans to recommend a revised dosing regimen based on models of pharmacokinetics.

Further studies of the risk for QT interval prolongation have been requested by the European Medicines Agency.

ACT is a combination of a rapidly acting artemisinin derivative with a longer-acting (more slowly eliminated) partner drug. The artemisinin component rapidly clears parasites from the blood (reducing parasite numbers by a factor of approximately 10 000 in each 48 h asexual cycle) and is also active against the sexual stages of the gametocytes that mediate onward transmission to mosquitos. The longer- acting partner drug clears the remaining parasites and provides protection against development of resistance to the artemisinin derivative. Partner drugs with longer elimination half-lives also provide a period of post-treatment prophylaxis.

The GDG recommended dihydroartemisinin + piperaquine for use in 2009 but re-evaluated the evidence in 2013 because additional data on its safety had become available. The group noted the small absolute prolongation of the QT interval with dihydroartemisinin + piperaquine but was satisfied that the increase was of comparable magnitude to that

observed with chloroquine and was not important clinically *[179][182]*.

Strong recommendation for , Low certainty evidence

Artesunate-pyronaridine for uncomplicated malaria (2022)

Artesunate-pyronaridine (ASPY) is recommended as an artemisinin-based combination therapy option for the treatment of uncomplicated *P. falciparum* malaria.

- *ASPY should be avoided by individuals with known liver disease (clinically apparent liver disease) because ASPY is associated with liver transaminitis.*
- *Pharmacovigilance should be strengthened where ASPY is used for the treatment of malaria.*

Practical Info

As with the deployment of any new malaria treatment, pharmacovigilance and resistance surveillance systems should be strengthened.

Evidence To Decision

Benefits and harms

- ASPY, with large treatment effects, has been shown to be non-inferior in efficacy compared to the currently recommended ACTs. The overall benefit of this additional ACT is its potential to provide an alternative treatment, thereby reducing pressure on the partner medicines in the face of emerging artemisinin partner drug resistance.
- Compared to other ACTs, ASPY may have fewer PCR-adjusted and PCR-unadjusted failures at day 28, while results for day 42 are inconclusive. Data for children are limited.
- Following careful safety reviews, the conclusions are that the use of ASPY can be accompanied by mild, reversible and asymptomatic elevations of some liver enzymes, but that these elevations are not associated with clinically detected hepatotoxicity. ASPY is more likely than artemether-lumefantrine or artesunate-mefloquine to increase aspartate transaminase (AST) and alanine aminotransferase (ALT) > 5 times, but the risks are similar to those of artesunate-amodiaquine; there is no clear association of ASPY with increased bilirubin. There is no evidence to date to suggest that these transiently elevated transaminases result in serious liver injury.
- The risk of vomiting appears to be significantly higher in young children (7.7%) and infants (11.2%) than in older children (3.1%) and adults (2.8%) *[183]*. However, the overall risk of vomiting with ASPY is similar to the risks with other ACTs (OR: 0.91; 95% CI: 0.71–1.17; nine studies; n=5534) *[184]*.
- There are no data available from patients with pre-existing liver conditions (e.g. hepatitis B or C) or from those with risk factors for liver disease (e.g. receiving medicines known to be hepatotoxic, use of potentially hepatotoxic herbal medicines, alcohol abuse). There is, however, some early reassuring data from a study *[183]* that included limited data on inadvertent exposures of patients with HIV (15 exposures) and 158 persons with elevated liver enzymes (AST or ALT > 2 times the upper limit of normal [ULN]) at baseline. Caution is advised in these patients when considering ASPY as treatment, as these risk factors, as well as coadministration of potential hepatotoxic medicines (including paracetamol commonly used in patients with malaria), might have a cumulative adverse effect on the liver.

Certainty of the Evidence

Low

The GDG judged the overall certainty of the assessed evidence to be low mostly due to imprecision and indirectness.

Values and preferences

The GDG determined that there was probably no important uncertainty or variability in individual patients' values

and preferences, but country-level value judgements are still important, as these could be influenced by the prevalence of antimalarial partner drug resistance and the prevalence of hepatic diseases.

Resources

Research on formal cost analysis, and cost estimates related to scale are required. However, changing first- or second-line malaria treatment is quite resource-intensive, requiring staff training and patient information and introducing supply chain and logistical issues. However, introducing ASPY is not expected to be different from other ACTs already in use, as any additional cost would be minimal based on the actual cost of the medicine.

Equity

The GDG considered that ASPY is likely to enhance equity, especially in areas of emerging resistance to existing combinations. The addition of ASPY as a treatment option for malaria will probably increase health equity.

Acceptability

Although in some countries there is limited experience of its use, ASPY is probably acceptable given that some countries already include ASPY in therapeutic efficacy studies. Aside from the additional resource implications with the introduction of a new antimalarial regimen, oral treatments are generally well accepted. Some issues might arise when hepatic risk profiles need to be assessed in the target population.

Feasibility

Policy changes are feasible, since some countries have already started to use ASPY. The medicine is available, and the treatment regimen is similar to that of other approved ACTs. ASPY has also received a positive scientific opinion from the European Medicines Agency under Article 58 and is thus included in the WHO list of prequalified antimalarial medicines. However, the feasibility of strengthening pharmacovigilance will be highly variable from country to country.

Justification

The GDG reached a consensus on a strong recommendation for the intervention, despite the low certainty of evidence because of:

- the large magnitude of treatment effect, as well as its non-inferiority and comparability to the other currently recommended ACTs;
- its tolerability and generally mild, reversible adverse events; and
- the probable increased equity from access to an additional treatment option, specifically in the face of increasing ACT partner drug resistance.

Research Needs

The GDG highlighted the following evidence gaps requiring further research. These relate to:

- individual patient data meta-analysis comparing hepatic safety and gastrointestinal tolerability (particularly vomiting in young children and infants within one hour of dosing, as this could alter efficacy) between ASPY and other ACTs;
- continued assessment of efficacy, safety and tolerability of all ACTs, including ASPY, across malaria-endemic regions, especially in African children;
- further monitoring of efficacy, particularly in children in different settings, and monitoring for adverse events from inadvertent pregnancy exposures; and
- identification and validation of molecular markers of resistance to pyronaridine.

5.2.1.1.1 Duration of treatment

A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.

Strong recommendation for , High certainty evidence

Duration of ACT treatment (2015)

ACT regimens should provide 3 days' treatment with an artemisinin derivative.

Evidence To Decision

Benefits and harms

Desirable effects

- Fewer patients taking ACTs containing 3 days of an artemisinin derivative experience treatment failure within the first 28 days (high-quality evidence).
- Fewer participants taking ACTs containing 3 days of an artemisinin derivative have gametocytaemia at day 7 (high-quality evidence).

Certainty of the Evidence

High

For all critical outcomes: High.

Justification

GRADE

In four randomized controlled trials in which the addition of 3 days of artesunate to SP was compared directly with 1 day of artesunate with SP:

Three days of artesunate reduced the PCR-adjusted treatment failure rate within the first 28 days from that with 1 day of artesunate (RR, 0.45; 95% CI, 0.36–0.55, four trials, 1202 participants, high-quality evidence).

Three days of artesunate reduced the number of participants who had gametocytaemia at day 7 from that with 1 day of artesunate (RR, 0.74; 95% CI, 0.58–0.93, four trials, 1260 participants, high-quality evidence).

Other considerations

The guideline development group considered that 3 days of artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk of drug resistance resulting from incomplete treatment.

Remarks

Longer ACT treatment may be required to achieve > 90% cure rate in areas with artemisinin-resistant *P. falciparum*,

but there are insufficient trials to make definitive recommendations. A 3-day course of the artemisinin component of ACTs covers two asexual cycles, ensuring that only a small fraction of parasites remain for clearance by the partner drug, thus reducing the potential development of resistance to the partner drug. Shorter courses (1–2 days) are therefore not recommended, as they are less effective, have less effect on gametocytes and provide less protection for the slowly eliminated partner drug.

Rationale for the recommendation:
The Guideline Development Group considers that 3 days of an artemisinin derivative are necessary to provide sufficient efficacy, promote good adherence and minimize the risk for drug resistance due to incomplete treatment.

5.2.1.1.2 Dosing of ACTs

ACT regimens must ensure optimal dosing to prolong their useful therapeutic life, i.e. to maximize the likelihood of rapid clinical and parasitological cure, minimize transmission and retard drug resistance.

It is essential to achieve effective antimalarial drug concentrations for a sufficient time (exposure) in all target populations in order to ensure high cure rates. The dosage recommendations below are derived from understanding the relationship between dose and the profiles of exposure to the drug (pharmacokinetics) and the resulting therapeutic efficacy (pharmacodynamics) and safety. Some patient groups, notably younger children, are not dosed optimally with the “dosage regimens recommended by manufacturers, which compromises efficacy and fuels resistance. In these guidelines when there was pharmacological evidence that certain patient groups are not receiving optimal doses, dose regimens were adjusted to ensure similar exposure across all patient groups.

Weight-based dosage recommendations are summarized below. While age-based dosing may be more practical in children, the relation between age and weight differs in different populations. Age-based dosing can therefore result in under- dosing or over-dosing of some patients, unless large, region-specific weight-for-age databases are available to guide dosing in that region.

Factors other than dosage regimen may also affect exposure to a drug and thus treatment efficacy. The drug exposure of an individual patient also depends on factors such as the quality of the drug, the formulation, adherence and, for some drugs, co-administration with fat. Poor adherence is a major cause of treatment failure and drives the emergence and spread of drug resistance. Fixed-dose combinations encourage adherence and are preferred to loose (individual) tablets. Prescribers should take the time necessary to explain to patients why they should complete antimalarial course.

Artemether + lumefantrine
Formulations currently available: Dispersible or standard tablets containing 20 mg artemether and 120 mg lumefantrine, and standard tablets containing 40 mg artemether and 240 mg lumefantrine in a fixed-dose combination formulation. The flavoured dispersible tablet paediatric formulation facilitates use in young children.

Target dose range: A total dose of 5–24 mg/kg bw of artemether and 29–144 mg/ kg bw of lumefantrine

Recommended dosage regimen: Artemether + lumefantrine is given twice a day for 3 days (total, six doses). The first two doses should, ideally, be given 8 h apart.

Body weight (kg)	Dose (mg) of artemether + lumefantrine given twice daily for 3 days
5 to < 15	20 + 120
15 to < 25	40 + 240
25 to < 35	60 + 360
≥ 35	80 + 480

Factors associated with altered drug exposure and treatment response:

- Decreased exposure to lumefantrine has been documented in young children (<3 years) as well as pregnant women, large adults, patients taking mefloquine, rifampicin or efavirenz and in smokers. As these target populations may be at increased risk for treatment failure, their responses to treatment should be monitored more closely and their full adherence ensured.
- Increased exposure to lumefantrine has been observed in patients concomitantly taking lopinavir-lopinavir/ritonavir-based antiretroviral agents but with no increase in toxicity; therefore, no dosage adjustment is indicated.

Additional comments:

- An advantage of this ACT is that lumefantrine is not available as a monotherapy and has never been used alone for the treatment of malaria.
- Absorption of lumefantrine is enhanced by co-administration with fat. Patients or caregivers should

be informed that this ACT should be taken immediately after food or a fat containing drink (e.g. milk), particularly on the second and third days of treatment.

Artesunate + amodiaquine
Formulations currently available: A fixed-dose combination in tablets containing 25 + 67.5 mg, 50 + 135 mg or 100 + 270 mg of artesunate and amodiaquine, respectively

Target dose and range: The target dose (and range) are 4 (2–10) mg/kg bw per day artesunate and 10 (7.5–15) mg/kg bw per day amodiaquine once a day for 3 days. A total therapeutic dose range of 6–30 mg/kg bw per day artesunate and 22.5–45 mg/kg bw per dose amodiaquine is recommended.

Body weight (kg)	Artesunate + amodiaquine dose (mg) given daily for 3 days
4.5 to < 9	25 + 67.5
9 to < 18	50 + 135
18 to < 36	100 + 270
≥ 36	200 + 540

Factors associated with altered drug exposure and treatment response:

Treatment failure after amodiaquine monotherapy was more frequent among children who were underweight for their age. Therefore, their response to artesunate + amodiaquine treatment should be closely monitored.

Artesunate + amodiaquine is associated with severe neutropenia, particularly in patients co-infected with HIV and especially in those on zidovudine and/or cotrimoxazole. Concomitant use of efavirenz increases exposure to amodiaquine and hepatotoxicity. Thus, concomitant use of artesunate + amodiaquine by patients taking zidovudine, efavirenz and cotrimoxazole should be avoided, unless this is the only ACT promptly available.

Additional comments:

No significant changes in the pharmacokinetics of amodiaquine or its metabolite desethylamodiaquine have been observed during the second and third trimesters of pregnancy; therefore, no dosage adjustments are recommended.

No effect of age has been observed on the plasma concentrations of amodiaquine and desethylamodiaquine, so no dose adjustment by age is indicated. Few data are available on the pharmacokinetics of amodiaquine in the first year of life.

Artesunate + mefloquine
Formulations currently available: A fixed-dose formulation of paediatric tablets containing 25 mg artesunate and 55 mg mefloquine hydrochloride (equivalent to 50 mg mefloquine base) and adult tablets containing 100 mg artesunate and 220 mg mefloquine hydrochloride (equivalent to 200 mg mefloquine base)

Target dose and range: Target doses (ranges) of 4 (2–10) mg/kg bw per day artesunate and 8.3 (7–11) mg/kg bw per day mefloquine, given once a day for 3 days

Body weight (kg)	Artesunate + mefloquine dose (mg) given daily for 3 days
5 to < 9	25 + 55
9 to < 18	50 + 110
18 to < 30	100 + 220
≥ 30	200 + 440

Additional comments:

Mefloquine was associated with increased incidences of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these symptoms are seldom debilitating, and, where this ACT has been used, it has generally been well tolerated. To reduce acute vomiting and optimize absorption, the total mefloquine dose should preferably be split over 3 days, as in current fixed-dose combinations.

As concomitant use of rifampicin decreases exposure to mefloquine, potentially decreasing its efficacy, patients taking this drug should be followed up carefully to identify treatment failures.

Artesunate + sulfadoxine–pyrimethamine
Formulations: Currently available as blister-packed, scored tablets containing 50 mg artesunate and fixed dose combination tablets comprising 500 mg sulfadoxine + 25 mg pyrimethamine. There is no fixed-dose combination.

Target dose and range: A target dose (range) of 4 (2–10) mg/kg bw per day artesunate given once a day for 3 days and a single administration of at least 25 / 1.25 (25–70 / 1.25–3.5) mg/kg bw sulfadoxine / pyrimethamine given as a single dose on day 1.

Body weight (kg)	Artesunate dose given daily for 3 days (mg)	Sulfadoxine / pyrimethamine dose (mg) given as a single dose on day 1
5 to < 10	25 mg	250 / 12.5
10 to < 25	50 mg	500 / 25
25 to < 50	100 mg	1000 / 50
≥ 50	200 mg	1500 / 75

Factors associated with altered drug exposure and treatment response: The low dose of folic acid (0.4 mg daily) that is required to protect the fetuses of pregnant women from neural tube defects do not reduce the efficacy of SP, whereas higher doses (5 mg daily) do significantly reduce its efficacy and should not be given concomitantly.

Additional comments:

The disadvantage of this ACT is that it is not available as a fixed-dose combination. This may compromise adherence and increase the risk for distribution of loose artesunate tablets, despite the WHO ban on artesunate monotherapy.

Resistance is likely to increase with continued widespread use of SP, sulfalene– pyrimethamine and cotrimoxazole (trimethoprim-sulfamethoxazole). Fortunately, molecular markers of resistance to antifols and sulfonamides correlate well with therapeutic responses. These should be monitored in areas in which this drug is used.

Strong recommendation for

Revised dose recommendation for dihydroartemisinin + piperaquine in young children (2015)

Children weighing <25kg treated with dihydroartemisinin + piperaquine should receive a minimum of 2.5 mg/kg bw per day of dihydroartemisinin and 20 mg/ kg bw per day of piperaquine daily for 3 days.

*Not evaluated using the GRADE framework

Practical Info

Formulations: Currently available as a fixed-dose combination in tablets containing 40 mg dihydroartemisinin and 320 mg piperaquine and paediatric tablets contain 20 mg dihydroartemisinin and 160 mg piperaquine.

Target dose and range: A target dose (range) of 4 (2–10) mg/kg bw per day dihydroartemisinin and 18 (16–27) mg/kg bw per day piperaquine given once a day for 3 days for adults and children weighing ≥ 25 kg. The target doses and ranges for children weighing < 25 kg are 4 (2.5–10) mg/kg bw per day dihydroartemisinin and 24 (20–32) mg/kg bw per day piperaquine once a day for 3 days.

Recommended dosage regimen: The dose regimen currently recommended by the manufacturer provides adequate exposure to piperaquine and excellent cure rates (> 95%), except in children < 5 years, who have a threefold increased risk for treatment failure. Children in this age group have significantly lower plasma piperaquine concentrations than older children and adults given the same mg/kg bw dose. Children weighing < 25 kg should receive at least 2.5 mg/kg bw dihydroartemisinin and 20 mg/kg bw piperaquine to achieve the same exposure as children weighing ≥ 25 kg and adults.

Dihydroartemisinin + piperaquine should be given daily for 3 days.

Body weight (kg)	Dihydroartemisinin + piperaquine dose (mg) given daily for 3 days
5 to < 8	20 + 160
8 to < 11	30 + 240
11 to < 17	40 + 320
17 to < 25	60 + 480
25 to < 36	80 + 640
36 to < 60	120 + 960
60 < 80	160 + 1280
>80	200 + 1600

Factors associated with altered drug exposure and treatment response:

High-fat meals should be avoided, as they significantly accelerate the absorption of piperaquine, thereby increasing

the risk for potentially arrhythmogenic delayed ventricular repolarization (prolongation of the corrected electrocardiogram QT interval). Normal meals do not alter the absorption of piperaquine.

As malnourished children are at increased risk for treatment failure, their response to treatment should be monitored closely.

- Dihydroartemisinin exposure is lower in pregnant women.
- Piperaquine is eliminated more rapidly by pregnant women, shortening the post-treatment prophylactic effect of dihydroartemisinin + piperaquine. As this does not affect primary efficacy, no dosage adjustment is recommended for pregnant women.

Additional comments: Piperaquine prolongs the QT interval by approximately the same amount as chloroquine but by less than quinine. It is not necessary to perform an electrocardiogram before prescribing dihydroartemisinin + piperaquine, but this ACT should not be used in patients with congenital QT prolongation or who have a clinical condition or are on medications that prolong the QT interval. There has been no evidence of cardiotoxicity in large randomized trials or in extensive deployment.

Justification

The dosing subgroup reviewed all available dihydroartemisinin-piperaquine pharmacokinetic data (6 published studies and 10 studies from the WWARN database; total 652 patients) *[182][185]* and then conducted simulations of piperaquine exposures for each weight group. These showed lower exposure in younger children with higher risks of treatment failure. The revised dose regimens are predicted to provide equivalent piperaquine exposures across all age groups.

Other considerations
This dose adjustment is not predicted to result in higher peak piperaquine concentrations than in older children and adults, and as there is no evidence of increased toxicity in young children, the GRC concluded that the predicted benefits of improved antimalarial exposure are not at the expense of increased risk.

5.2.1.2 Recurrent falciparum malaria

Recurrence of *P. falciparum* malaria can result from re-infection or recrudescence (treatment failure). Treatment failure may result from drug resistance or inadequate exposure to the drug due to sub-optimal dosing, poor adherence, vomiting, unusual pharmacokinetics in an individual, or substandard medicines. It is important to determine from the patient's history whether he or she vomited the previous treatment or did not complete a full course of treatment.

When possible, treatment failure must be confirmed parasitologically. This may require referring the patient to a facility with microscopy or LDH-based RDTs, as *P. falciparum* histidine-rich protein-2 (*Pf*HRP2)-based tests may remain positive for weeks after the initial infection, even without recrudescence. Referral may be necessary anyway to obtain second-line treatment. In individual patients, it may not be possible to distinguish recrudescence from re-infection, although lack of resolution of fever and parasitaemia or their recurrence within 4 weeks of treatment are considered failures of treatment with currently recommended ACTs. In many cases, treatment failures are missed because patients are not asked whether they received antimalarial treatment within the preceding 1–2 months. Patients who present with malaria should be asked this question routinely.

Failure within 28 days
The recommended second-line treatment is an alternative ACT known to be effective in the region. Adherence to 7-day treatment regimens (with artesunate or quinine both of which should be co-administered with + tetracycline, or doxycycline or clindamycin) is likely to be poor if treatment is not directly observed; these regimens are no longer generally recommended. The distribution and use of oral artesunate monotherapy outside special centres are strongly discouraged, and quinine-containing regimens are not well tolerated.

Failure after 28 days
Recurrence of fever and parasitaemia > 4 weeks after treatment may be due to either recrudescence or a new infection. The distinction can be made only by PCR genotyping of parasites from the initial and the recurrent infections.

As PCR is not routinely used in patient management, all presumed treatment failures after 4 weeks of initial treatment should, from an operational standpoint, be considered new infections and be treated with the first-line ACT. However, reuse of mefloquine within 60 days of first treatment is associated with an increased risk for neuropsychiatric reactions, and an alternative ACT should be

used.

5.2.1.3 Reducing the transmissibility of treated P. falciparum infections in areas of low-intensity transmission

Strong recommendation for , Low certainty evidence

Reducing the transmissibility of treated *P. falciparum* infections (2015)

In low-transmission areas, a single dose of 0.25 mg/kg bw primaquine should be given with an ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.

Practical Info

In light of concern about the safety of the previously recommended dose of 0.75 mg/kg bw in individuals with G6PD deficiency, a WHO panel reviewed the safety of primaquine as a *P. falciparum* gametocytocide and concluded that a single dose of 0.25 mg/kg bw of primaquine base is unlikely to cause serious toxicity, even in people with G6PD deficiency *[188]*. Thus, where indicated a single dose of 0.25mg/kg bw of primaquine base should be given on the first day of treatment, in addition to an ACT, to all patients with parasitologically confirmed *P. falciparum* malaria except for pregnant women, infants < 6 months of age and women breastfeeding infants < 6 months of age, because there are insufficient data on the safety of its use in these groups.

Dosing table based on the most widely currently available tablet strength (7.5mg base)

Body weight (kg)	Single dose of primaquine (mg base)
10[a] to < 25 3.75	3.75
25 to < 50 7.5	7.5
50 to 100 15	15

[a] Dosing of young children weighing < 10 kg is limited by the tablet sizes currently available.

Please refer to the *Policy brief on single-dose primaquine as a gametocytocide in Plasmodium falciparum malaria [189]*.

Evidence To Decision

Benefits and harms

Desirable effects

- Single doses of primaquine > 0.4 mg/kg bw reduced gametocyte carriage at day 8 by around two thirds (moderate-quality evidence).
- There are too few trials of doses < 0.4 mg/kg bw to quantify the effect on gametocyte carriage (low-quality evidence).
- Analysis of observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.

Undesirable effects

- People with severe G6PD deficiency are at risk for haemolysis. At this dose, however, the risk is thought to be small; there are insufficient data to quantify this risk.

Certainty of the Evidence Low

Overall certainty of evidence for all critical outcomes: low.

Justification

GRADE

In an analysis of observational studies of single-dose primaquine, data from mosquito feeding studies on 180 people suggest that adding 0.25 mg/kg primaquine to treatment with an ACT can rapidly reduce the infectivity of gametocytes to mosquitoes.

In a systematic review of eight randomized controlled trials of the efficacy of adding single-dose primaquine to ACTs for reducing the transmission of malaria, in comparison with ACTs alone *[186]*:

- single doses of > 0.4 mg/kg bw primaquine reduced gametocyte carriage at day 8 by about two thirds (RR, 0.34; 95% CI, 0.19–0.59, two trials, 269 participants, *high-certainty evidence*); and
- single doses of primaquine > 0.6 mg/kg bw reduced gametocyte carriage at day 8 by about two thirds (RR, 0.29; 95% CI, 0.22–0.37, seven trials, 1380 participants, *high-certainty evidence*).

There have been no randomized controlled trials of the effects on the incidence of malaria or on transmission to mosquitos.

Other considerations

The guideline development group considered that the evidence of a dose– response relation from observational studies of mosquito feeding was sufficient to conclude the primaquine dose of 0.25mg/kg bw significantly reduced *P. falciparum* transmissibility.

The population benefits of reducing malaria transmission with gametocytocidal drugs such as primaquine require that a very high proportion of treated patients receive these medicines and that there is no large transmission reservoir of asymptomatic parasite carriers. This strategy is therefore likely to be effective only in areas of low-intensity malaria transmission, as a component of elimination programmes.

Remarks

This recommendation excludes high-transmission settings, as symptomatic patients make up only a small proportion of the total population carrying gametocytes within a community, and primaquine is unlikely to affect transmission.

A major concern of national policy-makers in using primaquine has been the small risk for haemolytic toxicity in G6PD-deficient people, especially where G6PD testing is not available.

Life-threatening haemolysis is considered unlikely with the 0.25mg/kg bw dose and without G6PD testing *[187]*.

Rationale for the recommendation: The Guideline Development Group considered the evidence on dose–response relations in the observational mosquito-feeding studies of reduced transmissibility with the dose of 0.25 mg/kg bw and the judgement of the WHO Evidence Review Group (November 2012). Their view was that the potential public health benefits of single low-dose (0.25 mg/kg bw) primaquine in addition to an ACT for falciparum malaria, without G6PD testing, outweigh the potential risk for adverse effects.

5.2.1.4 Special risk groups

Several important patient sub-populations, including young children, pregnant women and patients taking potent enzyme inducers (e.g. rifampicin, efavirenz), have altered pharmacokinetics, resulting in sub-optimal exposure to

antimalarial drugs. This increases the rate of treatment failure with current dosage regimens. The rates of treatment failure are substantially higher in hyperparasitaemic patients and patients in areas with artemisinin-resistant falciparum malaria, and these groups require greater exposure to antimalarial drugs (longer duration of therapeutic concentrations) than is achieved with current ACT dosage recommendations. It is often uncertain how best to achieve this. Options include increasing individual doses, changing the frequency or duration of dosing, or adding an additional antimalarial drug. Increasing individual doses may not, however, achieve the desired exposure (e.g., lumefantrine absorption becomes saturated), or the dose may be toxic due to transiently high plasma concentrations (piperaquine, mefloquine, amodiaquine, pyronaridine). An additional advantage of lengthening the duration of treatment (by giving a 5-day regimen) is that it provides additional exposure of the asexual cycle to the artemisinin component as well as augmenting exposure to the partner drug. The acceptability, tolerability, safety and effectiveness of augmented ACT regimens in these special circumstances should be evaluated urgently.

Large and obese adults

Large adults are at risk for under-dosing when they are dosed by age or in standard pre-packaged adult weight-based treatments. In principle, dosing of large adults should be based on achieving the target mg/kg bw dose for each antimalarial regimen. The practical consequence is that two packs of an antimalarial drug might have to be opened to ensure adequate treatment. For obese patients, less drug is often distributed to fat than to other tissues; therefore, they should be dosed on the basis of an estimate of lean body weight, ideal body weight. Patients who are heavy but not obese require the same mg/kg bw doses as lighter patients.

In the past, maximum doses have been recommended, but there is no evidence or justification for this practice. As the evidence for an association between dose, pharmacokinetics and treatment outcome in overweight or large adults is limited, and alternative dosing options have not been assessed in treatment trials, it is recommended that this gap in knowledge be assessed urgently. In the absence of data, treatment providers should attempt to follow up the treatment outcomes of large adults whenever possible.

5.2.1.4.1 Pregnant and lactating women

Malaria in pregnancy is associated with low-birth-weight infants, increased anaemia and, in low-transmission areas, increased risks for severe malaria, pregnancy loss and death. In high-transmission settings, despite the adverse effects on fetal growth, malaria is usually asymptomatic in pregnancy or is associated with only mild, non-specific symptoms. There is insufficient information on the safety, efficacy and pharmacokinetics of most antimalarial agents in pregnancy, particularly during the first trimester.

First trimester of pregnancy

Malaria in pregnancy is associated with low birthweight in infants, increased anaemia and, in low-transmission areas, increased risks for severe malaria, pregnancy loss and death. Malaria in pregnancy is, therefore, considered a priority problem. The risk of malaria infection is said to be highest in the first and second trimesters of pregnancy *[190]*. In a study in Benin, the prevalence of malaria infection in the first trimester was 21.8% and was significantly associated with maternal anaemia in the third trimester (adjusted odds ratio [aOR]: 2.25; 95% CI: 1.11–4.55) *[191]*. A modelling study among women in areas of stable malaria transmission suggested that over 60% of malaria infections during pregnancy occur by the end of the first trimester *[192]*.

Although ACTs have been shown to be more effective and better tolerated and provide longer post-treatment prophylaxis than oral quinine in the second and third trimesters of pregnancy, to date, WHO had recommended quinine + clindamycin instead of ACTs for the first trimester. This recommendation was due to concerns about the potential teratogenicity of the artemisinin observed in pre-clinical animal studies *[193][194]*.

WHO has generated a new recommendation based on a review of all updated evidence to date on the risks and benefits of using any ACT compared to quinine for the treatment of uncomplicated *P. falciparum* malaria in the first trimester of pregnancy. The new recommendation is given in the box below.

Second and third trimesters

Experience with artemisinin derivatives in the second and third trimesters (over 4000 documented pregnancies) is increasingly reassuring: no adverse effects on the mother or fetus have been reported. The current assessment of risk–benefit suggests that ACTs should be used to treat uncomplicated falciparum malaria in the second and third trimesters of pregnancy. The current standard six-dose artemether + lumefantrine regimen for the treatment of uncomplicated falciparum malaria has been evaluated in > 1000 women in the second and third trimesters in controlled trials and has been found to be well tolerated and safe. In a low-transmission setting on the Myanmar–Thailand border, however, the efficacy of the standard six-dose artemether + lumefantrine regimen was inferior to 7 days of artesunate monotherapy. The lower efficacy may have been due to lower drug concentrations in pregnancy, as was also recently observed in a high-transmission area in Uganda and the United Republic of Tanzania. Although many women in the second and third trimesters of pregnancy in Africa have been exposed to artemether + lumefantrine, further studies are under way to evaluate its efficacy, pharmacokinetics and safety in pregnant women. Similarly, many pregnant women in

Africa have been treated with amodiaquine alone or combined with SP or artesunate; however, amodiaquine use for the treatment of malaria in pregnancy has been formally documented in only > 1300 pregnancies. Use of amodiaquine in women in Ghana in the second and third trimesters of pregnancy was associated with frequent minor side- effects but not with liver toxicity, bone marrow depression or adverse neonatal outcomes.

Dihydroartemisinin + piperaquine was used successfully in the second and third trimesters of pregnancy in > 2000 women on the Myanmar–Thailand border for rescue therapy and in Indonesia for first-line treatment. SP, although considered safe, is not appropriate for use as an artesunate partner drug in many areas because of resistance to SP. If artesunate + SP is used for treatment, co-administration of daily high doses (5 mg) of folate supplementation should be avoided, as this compromises the efficacy of SP. A lower dose of folate (0.4–0.5 mg bw/day) or a treatment other than artesunate + SP should be used.

Mefloquine is considered safe for the treatment of malaria during the second and third trimesters; however, it should be given only in combination with an artemisinin derivative.

Quinine is associated with an increased risk for hypoglycaemia in late pregnancy, and it should be used (with clindamycin) only if effective alternatives are not available.

Primaquine and tetracyclines should not be used in pregnancy.

Dosing in pregnancy

Data on the pharmacokinetics of antimalarial agents used during pregnancy are limited. Those available indicate that pharmacokinetic properties are often altered during pregnancy but that the alterations are insufficient to warrant dose modifications at this time. With quinine, no significant differences in exposure have been seen during pregnancy. Studies of the pharmacokinetics of SP used in IPTp in many sites show significantly decreased exposure to sulfadoxine, but the findings on exposure to pyrimethamine are inconsistent. Therefore, no dose modification is warranted at this time.

Studies are available of the pharmacokinetics of artemether + lumefantrine, artesunate + mefloquine and dihydroartemisinin + piperaquine. Most data exist for artemether + lumefantrine; these suggest decreased overall exposure during the second and third trimesters. Simulations suggest that a standard six-dose regimen of lumefantrine given over 5 days, rather than 3 days, improves exposure, but the data are insufficient to recommend this alternative regimen at present. Limited data on pregnant women treated with dihydroartemesinin + piperaquine suggest lower dihydroartemisinin exposure and no overall difference in total piperaquine exposure, but a shortened piperaquine elimination half-life was noted. The data on artesunate + mefloquine are insufficient to recommend an adjustment of dosage. No data are available on the pharmacokinetics of artesunate + amodiaquine in pregnant women with falciparum malaria, although drug exposure was similar in pregnant and non-pregnant women with vivax malaria.

Lactating women

The amounts of antimalarial drugs that enter breast milk and are consumed by breastfeeding infants are relatively small. Tetracycline is contraindicated in breastfeeding mothers because of its potential effect on infants' bones and teeth. Pending further information on excretion in breast milk, primaquine should not be used for nursing women, unless the breastfed infant has been checked for G6PD deficiency.

Strong recommendation for , Low certainty evidence

Treatment in the first trimester of pregnancy (2022)

Pregnant women with uncomplicated *P. falciparum* malaria should be treated with artemether-lumefantrine during the first trimester.

- *Limited exposures to other ACTs (artesunate-amodiaquine, artesunate-mefloquine and dihydroartemisinin-piperaquine) suggest that the current evidence is insufficient to make a recommendation for routine use of these other ACTs in the first trimester of pregnancy. However, consistent with the previous WHO recommendation that provided for limited use of ACTs if the first-line recommended medicine was not available, these other ACTs may be considered for use where artemether-lumefantrine is not a recommended ACT for uncomplicated malaria or is not available, given the demonstrated poorer outcomes of quinine treatment, along with the challenges of adherence to a seven-day course of treatment.*
- *Antifolates are contraindicated in the first trimester of pregnancy. Therefore, ACTs containing sulfadoxine-pyrimethamine are contraindicated during the first trimester of pregnancy.*
- *There is currently no documented record of the use of artesunate-pyronaridine during the first trimester of pregnancy.*
- *Continued pharmacovigilance and clinical research, including prospective controlled trials on the efficacy and safety of antimalarial medicines for the treatment of malaria in pregnancy, should be supported and funded.*

Practical Info

As with the deployment of any new malaria treatment recommendations, pharmacovigilance and adverse events and pregnancy outcome surveillance systems should be strengthened.

Evidence To Decision

Benefits and harms

ACTs have large positive effects with respect to efficacy, effectiveness and tolerability compared to quinine in non-pregnant patients and women in the second and third trimesters of pregnancy. Systematic reviews have shown that treatment failures are six times more likely with quinine than with artemether-lumefantrine in the second and third trimesters of pregnancy *[195][196]*.

In various animal studies (including rodents and monkeys), artemisinin has been found to deplete embryonic erythroblasts at relatively low doses of 1/200–1/400 of the LD50 (equivalent to > 10 mg/kg body weight), leading to malformation or embryonic death *[193][197]*. The adverse effects include embryo resorption, pregnancy loss and congenital anomalies, including shortening of the long bones and heart defects (ventricular septal and great vessel defects) *[198][199]*. For this reason, despite its demonstrated lower efficacy in the second and third trimesters of pregnancy, quinine (in combination with clindamycin) was retained by WHO in 2015 for treatment in the first trimester until adequate numbers of human exposures to artemisinin could allow for more safety assessments in humans.

In weighing the risk–benefit ratio, safety risks from antimalarial treatment need to be weighed against the adverse effects of malaria in the first trimester *[200]*.

A recently updated individual patient data meta-analysis of 34 178 pregnancies included 737 well documented pregnancies exposed to artemisinin and 1076 exposed to non-artemisinin-based treatments in the first trimester. Of the exposures to artemisinin, 71% (525) were to artemether-lumefantrine *[201]*. This meta-analysis provided the basis for the re-evaluation of the treatment of malaria in the first trimester of pregnancy.

This updated individual patient data review showed that first-trimester treatment with artemether-lumefantrine was associated with significantly fewer adverse pregnancy outcomes than first-trimester treatment with quinine. Treatment with artemether-lumefantrine in the first trimester was associated with a statistically significant lower risk (42%) of adverse pregnancy outcomes compared to treatment with oral quinine (aHR: 0.58; 95% CI: 0.36–0.92) *[201]*. The numbers of exposures to the other ACTs (excluding artesunate-pyronaridine) were too small to allow for a subgroup analysis *[201]*. There is currently no documented record of the use of artesunate-pyronaridine during the first trimester of pregnancy. Combined with the known better tolerability and effectiveness and the longer duration of post-treatment prophylaxis, artemether-lumefantrine clearly has a more

favourable risk–benefit profile than quinine for treating uncomplicated falciparum malaria in the first trimester.

An analysis of all exposures to artemisinin-based treatment (ABT) in the first trimester of pregnancy as a means of addressing the concerns previously demonstrated in animal studies showed no differences between pregnancies exposed in the first trimester to artemisinin and those exposed to non-ABT in terms of the composite adverse pregnancy outcome (ABT=42/736 [5.7%] vs non-ABT=96/1074 [8.9%]; aHR: 0.71; 95% CI: 0.49–1.03). Analysis for adverse pregnancy outcomes against the individual parameters in the composite analysis, including miscarriage, stillbirth or congenital anomalies, also revealed no statistically significant difference. There was also no difference in the risk of these adverse pregnancy outcomes when exposures were restricted to the putative embryo-sensitive period. This meta-analysis had 8126 additional pregnancies with 60 additional artemisinin exposures in the first trimester compared to the review published in 2017 *[202]*. This analysis *[201]* strengthens previous findings of the 2017 review that the potential for artemisinin-based embryotoxicity observed in animal studies is not reflected in humans treated for malaria. The analysis also demonstrates how few pregnancy outcomes after ACT exposures in the first trimester of pregnancy can be documented.

The teratogenic effect of the artemisinin observed in animal studies was not apparent in any of the reviewed data on human exposure to ACTs in the first trimester of pregnancy. However, there are some reasons to exercise caution in drawing a definite conclusion on the safety of the artemisinin derivatives as a drug class. These reasons include: the possibility of immortal time bias, resulting in an inability to detect early fetal losses; potential bias in observational study designs with exposure to quinine as the main comparator; and current limited postnatal evaluation, e.g. for cardiovascular and other malformations *[203]*. In addition, most of the safety data are on artemether-lumefantrine. Although artemisinin derivatives are rapidly converted to dihydroartemisinin as their active metabolite, differences between the different derivatives, or differences caused by the combination with different partner drugs cannot be excluded.

In terms of the safety and tolerability of the currently recommended ACT partner antimalarials, the antifolate sulfadoxine-pyrimethamine is contraindicated during the first trimester of pregnancy, as it is known to have a potential teratogenic risk in humans at therapeutic doses *[204]*. There is currently no documented exposure to pyronaridine in the first trimester of pregnancy. Among 3428 pregnant women in the second or third trimester treated with an ACT for *P. falciparum* malaria (at any parasite density and regardless of symptoms), drug-related adverse events such as asthenia, poor appetite, dizziness, nausea and vomiting occurred significantly more frequently in the artesunate-mefloquine group (50.6%) and the artesunate-amodiaquine group (48.5%) than in the dihydroartemisinin-piperaquine group (20.6%) and the artemether-lumefantrine group (11.5%) ($p<0.001$ for comparison among the four groups) *[205]*.

There is a lack of documented exposures very early in gestation (gestational weeks 4–10), which is considered a critical period for teratogenic risk. Therefore, the potential for any given medicine, including quinine, to cause a specific teratogenic effect can only be reliably ascertained when it has been administered during this sensitive period (which is almost impossible to study, given how soon this critical window occurs after the last menstrual period) *[203]*.

Certainty of the Evidence

Low

The GDG judged the overall certainty of the assessed evidence across the different outcomes to be low due to bias inherent in observational studies. It was difficult to generalize across all ACTs because of the limited number of pregnant women in the first trimester treated with ACTs other than artemether-lumefantrine who were included in the review.

Values and preferences

The GDG judged that there may be important uncertainty or variability in patient values and preferences with regard to choosing between artemether-lumefantrine, other ACTs and quinine-based therapies, and in how different cultures would value the outcomes being monitored, such as perceptions around early trimester pregnancy losses, low birthweight and anaemia. However, artemether-lumefantrine compared to quinine is likely

to be a more attractive option because of its greater availability and the convenience of a shorter, better tolerated treatment. Policy-makers and implementers will obviously prefer simplified recommendations on using artemether-lumefantrine or other ACTs to treat pregnant women with uncomplicated *P. falciparum* malaria across all trimesters.

According to a systematic review of sociocultural factors *[206]*, malaria in pregnancy is interpreted in locally defined categories, despite the higher malaria risk associated with pregnancy. Local context and health workers' ideas and comments influence concerns about malaria in pregnancy interventions. Factors such as the understanding of antenatal care, health worker–client interactions, household decision-making, gender relations, cost and distance to health facilities affect pregnant women's access to these interventions and their health-seeking behaviour. It is difficult to ascertain whether any sociocultural factors would result in variability in the likely preference for artemether-lumefantrine or other ACTs over quinine treatment.

Resources

ACTs, of which artemether-lumefantrine is the most widely used, are the treatment of choice for uncomplicated falciparum malaria in nearly all malaria-endemic countries and are thus readily available. Conversely, the supply of quinine has become problematic because of the small proportion of the total population that receive this antimalarial treatment. Clindamycin, which is recommended in combination with quinine, is commonly unavailable and unaffordable in most endemic regions. In addition, the quinine + clindamycin regime is associated with a high pill burden, requiring between 56 and 70 tablets to be ingested over a seven-day period. In most country programmes, quinine monotherapy is thus currently recommended in the first trimester of pregnancy. However, in some countries in eastern and southern Africa, quinine is rarely available in public facilities, and many pregnant women in the first trimester are already being treated with artemether-lumefantrine, based on reports from the national malaria programmes.

Aligning the first-line treatment of uncomplicated *P. falciparum* malaria for the first trimester with that currently recommended for the second and third trimesters would simplify case management, service delivery, communications and supply chain management. Such an alignment was assessed as likely to result in large savings. However, research on formal cost analysis and cost estimates regarding the use of artemether-lumefantrine or other ACTs versus quinine in the first trimester of pregnancy are still lacking.

Equity

Despite the obvious efficiency to be gained by harmonizing the treatment regimens throughout pregnancy, no studies were found. However, health equity will increase, especially for vulnerable populations, if this more effective, more accessible and better tolerated treatment is recommended for the management of malaria in all trimesters of pregnancy.

Acceptability

In considering the acceptability of artemether-lumefantrine versus quinine treatments, the GDG looked to how quinine is presently being used and accepted.

Adherence to quinine is low because it is frequently associated with adverse effects, including cinchonism, nausea and hypoglycaemia *[195][207][208]*. In a review of 35 national guidelines, 66% recommended oral quinine as first-line treatment for uncomplicated malaria in the first trimester of pregnancy. Of these, only 29% included the combined use with clindamycin in their guidelines, reflecting the unavailability and/or cost of clindamycin *[209]*. Health care reliance on clinical diagnosis and poor adherence to treatment policy, especially in the first trimester, have been consistently reported. Prescribing practices have been driven by concerns over side effects and drug safety, patient preferences, drug availability and cost *[210]*.

With poor adherence to the presently recommended quinine-based treatments and better access to ACTs, it appears that artemether-lumefantrine will be a more acceptable option. A three-day ACT treatment regimen is

likely to be more acceptable than a seven-day treatment with quinine.

Policy-makers and health care workers will likely welcome the evidence-based decision recommending artemether-lumefantrine for all trimesters of pregnancy. In situations where artemether-lumefantrine is no longer recommended for the treatment of malaria because of reduced efficacy and/or it is not promptly available, the use of some of the other ACTs recommended in national guidelines can be considered, given the demonstrated poorer outcomes of quinine treatment, along with the challenges of adherence to a seven-day treatment course. However, artesunate plus sulfadoxine-pyrimethamine cannot be recommended in the first trimester of pregnancy given the potential teratogenicity of antifolates. Furthermore, the lack of documented outcomes following the use of artesunate-pyronaridine precludes its use in the first trimester.

Feasibility

One consideration in determining the feasibility of the recommendation on treatment of malaria in the first trimester is that the existing warning against the use of artemisinin in the first trimester implies the need to consistently screen for pregnancy among all women of childbearing potential prior to treatment for malaria. However, pregnancy screening is rarely done prior to initiating malaria treatment. As observed by national programmes, the contraindication of artemisinin in the first trimester has resulted in confusion, most problematically resulting in pregnant women in the first trimester with severe malaria not receiving the recommended parenteral artesunate, thereby increasing malaria morbidity and mortality in this particularly vulnerable subgroup *[211][212]*.

Given that ACTs, particularly artemether-lumefantrine, are already widely used in the treatment of malaria in pregnancy, although mainly in the second and third trimesters, uptake of artemether-lumefantrine (and other ACTs) should be feasible in the first trimester of pregnancy. There will also be less confusion once the recommendations are aligned across all trimesters of pregnancy, implying that artemether-lumefantrine or other ACTs should be more feasible and adherence to the implementation strategies should improve relative to that with quinine-based treatment.

Justification

The GDG reached a consensus on a strong recommendation for artemether-lumefantrine as the preferred treatment of uncomplicated *Plasmodium falciparum* malaria during the first trimester of pregnancy, despite the low certainty of evidence because:

- there was a large magnitude of beneficial effect of treatment on efficacy (demonstrated in the second and third trimesters of pregnancy), specifically a six-fold reduction in treatment failures following artemether-lumefantrine, compared to the currently recommended quinine-based therapies;
- artemether-lumefantrine was associated with trivial adverse events and significantly lower risk for adverse pregnancy outcomes in the first trimester of pregnancy;
- artemether-lumefantrine had much better tolerability compared to quinine-based therapies; and
- there is probably increased equity, acceptability and feasibility, resulting from better access to artemether-lumefantrine and more efficient implementation of ACTs compared to quinine-based treatments.

Despite limited exposures to other ACTs (artesunate-amodiaquine, artesunate-mefloquine and dihydroartemisinin-piperaquine), the current evidence does not raise any concerns. However, consistent with the previous WHO recommendation that provided for limited use of ACTs if the first-line recommended medicine was not available, these other ACTs may be used where artemether-lumefantrine is not a recommended ACT for uncomplicated malaria or is not available, given the demonstrated poorer outcomes of quinine treatment, along with the challenges of adherence to a seven-day course of treatment. Exceptions are where the ACT partner drug is contraindicated, for example sulfadoxine-pyrimethamine, or its safety is unknown, for example pyronaridine. These three alternative ACTs (artesunate-amodiaquine, artesunate-mefloquine and dihydroartemisinin-piperaquine) are considered preferable to quinine-based treatments in the first trimester, as the latter are not as effective, not well tolerated and adherence is more challenging. Furthermore, quinine, the current WHO-recommended treatment, is associated with similar risks of poor birth outcomes compared to ACTs overall.

Research Needs

- Although the safety of ACTs is reassuring and the independent patient data meta-analysis indicated that there is no apparent effect of gestational age on the risk of PCR-corrected treatment efficacy, collecting further evidence from clinical studies and close surveillance on the safety of ACT treatment in the first trimester must be continued and funded. This is particularly the case for artesunate-amodiaquine, artesunate-mefloquine, dihydroartemisinin-piperaquine and artesunate-pyronaridine, given the relatively few pregnant women in the first trimester with documented exposures to these drugs compared to artemether-lumefantrine.
- Operational studies including pregnancy registries are needed to strengthen pharmacovigilance among pregnant women and capture data from mass drug administration programmes and other interventions that may result in inadvertent exposures to ACTs during the first trimester.
- Continued pharmacovigilance and clinical research, such as controlled experimental studies on the efficacy and safety of antimalarial medicines, including new antimalarials, for the treatment of malaria in pregnancy, should be supported and funded given the high burden of malaria in pregnancy globally.

5.2.1.4.2 Young children and infants

Artemisinin derivatives are safe and well tolerated by young children; therefore, the choice of ACT is determined largely by the safety and tolerability of the partner drug.

SP (with artesunate) should be avoided in the first weeks of life because it displaces bilirubin competitively and could thus aggravate neonatal hyperbilibinaemia. Primaquine should be avoided in the first 6 months of life (although there are no data on its toxicity in infants), and tetracyclines should be avoided throughout infancy. With these exceptions, none of the other currently recommended antimalarial treatments has shown serious toxicity in infancy.

Delay in treating *P. falciparum* malaria in infants and young children can have fatal consequences, particularly for more severe infections. The uncertainties noted above should not delay treatment with the most effective drugs available. In treating young children, it is important to ensure accurate dosing and retention of the administered dose, as infants are more likely to vomit or regurgitate antimalarial treatment than older children or adults. Taste, volume, consistency and gastrointestinal tolerability are important determinants of whether the child retains the treatment. Mothers often need advice on techniques of drug administration and the importance of administering the drug again if it is regurgitated within 1 h of administration. Because deterioration in infants can be rapid, the threshold for use of parenteral treatment should be much lower.

Optimal antimalarial dosing in young children
Although dosing on the basis of body area is recommended for many drugs in young children, for the sake of simplicity, antimalarial drugs have been administered as a standard dose per kg bw for all patients, including young children and infants. This approach does not take into account changes in drug disposition that occur with development. The currently recommended doses of lumefantrine, piperaquine, SP, artesunate and chloroquine result in lower drug concentrations in young children and infants than in older patients. Adjustments to previous dosing regimens for dihydroartemisinin + piperaquine in uncomplicated malaria and for artesunate in severe malaria are now recommended to improve the drug exposure in this vulnerable population. The available evidence for artemether + lumefantrine, SP and chloroquine does not indicate dose modification at this time, but young children should be closely monitored, as reduced drug exposure may increase the risk for treatment failure. Limited studies of amodiaquine and mefloquine showed no significant effect of age on plasma concentration profiles.

In community situations where parenteral treatment is needed but cannot be given, such as for infants and young children who vomit antimalarial drugs repeatedly or are too weak to swallow or are very ill, give rectal artesunate and transfer the patient to a facility in which parenteral treatment is possible. Rectal administration of a single dose of artesunate as pre-referral treatment reduces the risks for death and neurological disability, as long as this initial treatment is followed by appropriate parenteral antimalarial treatment in hospital. Further evidence on pre-referral rectal administration of artesunate and other antimalarial drugs is given in section 5.5.3 Treating severe malaria - pre-referral treatment options.

Optimal antimalarial dosing in infants
See recommendation for Infants less than 5 kg body weight below.

Optimal antimalarial dosing in malnourished young children
Malaria and malnutrition frequently coexist. Malnutrition may result in inaccurate dosing when doses are based on age (a dose may be too high for an infant with a low weight for age) or on weight (a dose may be too low for an infant with a low weight for age). Although many studies of the efficacy of antimalarial drugs have been conducted in populations and settings where malnutrition was prevalent, there are few studies of the disposition of the drugs specifically in malnourished individuals, and these seldom

distinguished between acute and chronic malnutrition. Oral absorption of drugs may be reduced if there is diarrhoea or vomiting, or rapid gut transit or atrophy of the small bowel mucosa. Absorption of intramuscular and possibly intrarectal drugs may be slower, and diminished muscle mass may make it difficult to administer repeated intramuscular injections to malnourished patients. The volume of distribution of some drugs may be larger and the plasma concentrations lower. Hypoalbuminaemia may reduce protein binding and increase metabolic clearance, but concomitant hepatic dysfunction may reduce the metabolism of some drugs; the net result is uncertain.

Small studies of the pharmacokinetics of quinine and chloroquine showed alterations in people with different degrees of malnutrition. Studies of SP in IPTp and of amodiaquine monotherapy and dihydroartemisinin + piperaquine for treatment suggest reduced efficacy in malnourished children. A pooled analysis of data for individual patients showed that the concentrations of lumefantrine on day 7 were lower in children < 3 years who were underweight for age than in adequately nourished children and adults. Although these findings are concerning, they are insufficient to warrant dose modifications (in mg/kg bw) of any antimalarial drug in patients with malnutrition.

Strong recommendation for

Young children and infants (2015)

Infants weighing < 5 kg with uncomplicated *P. falciparum* malaria should be treated with an ACT at the same mg/kg bw target dose as for children weighing 5 kg.

*Not evaluated using the GRADE framework

Practical Info

The pharmacokinetics properties of many medicines in infants differ markedly from those in adults because of the physiological changes that occur in the first year of life. Accurate dosing is particularly important for infants. The only antimalarial agent that is currently contraindicated for infants (< 6 months) is primaquine.

ACT is recommended and should be given according to body weight at the same mg/kg bw dose for all infants, including those weighing < 5 kg, with close monitoring of treatment response. The lack of infant formulations of most antimalarial drugs often necessitates division of adult tablets, which can lead to inaccurate dosing. When available, paediatric formulations and strengths are preferred, as they improve the effectiveness and accuracy of ACT dosing.

Evidence To Decision

Benefits and harms

Undesirable effects:

- There is some evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine may achieve lower plasma concentrations in infants than in older children and adults.

Justification

Evidence supporting the recommendation

Data available were not suitable for evaluation using the GRADE methodology.

In most clinical studies, subgroups of infants and older children were not distinguished, and the evidence for young infants (< 5 kg) is insufficient for confidence in current treatment recommendations. Nevertheless, despite these uncertainties, infants need prompt, effective treatment of malaria. There is limited evidence that artemether + lumefantrine and dihydroartemisinin + piperaquine achieve lower plasma concentrations in infants than in older children and adults.

Other considerations

The Guideline Development Group considered the currently available evidence too limited to warrant formal evidence review at this stage, and was unable to recommend any changes beyond the status quo. Further research is

warranted.

Rationale for the recommendation
Treat infants weighing < 5 kg with uncomplicated *P. falciparum* malaria with an ACT. The weight-adjusted dose should achieve the same mg/kg bw target dose as for children weighing 5 kg.

5.2.1.4.3 Patients co-infected with HIV

There is considerable geographical overlap between malaria and HIV infection, and many people are co-infected. Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. In HIV-infected pregnant women, the adverse effects of placental malaria on birth weight are increased. In areas of stable endemic malaria, HIV-infected patients who are partially immune to malaria may have more frequent, higher-density infections, while in areas of unstable transmission, HIV infection is associated with increased risks for severe malaria and malaria-related deaths. Limited information is available on how HIV infection modifies therapeutic responses to ACTs. Early studies suggested that increasing HIV-related immunosuppression was associated with decreased treatment response to antimalarial drugs. There is presently insufficient information to modify the general malaria treatment recommendations for patients with HIV/AIDS.

Patients co-infected with tuberculosis
Rifamycins, in particular rifampicin, are potent CYP3A4 inducers with weak antimalarial activity. Concomitant administration of rifampicin during quinine treatment of adults with malaria was associated with a significant decrease in exposure to quinine and a five-fold higher recrudescence rate. Similarly, concomitant rifampicin with mefloquine in healthy adults was associated with a three-fold decrease in exposure to mefloquine. In adults co-infected with HIV and tuberculosis who were being treated with rifampicin, administration of artemether + lumefantrine resulted in significantly lower exposure to artemether, dihydroartemisinin and lumefantrine (nine-, six- and three-fold decreases, respectively).There is insufficient evidence at this time to change the current mg/kg bw dosing recommendations; however, as these patients are at higher risk of recrudescent infections they should be monitored closely.

Good practice statement

Patients co-infected with HIV (2015)

In people who have HIV/AIDS and uncomplicated *P. falciparum* malaria, artesunate + SP is not recommended if they are being treated with co-trimoxazole, and artesunate + amodiaquine is not recommended if they are being treated with efavirenz or zidovudine.

Justification

More data are available on use of artemether + lumefantrine with antiretroviral treatment. A study in children with uncomplicated malaria in a high-transmission area of Africa showed a decreased risk for recurrent malaria after treatment with artemether + lumefantrine in children receiving lopinavir–ritonavir-based antiretroviral treatment as compared with non-nucleoside reverse transcriptase inhibitor-based antiretroviral treatment. Evaluation of pharmacokinetics in these children and in healthy volunteers showed significantly higher exposure to lumefantrine and lower exposure to dihydroartemisinin with lopinavir–ritonavir-based antiretroviral treatment, but no adverse consequences. Conversely, efavirenz-based antiretroviral treatment was associated with a two- to fourfold decrease in exposure to lumefantrine in healthy volunteers and malaria-infected adults and children, with increased rates of recurrent malaria after treatment. Close monitoring is required. Increasing artemether + lumefantrine dosing with efavirenz-based antiretroviral treatment has not yet been studied. Exposure to lumefantrine and other non-nucleoside reverse transcriptase inhibitor-based antiretroviral treatment, namely nevirapine and etravirine, did not show consistent changes that would require dose adjustment.

Studies of administration of quinine with lopinavir–ritonavir or ritonavir alone in healthy volunteers gave conflicting results. The combined data are insufficient to justify dose adjustment. Single-dose atovaquone–proguanil with efavirenz, lopinavir–ritonavir or atazanavir–ritonavir were all associated with a significantly decreased area under the concentration–time curve for atovaquone (two- to fourfold) and proguanil (twofold), which could well compromise treatment or prophylactic efficacy. There is insufficient evidence to change the current mg/kg bw dosing

recommendations; however, these patients should also be monitored closely.

5.2.1.4.4 Non-immune travellers

Travellers who acquire malaria are often non-immune people living in cities in endemic countries with little or no transmission or are visitors from non-endemic countries travelling to areas with malaria transmission. Both are at higher risk for severe malaria. In a malaria-endemic country, they should be treated according to national policy, provided the treatment recommended has a recent proven cure rate > 90%. Travellers who return to a non-endemic country and then develop malaria present a particular problem, and the case fatality rate is often high; doctors in non-malarious areas may be unfamiliar with malaria and the diagnosis is commonly delayed, and effective antimalarial drugs may not be registered or may be unavailable. However, prevention of transmission or the emergence of resistance are not relevant outside malaria-endemic areas. If the patient has taken chemoprophylaxis, the same medicine should not be used for treatment. Treatment of *P. vivax*, *P. ovale* and *P. malariae* malaria in travellers should be the same as for patients in endemic areas (see section 5.4).

There may be delays in obtaining artesunate, artemether or quinine for the management of severe malaria outside endemic areas. If only parenteral quinidine is available, it should be given, with careful clinical and electrocardiographic monitoring (see section 5.5 Treating severe malaria).

Strong recommendation for , High certainty evidence

Non-immune travellers (2015)

Travellers with uncomplicated *P. falciparum* malaria returning to non-endemic settings should be treated with an ACT.

Evidence To Decision

Certainty of the Evidence High

Justification

GRADE

Studies have consistently demonstrated that the five WHO recommended ACTs have less than 5% PCR-adjusted treatment failure rates in settings without resistance to the partner drug (high quality evidence).

Other considerations

The Guideline Development Group considered the evidence of superiority of ACTs over non-ACTs from endemic settings to be equally applicable to those travelling from non-endemic settings.

5.2.1.4.5 Uncomplicated hyperparasitaemia

Uncomplicated hyperparasitaemia is present in patients who have ≥ 4% parasitaemia but no signs of severity. They are at increased risk for severe malaria and for treatment failure and are considered an important source of antimalarial drug resistance.

Good practice statement

Hyperparasitaemia (2015)

People with *P. falciparum* hyperparasitaemia are at increased risk for treatment failure, severe malaria and death and should be closely monitored, in addition to receiving an ACT.

Justification

In falciparum malaria, the risk for progression to severe malaria with vital organ dysfunction increases at higher parasite densities. In low-transmission settings, mortality begins to increase when the parasite density exceeds 100 000/µL (~2% parasitaemia). On the north-west border of Thailand, before the general introduction of ACT, parasitaemia > 4% without signs of severity was associated with a 3% mortality rate (about 30-times higher than from uncomplicated falciparum malaria with lower densities) and a six-times higher risk of treatment failure. The relationship between parasitaemia and risks depends on the epidemiological context: in higher-transmission settings, the risk of developing severe malaria in patients with high parasitaemia is lower, but "uncomplicated hyperparasitaemia" is still associated with a significantly higher rate of treatment failure.

Patients with a parasitaemia of 4–10% and no signs of severity also require close monitoring, and, if feasible, admission to hospital. They have high rates of treatment failure. Non-immune people such as travellers and individuals in low-transmission settings with a parasitaemia > 2% are at increased risk and also require close attention. Parasitaemia > 10% is considered to indicate severe malaria in all settings.

It is difficult to make a general recommendation about treatment of uncomplicated hyperparasitaemia, for several reasons: recognizing these patients requires an accurate, quantitative parasite count (they will not be identified from semi-quantitative thick film counts or RDTs), the risks for severe malaria vary considerably, and the risks for treatment failure also vary. Furthermore, little information is available on therapeutic responses in uncomplicated hyperparasitaemia. As the artemisinin component of an ACT is essential in preventing progression to severe malaria, absorption of the first dose must be ensured (atovaquone – proguanil alone should not be used for travellers presenting with uncomplicated hyperparasitaemia). Longer courses of treatment are more effective; both giving longer courses of ACT and preceding the standard 3-day ACT regimen with parenteral or oral artesunate have been used.

5.2.1.5 Uncomplicated malaria caused by P. vivax, P. ovale, P. malariae or P. knowlesi

Plasmodium vivax accounts for approximately half of all malaria cases outside Africa *[4][213][214]*. It is prevalent in the Middle East, Asia, the Western Pacific and Central and South America. With the exception of the Horn, it is rarer in Africa, where there is a high prevalence of the Duffy-negative phenotype, particularly in West Africa, although cases are reported in both Mauritania and Mali *[214]*. In most areas where *P. vivax* is prevalent, the malaria transmission rates are low (except on the island of New Guinea). Affected populations achieve only partial immunity to this parasite, and so people of all ages are at risk for *P. vivax* malaria *[214]*. Where both *P. falciparum* and *P. vivax* are prevalent, the incidence rates of *P. vivax* tend to peak at a younger age than for *P. falciparum*. This is because each *P. vivax* inoculation may be followed by several relapses. The other human malaria parasite species, *P. malariae* and *P. ovale* (which is in fact two sympatric species), are less common. *P. knowlesi*, a simian parasite, causes occasional cases of malaria in or near forested areas of South-East Asia and the Indian subcontinent *[215]*. In parts of the island of Borneo, *P. knowlesi* is the predominant cause of human malaria and an important cause of severe malaria

Of the six species of *Plasmodium* that affect humans, only *P. vivax* and the two species of *P. ovale [216]* form hypnozoites, which are dormant parasite stages in the liver that cause relapse weeks to years after the primary infection. *P. vivax* preferentially invades reticulocytes, and repeated illness causes chronic anaemia, which can be debilitating and sometimes life-threatening, particularly in young children *[217]*. Recurrent vivax malaria is an important impediment to human and economic development in affected populations. In areas where *P. falciparum* and *P. vivax* co-exist, intensive malaria control often has a greater effect on *P. falciparum*, as *P. vivax*, is more resilient to interventions.

Although *P. vivax* has been considered to be a benign form of malaria, it may sometimes cause severe disease *[218]*. The major complication is anaemia in young children. In Papua province, Indonesia *[218]*, and in Papua New Guinea *[219]*, where malaria transmission is intense, *P. vivax* is an important cause of malaria morbidity and mortality, particularly in young infants and children. Occasionally, older patients develop vital organ involvement similar to that in severe and complicated *P. falciparum* malaria *[220][221]*. During pregnancy, infection with *P. vivax*, as with *P. falciparum*, increases the risk for abortion and reduces birth weight *[222][207]*. In primigravidae, the reduction in birth weight is approximately two thirds that associated with *P. falciparum*. In one large series, this effect increased with successive pregnancies *[222]*.

P. knowlesi is a zoonosis that normally affects long- and pig-tailed macaque monkeys. It has a daily asexual cycle, resulting in a rapid replication rate and high parasitaemia. *P. knowlesi* may cause a fulminant disease similar to severe falciparum malaria (with the exception of coma, which does not occur) *[223][224]*. Co-infection with other species is common.

Diagnosis
Diagnosis of *P. vivax*, *P. ovale*, and *P. malariae* malaria is based on microscopy. *P. knowlesi* is frequently misdiagnosed under the microscope, as the young ring forms are similar to those of *P. falciparum*, the late trophozoites are similar to those of *P. malariae*, and parasite development is asynchronous. Rapid diagnostic tests based on immunochromatographic methods are available for the detection of *P. vivax* malaria; however, they are relatively insensitive for detecting *P. malariae* and *P. ovale* parasitaemia. Rapid diagnostic antigen tests for human *Plasmodium* species show poor sensitivity for *P. knowlesi* infections in humans with low parasitaemia *[225]*.

Treatment
The objectives of treatment of vivax malaria are twofold: to cure the acute blood stage infection and to clear hypnozoites from the liver to prevent future relapses. This is known as "radical cure".

In areas with chloroquine-sensitive *P. vivax*
For chloroquine-sensitive vivax malaria, oral chloroquine at a total dose of 25 mg base/kg bw is effective and well tolerated. Lower total doses are not recommended, as these encourage the emergence of resistance. Chloroquine is given at an initial dose of 10 mg base/kg bw, followed by 10 mg/kg bw on the second day and 5 mg/kg bw on the third day. In the past, the initial 10 mg/kg bw dose was followed by 5 mg/kg bw at 6 h, 24 h and 48 h. As residual chloroquine suppresses the first relapse of tropical *P. vivax* (which emerges about 3 weeks after onset of the primary illness), relapses begin to occur 5–7 weeks after treatment if radical curative treatment with primaquine is not given.

ACTs are highly effective in the treatment of vivax malaria, allowing simplification (unification) of malaria treatment; i.e. all malaria infections can be treated with an ACT. The exception is artesunate + SP, where resistance significantly compromises its efficacy. Although good efficacy of artesunate + SP was reported in one study in Afghanistan, in several other areas (such as South-East Asia) *P. vivax* has become resistant to SP more rapidly than *P. falciparum*. The initial response to all ACTs is rapid in vivax malaria, reflecting the high sensitivity to artemisinin derivatives, but, unless primaquine is given, relapses commonly follow. The subsequent recurrence patterns differ, reflecting the elimination kinetics of the partner drugs. Thus, recurrences, presumed to be relapses, occur earlier after artemether + lumefantrine than after dihydroartemisinin + piperaquine or artesunate + mefloquine because lumefantrine is eliminated more rapidly than either mefloquine or piperaquine. A similar temporal pattern of recurrence with each of the drugs is seen in the *P. vivax* infections that follow up to one third of acute falciparum malaria infections in South-East Asia.

In areas with chloroquine-resistant *P. vivax*
ACTs containing piperaquine, mefloquine or lumefantrine are the recommended treatment, although artesunate + amodiaquine may also be effective in some areas.

In the systematic review of ACTs for treating *P. vivax* malaria, dihydroartemisinin + piperaquine provided a longer prophylactic effect than ACTs with shorter half-lives (artemether + lumefantrine, artesunate + amodiaquine), with significantly fewer recurrent parasitaemias during 9 weeks of follow-up (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants). The half-life of mefloquine is similar to that of piperaquine, but use of dihydroartemisinin + piperaquine in *P. vivax* mono-infections has not been compared directly in trials with use of artesunate + mefloquine.

Uncomplicated *P. ovale*, *P. malariae* or *P. knowlesi* malaria
Resistance of *P. ovale*, *P. malariae* and *P. knowlesi* to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. In only one study, conducted in Indonesia, was resistance to chloroquine reported in *P. malariae*.

The blood stages of *P. ovale*, *P. malariae* and *P. knowlesi* should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.

Mixed malaria infections
Mixed malaria infections are common in endemic areas. For example, in Thailand, despite low levels of malaria transmission, 8% of patients with acute vivax malaria also have *P. falciparum* infections, and one third of acute *P. falciparum* infections are followed by a presumed relapse of vivax malaria (making vivax malaria the most common complication of falciparum malaria).

Mixed infections are best detected by nucleic acid-based amplification techniques, such as PCR; they may be underestimated with routine microscopy. Cryptic *P. falciparum* infections in vivax malaria can be revealed in approximately 75% of cases by RDTs based on the *Pf*HRP2 antigen, but several RDTs cannot detect mixed infection or have low sensitivity for detecting cryptic vivax malaria. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.

Good practice statement

Blood stage infection (2015)

If the malaria species is not known with certainty, adults and children should be treated as for uncomplicated *P. falciparum* malaria.

Strong recommendation for , High certainty evidence

Blood stage infection (2015)

In areas with chloroquine-susceptible infections, adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria should be treated with either an ACT or chloroquine.

In areas with chloroquine-resistant infections, adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria should be treated with an ACT.

* For details of treatment using ACTs in the first trimester of pregnancy, see section 5.2.1.4.1.

Practical Info

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Uncomplicated *P. ovale*, *P. malariae* or *P. knowlesi* malaria
Resistance of *P. ovale*, *P. malariae* and *P. knowlesi* to antimalarial drugs is not well characterized, and infections caused by these three species are generally considered to be sensitive to chloroquine. In only one study, conducted in Indonesia, was resistance to chloroquine reported in *P. malariae*.

The blood stages of *P. ovale*, *P. malariae* and *P. knowlesi* should therefore be treated with the standard regimen of ACT or chloroquine, as for vivax malaria.

Mixed Malaria Infections
Mixed malaria infections are common in endemic areas. For example, in Thailand, despite low levels of malaria transmission, 8% of patients with acute vivax malaria also have *P. falciparum* infections, and one third of acute *P. falciparum* infections are followed by a presumed relapse of vivax malaria (making vivax malaria the most common complication of falciparum malaria).

Mixed infections are best detected by nucleic acid-based amplification techniques, such as PCR; they may be

underestimated with routine microscopy. Cryptic *P. falciparum* infections in vivax malaria can be revealed in approximately 75% of cases by RDTs based on the PfHRP2 antigen, but several RDTs cannot detect mixed infection or have low sensitivity for detecting cryptic vivax malaria. ACTs are effective against all malaria species and so are the treatment of choice for mixed infections.

Evidence To Decision

Benefits and harms

Desirable effects:

- ACTs clear parasites more quickly than chloroquine (high-quality evidence).
- ACTs with long half-lives provide a longer period of suppressive post-treatment prophylaxis against relapses and new infections (high-quality evidence).
- Simplified national protocols for all forms of uncomplicated malaria.
- Adequate treatment of undiagnosed *P. falciparum* in mixed infections.

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Justification

GRADE

In a systematic review of ACTs for the treatment of *P. vivax* malaria *[226]*, five trials were conducted in Afghanistan, Cambodia, India, Indonesia and Thailand between 2002 and 2011 with a total of 1622 participants which compared ACTs directly with chloroquine. In comparison with chloroquine:

ACTs cleared parasites from the peripheral blood more quickly (parasitaemia after 24 h of treatment: RR, 0.42; 95% CI, 0.36–0.50, four trials, 1652 participants, high-quality evidence); and

ACTs were at least as effective in preventing recurrent parasitaemia before day 28 (RR, 0.58; 95% CI, 0.18–1.90, five trials, 1622 participants, high-quality evidence).

In four of these trials, few cases of recurrent parasitaemia were seen before day 28 with both chloroquine and ACTs. In the fifth trial, in Thailand in 2011, increased recurrent parasitaemia was seen after treatment with chloroquine (9%), but was infrequent after ACT (2%) (RR, 0.25; 95% CI, 0.09–0.66, one trial, 437 participants).

ACT combinations with long half-lives provided a longer prophylactic effect after treatment, with significantly fewer cases of recurrent parasitaemia between day 28 and day 42 or day 63 (RR, 0.57; 95% CI, 0.40–0.82, three trials, 1066 participants, moderate-quality evidence).

Other considerations

The guideline development group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. Countries where chloroquine is used for treatment of vivax malaria should monitor for chloroquine resistance and change to ACT when the treatment failure rate is > 10% at day 28.

Remarks

Current methods cannot distinguish recrudescence from relapse or relapse from newly acquired infections, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin are < 10%.

Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. When primaquine is given routinely for 14 days, it may mask low-level chloroquine resistance and prevent vivax recurrence within 28 days.

Rationale for the recommendation

The Guideline Development Group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. In

these settings, chloroquine may still be considered, but countries should monitor chloroquine resistance and change to ACT when the treatment failure rate is > 10% on day 28.

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Remarks
Current methods do not distinguish recrudescence from relapse or relapse from newly acquired infection, but the aim of treatment is to ensure that the rates of recurrent parasitaemia of any origin is < 10% within 28 days.

When primaquine is not given for radical cure, slowly eliminated ACT that prevents recurrent parasitaemia before day 28 should be used (dihydroartemisinin + piperaquine or artesunate + mefloquine).

Primaquine has significant asexual stage activity against vivax malaria and augments the therapeutic response to chloroquine. When primaquine is given routinely for 14 days, it may mask low-level chloroquine resistance and prevent vivax recurrence within 28 days.

When primaquine is given routinely for 14 days, ACTs with shorter half-lives (artemether + lumefantrine, or artesunate + amodiaquine) may be sufficient to keep the rate of recurrent parasitaemia before day 28 below 10%.

Rationale for the recommendation
The Guideline Development Group recognized that, in the few settings in which *P. vivax* is the only endemic species and where chloroquine resistance remains low, the increased cost of ACT may not be worth the small additional benefits. In these settings, chloroquine may still be considered, but countries should monitor chloroquine resistance and change to ACT when the treatment failure rate is > 10% on day 28.

Good practice statement

Blood stage infection (2015)

The G6PD status of patients should be used to guide administration of primaquine for preventing relapse.

Practical Info

Please refer to *Testing for G6PD deficiency for safe use of primaquine in radical cure of P. vivax and P. ovale (Policy brief) [227]* and *Guide to G6PD deficiency rapid diagnostic testing to support P. vivax radical cure [172]*.

Strong recommendation for , High certainty evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

To prevent relapse, children and adults (except pregnant women, infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) should be treated with a 14-day course of primaquine in all transmission settings.

Practical Info

Primaquine for preventing relapse
To achieve radical cure (cure and prevention of relapse), relapses originating from liver hypnozoites must be prevented by giving primaquine. The frequency and pattern of relapses varies geographically, with relapse rates generally ranging from 8% to 80%. Temperate long-latency *P. vivax* strains are still prevalent in many areas. Recent evidence suggests that, in endemic areas where people are inoculated frequently with *P. vivax*, a significant proportion of the population harbours dormant but “activatable” hypnozoites. The exact mechanism of activation of dormant hypnozoites is unclear. There is evidence that systemic parasitic and bacterial infections, but not viral infections, can activate *P. vivax* hypnozoites, which explains why *P. vivax* commonly follows *P. falciparum* infections in endemic areas where both parasites are prevalent. Thus, the radical curative efficacy of primaquine must be set against the prevalent relapse frequency and the likely burden of “activatable” hypnozoites. Experimental studies on vivax malaria and the relapsing simian malaria *P. cynomolgi* suggest that the total dose of 8-aminoquinoline given is the main determinant of radical curative efficacy. In most

therapeutic assessments, primaquine has been given for 14 days. Total doses of 3.5 mg base/kg bw (0.25 mg/kg bw per day) are required for temperate strains and 7 mg base/kg bw (0.5 mg/kg bw per day) is needed for the tropical, frequent-relapsing *P. vivax* prevalent in East Asia and Oceania. Primaquine causes dose-limiting abdominal discomfort when taken on an empty stomach; it should always be taken with food.

Use of primaquine to prevent relapse in high-transmission settings was not recommended previously, as the risk for new infections was considered to outweigh any benefits of preventing relapse. This may have been based on underestimates of the morbidity and mortality associated with multiple relapses, particularly in young children. Given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends that primaquine be used in all settings.

Primaquine formulation: If available, administer scored tablets containing 7.5 or 15 mg of primaquine. Smaller-dose tablets containing 2.5 and 5 mg base are available in some areas and facilitate accurate dosing in children. When scored tablets are not available, 5 mg tablets can be used.

Therapeutic dose: 0.25–0.5 mg/kg bw per day primaquine once a day for 14 days.
Use of primaquine to prevent relapse in high-transmission settings was not recommended previously, as the risk for new infections was considered to outweigh any benefits of preventing relapse. This may have been based on underestimates of the morbidity and mortality associated with multiple relapses, particularly in young children. Given the benefits of preventing relapse and in the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends that primaquine be used in all settings.

Evidence To Decision

Benefits and harms

Desirable effects:

- 14-day courses of primaquine added to chloroquine reduce relapse rates to a greater extent than chloroquine alone (high-quality evidence).
- 14-day courses of primaquine added to chloroquine may result in fewer relapses than 7-day courses (low-quality evidence).

Undesirable effects:

- Primaquine is known to cause haemolysis in people with G6PD deficiency.
- Of the 15 trials included in the Cochrane review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. None of the trials reported serious or treatment-limiting adverse events.

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Justification

GRADE

In a systematic review of primaquine for radical cure of *P. vivax* malaria *[231]*, 14 days of primaquine was compared with placebo or no treatment in 10 trials, and 14 days was compared with 7 days in one trial. The trials were conducted in Colombia, Ethiopia, India, Pakistan and Thailand between 1992 and 2006.

In comparison with placebo or no primaquine:

- 14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 15 months of follow-up by about 40% (RR, 0.60; 95% CI, 0.48–0.75, 10 trials, 1740 participants, high-quality evidence).

In comparison with 7 days of primaquine:

- 14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 6 months of follow-up by over 50% (RR,

0.45; 95% CI, 0.25–0.81, one trial, 126 participants, low-quality evidence).

No direct comparison has been made of higher doses (0.5 mg/kg bw for 14 days) with the standard regimen (0.25 mg/kg bw for 14 days).

Twelve of the 15 trials included in the review explicitly excluded people with G6PD deficiency; the remaining three did not report on this aspect. No serious adverse events were reported.

Other considerations
In the absence of evidence to recommend alternatives, the guideline development group considers 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest regimen for people with mild-to-moderate G6PD deficiency.

Remarks
The widely used primaquine regimen of 0.25 mg base/kg bw per day for 14 days is based on studies of long-latency Korean *P. vivax*.

In South-East Asia and Oceania, *P. vivax* relapses at 3-week intervals and is more resistant to primaquine. Consequently, higher doses of primaquine have been used (0.375–0.5 mg base/kg bw per day), but there are few data from comparative trials.

Primaquine is contraindicated in pregnancy and lactation < 6 months post-partum, unless the infant has been tested for G6PD deficiency. It could be given to women who have delivered and ceased breastfeeding.

Rationale for the recommendation:
Primaquine has not previously been recommended in high-transmission settings, where the risk of new infections was considered to outweigh any benefits of reduced spontaneous relapses.

In the light of changing epidemiology worldwide and more aggressive targets for malaria control and elimination, the group now recommends primaquine for radical cure of *P. vivax* in all settings.

Strong recommendation for , Very low certainty evidence

Short-course standard dose primaquine treatment (2022)

To prevent relapse, an additional treatment option of using primaquine 0.5 mg/kg/day for seven days is recommended to treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency).

- *As recommended previously, the G6PD status of patients should be used to guide administration of primaquine for preventing relapse.*
- *A shorter regimen can lead to better adherence compared to the standard 14-day regimen and thus to fewer relapses.*

Practical Info

- Health facilities should continue to monitor for vomiting, anaemia, haemolysis and adherence to treatment.
- Safety monitoring is critical, so strengthening of pharmacovigilance systems is generally needed.
- Surveillance for risk of false-negative results with G6PD tests and for lack of G6PD testing is essential.

Evidence To Decision

Benefits and harms

There seems to be no difference in the recurrence of parasitaemia with the seven-day regimen compared to the 14-day regimen using the standard dose, and, therefore, the desirable treatment effect is considered to be moderate. It is reasonable to assume that compliance will be higher with a shorter course of treatment than with a 14-day

course and may thus decrease the burden of *P. vivax* relapses. There seems to be no difference in the safety and tolerability of the standard dose (0.5 mg/kg/day for seven days) compared to 0.25 mg/kg/day for 14 days.

Certainty of the Evidence

Very low

The GDG judged the overall certainty of the evidence to be very low due to the risk of bias, indirectness and serious imprecision.

Values and preferences

Informed prescribing of primaquine may be a challenge in many settings. The purpose of prescribing primaquine for radical cure of malaria may not be obvious to the patient, as it is prescribed after asexual stages are treated and so does not affect symptom relief from malaria. These factors feed into the value placed on the intervention. The implementers judgement may possibly vary based on how patients value the impact of a shorter regimen and whether this leads to better adherence, compared to the possibility of increased adverse events.

Resources

Given that the total dosage will be the same but with a shortened course, differences in costs and savings will be negligible. However, prescriber training and end-user information to improve rates of prescribing primaquine and compliance might be needed. As with the current recommendation for the use of primaquine, G6PD testing to guide the dosing of primaquine needs to be included in the costing for resources.

Equity

Equity may vary depending on the different populations affected. As malaria is a poverty-related disease, improving treatment efficacy will probably increase equity. Shorter treatment courses with proper health information will likely lead to fewer relapses. It is assumed that the burden of these relapses falls disproportionately on the poorer population. However, there is a possibility of reduced equity if poorer populations have more limited access to the G6PD testing required prior to therapy.

Acceptability

The intervention of 0.5 mg/kg/day for seven days is probably more acceptable and may be preferred by stakeholders to the current 0.25 mg/kg/day for 14 days.

Feasibility

Feasibility should improve with a shorter treatment course, provided that updated treatment guidelines and training with the appropriate supporting infrastructure can be delivered.

Justification

The GDG reached a consensus on a strong recommendation for the intervention, despite the very low certainty of evidence because:

- the moderate magnitude of treatment effect was comparable to that of the standard regimen of 0.25 mg/kg/day for 14 days;
- no significant serious adverse events were detected;
- there is probably increased equity from access to an additional treatment option; and
- there is an expected increase in adherence because of the shorter course.

Research Needs

The GDG highlighted the following evidence gaps requiring further research.

- Studies are needed on the supporting criteria in decision-making, such as patients' values and preferences relating to the critical outcomes, costs, equity and acceptability, as well as feasibility studies on the different antimalarial treatment options.
- Studies are needed on the optimal primaquine dosage by region (high versus low relapse periodicity) and by subgroup (including young children).

Conditional recommendation against , Very low certainty evidence

Short-course standard high-dose primaquine treatment (2022)

To prevent relapse, an additional treatment option of using primaquine 1.0 mg/kg/day for seven days to treat *P. vivax* or *P. ovale* malaria is not recommended.

- *There is a significantly increased risk of serious adverse events (moderate to large undesirable effect) at this daily dosing of the standard high dose.*

Evidence To Decision

Benefits and harms

- Using the higher dose regimen, there seems to be no difference between the seven-day and the 14-day regimen in terms of the recurrence of parasitaemia. It is reasonable to assume that compliance will be higher with a shorter treatment course, which may thus decrease the burden of *P. vivax* relapses. Therefore, the desirable treatment effect of the seven-day regimen relative to the 14-day regimen is considered moderate.
- However, there is a significantly increased risk of severe adverse events (i.e. moderate to large undesirable effect) for the standard high dose (1 mg/kg) given as a seven-day regimen.
- Note that the systematic review was unable to assess whether the adverse haematological effects of primaquine (when given with chloroquine) may be outweighed by the effect of preventing anaemia due to fewer malaria relapses by day 42 (as was shown in the independent patient data meta-analysis *[230]*).
- Haemolysis in G6PD heterozygous female patients with intermediate enzyme levels not detected by a quantitative G6PD test remains a concern.
- Gastrointestinal tolerability of the seven-day high-dose regimen seems worse compared to standard 14 day treatment course, but this can potentially be mitigated by intake with food.

Certainty of the Evidence

Very low

The GDG judged the overall certainty of the evidence to be very low due to risk of indirectness, imprecision and risk of bias in adverse event outcomes.

Values and preferences

Preferences may possibly vary in different settings depending on how national malaria programmes value the impact of a shorter regimen, which may possibly lead to better adherence, compared to the probable increased risk of serious adverse events.

Resources

Proper instruction and follow-up (especially for complications due to haemolysis) and management of adverse

events can be an additional cost factor. The costs of G6PD screening should be included in the cost analysis if the 1 mg/kg/day regimen is used.

Equity

Impact on equity may vary depending on the population and risk of serious adverse events. Although a shorter regimen may lead to better adherence and fewer relapses, the significant increase in adverse events may tilt the balance. There is the possibility of reduced equity if poorer populations have less access to G6PD testing. Haemolysis in G6PD heterozygous female patients with intermediate enzyme levels not detected by a quantitative G6PD test remains a concern.

Acceptability

The shorter regimen is probably more acceptable. At the same time, the significant increase in adverse events is probably unacceptable in most settings. Gastrointestinal tolerability of the seven-day high-dose regimen seems worse than in standard 14 day treatment course, although this can potentially be mitigated by intake with food.

Feasibility

Feasibility improves with a shorter treatment course, but the concomitant G6PD screening and monitoring and management of expected adverse events might not be feasible or affordable in some settings.

Justification

The GDG reached a consensus on a recommendation against this regimen because:

- there were significant serious adverse events at this higher daily dosage.

Research Needs

The GDG highlighted the following evidence gaps requiring further research.

- Larger effectiveness and safety studies are needed, focusing on gastrointestinal tolerability with and without food and the impact of G6PD testing on haemolysis risk (in particular in heterozygous women).
- Studies are needed on primaquine optimal dosage in areas where the Chesson strain is prevalent, as higher total doses of primaquine may be required in these settings.
- Implementation research is needed to increase the acceptability and use of G6PD point-of-care testing.

Conditional recommendation for , Very low certainty evidence

Preventing relapse in people with G6PD deficiency (2015)

In people with G6PD deficiency, primaquine base at 0.75 mg/kg bw once a week for 8 weeks can be given to prevent relapse, with close medical supervision for potential primaquine-induced haemolysis.

Practical Info

- In patients known to be G6PD deficient, primaquine may be considered at a dose of 0.75 mg base/kg bw once a week for 8 weeks. The decision to give or withhold primaquine should depend on the possibility of giving the treatment under close medical supervision, with ready access to health facilities with blood transfusion services.
- Some heterozygote females who test as normal or not deficient in qualitative G6PD screening tests have intermediate G6PD activity and can still haemolyse substantially. Intermediate deficiency (30–80% of normal) and normal enzyme activity (> 80% of normal) can be differentiated only with a quantitative test. In the absence of

quantitative testing, all females should be considered as potentially having intermediate G6PD activity and given the 14-day regimen of primaquine, with counselling on how to recognize symptoms and signs of haemolytic anaemia. They should be advised to stop primaquine and be told where to seek care should these signs develop.

- If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

Evidence To Decision

Benefits and harms

Desirable effects:

- There are no comparative trials of the efficacy or safety of primaquine in people with G6PD deficiency.

Undesirable effects:

- Primaquine is known to cause haemolysis in people with G6PD deficiency.
- Of the 15 trials included in the systematic review, 12 explicitly excluded people with G6PD deficiency; in three trials, it was unclear whether participants were tested for G6PD deficiency or excluded. None of the trials reported serious or treatment-limiting adverse events.

Certainty of the Evidence

Very low

Overall certainty of evidence for all critical outcomes: very low.

Justification

GRADE

In a systematic review of primaquine for radical cure of *P. vivax* malaria *[231]*, 14 days of primaquine was compared with placebo or no treatment in 10 trials, and 14 days was compared with 7 days in one trial. The trials were conducted in Colombia, Ethiopia, India, Pakistan and Thailand between 1992 and 2006.

In comparison with placebo or no primaquine:

14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 15 months of follow-up by about 40% (RR, 0.60; 95% CI, 0.48–0.75, 10 trials, 1740 participants, high-quality evidence).

In comparison with 7 days of primaquine:

14 days of primaquine (0.25 mg/kg bw per day) reduced relapses during 6 months of follow-up by over 50% (RR, 0.45; 95% CI, 0.25–0.81, one trial, 126 participants, low-quality evidence).

No direct comparison has been made of higher doses (0.5 mg/kg bw for 14 days) with the standard regimen (0.25 mg/kg bw for 14 days).

Twelve of the 15 trials included in the review explicitly excluded people with G6PD deficiency; the remaining three did not report on this aspect. No serious adverse events were reported.

Other considerations

In the absence of evidence to recommend alternatives, the guideline development group considers 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest regimen for people with mild-to-moderate G6PD deficiency.

Primaquine and glucose-6-phosphate dehydrogenase deficiency

Any person (male or female) with red cell G6PD activity < 30% of the normal mean has G6PD deficiency and will experience haemolysis after primaquine. Heterozygote females with higher mean red cell activities may still show substantial haemolysis. G6PD deficiency is an inherited sex-linked genetic disorder, which is associated with some protection against *P. falciparum* and *P. vivax* malaria but increased susceptibility to oxidant haemolysis. The prevalence of

G6PD deficiency varies, but in tropical areas it is typically 3–35%; high frequencies are found only in areas where malaria is or has been endemic. There are many (> 180) different G6PD deficiency genetic variants; nearly all of which make the red cells susceptible to oxidant haemolysis, but the severity of haemolysis may vary. Primaquine generates reactive intermediate metabolites that are oxidant and cause variable haemolysis in G6PD-deficient individuals. It also causes methemoglobinaemia. The severity of haemolytic anaemia depends on the dose of primaquine and on the variant of the G6PD enzyme. Fortunately, primaquine is eliminated rapidly so haemolysis is self-limiting once the drug is stopped. In the absence of exposure to primaquine or another oxidant agent, G6PD deficiency rarely causes clinical manifestations so, many patients are unaware of their G6PD status. Screening for G6PD deficiency is not widely available outside hospitals, but rapid screening tests that can be used at points of care have recently become commercially available.

Remarks
Primaquine is contraindicated in pregnancy and lactation, unless the infant has been tested for G6PD deficiency. It could be given to women once they have delivered and ceased breastfeeding.

Rationale for the recommendation:
In the absence of evidence to recommend alternatives, the Guideline Development Group considers a regimen of 0.75 mg/kg bw primaquine given once weekly for 8 weeks to be the safest for people with G6PD deficiency.

Good practice statement

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine should be based on an assessment of the risks and benefits of adding primaquine.

Justification

If G6PD testing is not available, a decision to prescribe or withhold primaquine should be based on the balance of the probability and benefits of preventing relapse against the risks of primaquine-induced haemolytic anaemia. This depends on the population prevalence of G6PD deficiency, the severity of the prevalent genotypes and on the capacity of health services to identify and manage primaquine-induced haemolytic reactions.

Conditional recommendation for , Moderate certainty evidence

Pregnant and breastfeeding women (2015)

In women who are pregnant or breastfeeding, weekly chemoprophylaxis with chloroquine can be given until delivery and breastfeeding are completed, then, on the basis of G6PD status, primaquine can be given to prevent future relapse.

Practical Info

Primaquine is contraindicated in pregnant women and in lactating women (unless the infant is known not to be G6PD deficient).

As an alternative, chloroquine prophylaxis could be given to suppress relapses after acute vivax malaria during pregnancy. Once the infant has been delivered and the mother has completed breastfeeding, primaquine could then be given to achieve radical cure.

Few data are available on the safety of primaquine in infancy, and in the past primaquine was not recommended for infants. There is, however, no specific reason why primaquine should not be given to children aged 6 months to 1 year (provided they do not have G6PD deficiency), as this age group may suffer multiple relapses from vivax malaria. The guideline development group therefore recommended lowering the age restriction to 6 months.

Evidence To Decision

Benefits and harms

Desirable effects:

- Chloroquine prophylaxis reduced recurrent *P. vivax* malaria in pregnant women (moderate-quality evidence).

Certainty of the Evidence

Moderate

Overall certainty of evidence for all critical outcomes: moderate.

Justification

GRADE

In a systematic review of malaria chemoprophylaxis in pregnant women *[232]*, chloroquine prophylaxis against *P. vivax* during pregnancy was directly evaluated in one trial conducted in Thailand in 2001. In comparison with no chemoprophylaxis:

Chloroquine prophylaxis substantially reduced recurrent *P. vivax* malaria (RR, 0.02; 95% CI, 0.00–0.26, one trial, 951 participants, moderate- quality evidence).

Recommendation

Primaquine is contraindicated in pregnant or breastfeeding women with *P. vivax* malaria. Therefore, consider weekly chemoprophylaxis with chloroquine until delivery and breastfeeding are completed, then treat with 14 days of primaquine to prevent future relapse.

5.2.2 Treating severe malaria

Mortality from untreated severe malaria (particularly cerebral malaria) approaches 100%. With prompt, effective antimalarial treatment and supportive care, the rate falls to 10–20% overall. Within the broad definition of severe malaria some syndromes are associated with lower mortality rates (e.g. severe anaemia) and others with higher mortality rates (e.g. acidosis). The risk for death increases in the presence of multiple complications.

Any patient with malaria who is unable to take oral medications reliably, shows any evidence of vital organ dysfunction or has a high parasite count is at increased risk for dying. The exact risk depends on the species of infecting malaria parasite, the number of systems affected, the degree of vital organ dysfunction, age, background immunity, pre-morbid, and concomitant diseases, and access to appropriate treatment. Tests such as a parasite count, haematocrit and blood glucose may all be performed immediately at the point of care, but the results of other laboratory measures, if any, may be available only after hours or days. As severe malaria is potentially fatal, any patient considered to be at increased risk should be given the benefit of the highest level of care available. The attending clinician should not worry unduly about definitions: the severely ill patient requires immediate supportive care, and, if severe malaria is a possibility, parenteral antimalarial drug treatment should be started without delay.

Definitions

Severe falciparum malaria: For epidemiological purposes, severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitaemia.

- Impaired consciousness: A Glasgow coma score < 11 in adults or a Blantyre coma score < 3 in children
- Prostration: Generalized weakness so that the person is unable to sit, stand or walk without assistance
- Multiple convulsions: More than two episodes within 24 h
- Acidosis: A base deficit of > 8 mEq/L or, if not available, a plasma bicarbonate level of < 15 mmol/L or venous plasma lactate ≥ 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, laboured breathing).
- Hypoglycaemia: Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
- Severe malarial anaemia: Haemoglobin concentration ≤ 5 g/dL or a haematocrit of ≤ 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) with a parasite count > 10 000/µL
- Renal impairment: Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L
- Jaundice: Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) with a parasite count > 100 000/ µL
- Pulmonary oedema: Radiologically confirmed or oxygen

saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
- Significant bleeding: Including recurrent or prolonged bleeding from the nose, gums or venepuncture sites; haematemesis or melaena
- Shock: Compensated shock is defined as capillary refill ≥ 3 s or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill).
- Hyperparasitaemia: *P. falciparum* parasitaemia > 10%

Severe vivax and knowlesi malaria: defined as for falciparum malaria but with no parasite density thresholds.

Severe knowlesi malaria is defined as for falciparum malaria but with two differences:

- *P. knowlesi* hyperparasitaemia: parasite density > 100 000/µL
- Jaundice and parasite density > 20 000/µL.

Therapeutic objectives
The main objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objectives are prevention of disabilities and prevention of recrudescent infection.

Death from severe malaria often occurs within hours of admission to a hospital or clinic, so it is essential that therapeutic concentrations of a highly effective antimalarial drug be achieved as soon as possible. Management of severe malaria comprises mainly clinical assessment of the patient, specific antimalarial treatment, additional treatment and supportive care.

Clinical assessment
Severe malaria is a medical emergency. An open airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated, so that medicines, including antimalarial drugs and fluids, can be given appropriately. An intravenous cannula should be inserted, and blood glucose (rapid test), haematocrit or haemoglobin, parasitaemia and, in adults, renal function should be measured immediately. A detailed clinical examination should be conducted, including a record of the coma score. Several coma scores have been advocated: the Glasgow coma scale is suitable for adults, and the simple Blantyre modification is easily performed in children. Unconscious patients should undergo a lumbar puncture for cerebrospinal fluid analysis to exclude bacterial meningitis.

The degree of acidosis is an important determinant of outcome; the plasma bicarbonate or venous lactate concentration should be measured, if possible. If facilities are available, arterial or capillary blood pH and gases should be measured in patients who are unconscious, hyperventilating or in shock. Blood should be taken for cross-matching, a full blood count, a platelet count, clotting studies, blood culture and full biochemistry (if possible). Careful attention should be paid to the patient's fluid balance in severe malaria in order to avoid over- or under-hydration. Individual requirements vary widely and depend on fluid losses before admission.

The differential diagnosis of fever in a severely ill patient is broad. Coma and fever may be due to meningoencephalitis or malaria. Cerebral malaria is not associated with signs of meningeal irritation (neck stiffness, photophobia or Kernig's sign), but the patient may be opisthotonic. As untreated bacterial meningitis is almost invariably fatal, a diagnostic lumbar puncture should be performed to exclude this condition. There is also considerable clinical overlap between septicaemia, pneumonia and severe malaria, and these conditions may coexist. When possible, blood should always be taken on admission for bacterial culture. In malaria-endemic areas, particularly where parasitaemia is common in young age groups, it is difficult to rule out septicaemia immediately in a shocked or severely ill obtunded child. In all such cases, empirical parenteral broad-spectrum antibiotics should be started immediately, together with antimalarial treatment.

Treatment of severe malaria
It is essential that full doses of effective parenteral (or rectal) antimalarial treatment be given promptly in the initial treatment of severe malaria. This should be followed by a full dose of effective ACT orally. Two classes of medicine are available for parenteral treatment of severe malaria: artemisinin derivatives (artesunate or artemether) and the cinchona alkaloids (quinine and quinidine). Parenteral artesunate is the treatment of choice for all severe malaria. The largest randomized clinical trials ever conducted on severe falciparum malaria showed a substantial reduction in mortality with intravenous or intramuscular artesunate as compared with parenteral quinine. The reduction in mortality was not associated with an increase in neurological sequelae in artesunate-treated survivors. Furthermore, artesunate is simpler and safer to use.

Pre-referral treatment options
See recommendation.

Adjustment of parenteral dosing in renal failure or hepatic dysfunction
The dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction. However quinine accumulates in severe vital organ dysfunction. If a patient with severe malaria has persisting acute kidney injury or there is no clinical improvement by 48 h, the dose of quinine should be reduced by one third, to 10 mg salt/kg bw every 12 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

Follow-on treatment
The current recommendation of experts is to give parenteral antimalarial drugs for the treatment of severe malaria for a minimum of 24 h once started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication, before giving the oral follow-up

treatment.

After initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT (artesunate + amodiaquine, artemether + lumefantrine or dihydroartemisinin + piperaquine). If the patient presented initially with impaired consciousness, ACTs containing mefloquine should be avoided because of an increased incidence of neuropsychiatric complications. When an ACT is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be used for follow-on treatment. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in cases of renal failure, but it should not be given to children < 8 years or pregnant women. As treatment with doxycycline is begun only when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the artesunate, artemether or quinine course. When available, clindamycin may be substituted in children and pregnant women.

Continuing supportive care

Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score and urine output. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.

Management of complications

Severe malaria is associated with a variety of manifestations and complications, which must be recognized promptly and treated as shown below.

Immediate clinical management of severe manifestations and complications of *P. falciparum* malaria

Manifestation or complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatments, intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, a cooling blanket and paracetamol.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam, lorazepam, midazolam or intramuscular paraldehyde. Check blood glucose.
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion. Although hypoglycaemia is defined as glucose < 2.2 mmol/L, the threshold for intervention is < 3 mmol/L for children < 5 years and <2.2 mmol/L for older children and adults.
Severe anaemia	Transfuse with screened fresh whole blood.
Acute pulmonary oedema[b]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure or continuous positive airway pressure in life-threatening hypoxaemia.
Acute kidney injury	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure, add haemofiltration or haemodialysis, or, if not available, peritoneal dialysis.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets, if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad- spectrum antimicrobials, correct haemodynamic disturbances.

[a] It is assumed that appropriate antimalarial treatment will have been started in all cases.

[b] Prevent by avoiding excess hydration

Additional aspects of management

Fluid therapy

Fluid requirements should be assessed individually. Adults with severe malaria are very vulnerable to fluid overload, while children are more likely to be dehydrated. The fluid regimen must also be adapted to the infusion of antimalarial drugs. Rapid bolus infusion of colloid or crystalloids is contraindicated. If available, haemofiltration should be started early for acute kidney injury or severe metabolic acidosis, which do not respond to rehydration. As the degree of fluid depletion varies considerably in patients with severe malaria, it is not possible to give general recommendations on fluid replacement; each patient must be assessed individually and fluid resuscitation based on the estimated deficit. In high-transmission settings, children commonly present with severe anaemia and hyperventilation (sometimes termed “respiratory distress”) resulting from severe metabolic acidosis and anaemia; they should be treated by blood transfusion. In

adults, there is a very thin dividing line between over-hydration, which may produce pulmonary oedema, and under-hydration, which contributes to shock, worsening acidosis and renal impairment. Careful, frequent evaluation of jugular venous pressure, peripheral perfusion, venous filling, skin turgor and urine output should be made.

Blood transfusion
Severe malaria is associated with rapid development of anaemia, as infected, once infected and uninfected erythrocytes are haemolysed and/or removed from the circulation by the spleen. Ideally, fresh, cross-matched blood should be transfused; however, in most settings, cross-matched virus-free blood is in short supply. As for fluid resuscitation, there are not enough studies to make strong evidence-based recommendations on the indications for transfusion; the recommendations given here are based on expert opinion. In high-transmission settings, blood transfusion is generally recommended for children with a haemoglobin level of < 5 g/100 mL (haematocrit < 15%). In low-transmission settings, a threshold of 20% (haemoglobin, 7 g/100 mL) is recommended. These general recommendations must, however, be adapted to the individual, as the pathological consequences of rapid development of anaemia are worse than those of chronic or acute anaemia when there has been adaptation and a compensatory right shift in the oxygen dissociation curve.

Exchange blood transfusion
Many anecdotal reports and several series have claimed the benefit of exchange blood transfusion in severe malaria, but there have been no comparative trials, and there is no consensus on whether it reduces mortality or how it might work. Various rationales have been proposed:

- removing infected red blood cells from the circulation and therefore lowering the parasite burden (although only the circulating, relatively non-pathogenic stages are removed, and this is also achieved rapidly with artemisinin derivatives);
- rapidly reducing both the antigen load and the burden of parasite-derived toxins, metabolites and toxic mediators produced by the host; and
- replacing the rigid unparasitized red cells by more easily deformable cells, therefore alleviating microcirculatory obstruction.

Exchange blood transfusion requires intensive nursing care and a relatively large volume of blood, and it carries significant risks. There is no consensus on the indications, benefits and dangers involved or on practical details such as the volume of blood that should be exchanged. It is, therefore, not possible to make any recommendation regarding the use of exchange blood transfusion.

Concomitant use of antibiotics
The threshold for administering antibiotic treatment should be low in severe malaria. Septicaemia and severe malaria are associated, and there is substantial diagnostic overlap,particularly in children in areas of moderate and high transmission.Thus broad- spectrum antibiotic treatment *should be given* with antimalarial drugs to all children with suspected severe malaria in areas of moderate and high transmission until a bacterial infection is excluded. After the start of antimalarial treatment, unexplained deterioration may result from a supervening bacterial infection.Enteric bacteria (notably *Salmonella*) predominated in many trial series in Africa, but a variety of bacteria have been cultured from the blood of patients with a diagnosis of severe malaria.

Patients with secondary pneumonia or with clear evidence of aspiration should be given empirical treatment with an appropriate broad-spectrum antibiotic. In children with persistent fever despite parasite clearance, other possible causes of fever should be excluded, such as systemic *Salmonella* infections and urinary tract infections, especially in catheterized patients. In the majority of cases of persistent fever, however, no other pathogen is identified after parasite clearance. Antibiotic treatment should be based on culture and sensitivity results or,if not available, local antibiotic sensitivity patterns.

Use of anticonvulsants
The treatment of convulsions in cerebral malaria with intravenous (or, if this is not possible, rectal) benzodiazepines or intramuscular paraldehyde is similar to that for repeated seizures from any cause. In a large, double-blind, placebo-controlled evaluation of a single prophylactic intramuscular injection of 20 mg/kg bw of phenobarbital to children with cerebral malaria, the frequency of seizures was reduced but the mortality rate was increased significantly. This resulted from respiratory arrest and was associated with additional use of benzodiazepine.

A 20 mg/kg bw dose of phenobarbital should not be given without respiratory support. It is not known whether a lower dose would be effective and safer or whether mortality would not increase if ventilation were given. In the absence of further information, prophylactic anticonvulsants are not recommended.

Treatments that are not recommended
In an attempt to reduce the high mortality from severe malaria, various adjunctive treatments have been evaluated, but none has proved effective and many have been shown to be harmful. Heparin, prostacyclin, desferroxamine, pentoxifylline, low- molecular-mass dextran, urea, high-dose corticosteroids, aspirin anti-TNF antibody, cyclosporine A,dichloroacetate, adrenaline, hyperimmune serum,*N*-acetylcysteine and bolus administration of albumin are not recommended.In addition,use of corticosteroids increases the risk for gastrointestinal bleeding and seizures and has been associated with prolonged coma resolution times when compared with placebo.

Treatment of severe malaria during pregnancy
Women in the second and third trimesters of pregnancy are more likely to have severe malaria than other adults, and, in low-transmission settings, this is often complicated by pulmonary oedema and hypoglycaemia. Maternal mortality is

approximately 50%, which is higher than in non-pregnant adults. Fetal death and premature labour are common. Parenteral antimalarial drugs should be given to pregnant women with severe malaria in full doses without delay. Parenteral artesunate is the treatment of choice in all trimesters. Treatment must not be delayed. If artesunate is unavailable, intramuscular artemether should be given, and if this is unavailable then parenteral quinine should be started immediately until artesunate is obtained.

Obstetric advice should be sought at an early stage, a paediatrician alerted and blood glucose checked frequently. Hypoglycaemia should be expected, and it is often recurrent if the patient is receiving quinine. Severe malaria may also present immediately after delivery. Postpartum bacterial infection is a common complication and should be managed appropriately.

Treatment of severe *P. vivax* malaria

Although *P. vivax* malaria is considered to be benign, with a low case-fatality rate, it may cause a debilitating febrile illness with progressive anaemia and can also occasionally cause severe disease, as in *P. falciparum* malaria. Reported manifestations of severe *P. vivax* malaria include severe anaemia, thrombocytopenia, acute pulmonary oedema and, less commonly, cerebral malaria, pancytopenia, jaundice, splenic rupture, haemoglobinuria, acute renal failure and shock.

Prompt effective treatment and case management should be the same as for severe *P. falciparum* malaria (see section 5.5.1). Following parenteral artesunate, treatment can be completed with a full treatment course of oral ACT or chloroquine (in countries where chloroquine is the treatment of choice). A full course of radical treatment with primaquine should be given after recovery.

Please refer to *Management of severe malaria - A practical handbook, 3rd edition [233].*

5.2.2.1 Artesunate

Strong recommendation for , High certainty evidence

Treating severe malaria (2015)

Adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) should be treated with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, treatment should be completed with 3 days of an ACT.

Practical Info

Artesunate is dispensed as a powder of artesunic acid, which is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 mL of 5% dextrose and given by intravenous injection or by intramuscular injection into the anterior thigh.

The solution should be prepared freshly for each administration and should not be stored. Artesunate is rapidly hydrolysed in-vivo to dihydroartemisinin, which provides the main antimalarial effect. Studies of the pharmacokinetics of parenteral artesunate in children with severe malaria suggest that they have less exposure than older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin. Body weight has been identified as a significant covariate in studies of the pharmacokinetics of orally and rectally administered artesunate, which suggests that young children have a larger apparent volume of distribution for both compounds and should therefore receive a slightly higher dose of parenteral artesunate to achieve exposure comparable to that of older children and adults.

Artesunate and post-treatment haemolysis

Delayed haemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers. Between 2010 and 2012, there were six reports involving a total of 19 European travellers with severe malaria who were treated with artesunate injection and developed delayed haemolysis. All except one were adults (median age, 50 years; range, 5–71 years). In a prospective study involving African children, the same phenomenon was reported in 5 (7%) of the 72 hyperparasitaemic children studied. Artesunate rapidly kills ring-stage parasites, which are then taken out of the red cells by the spleen; these infected erythrocytes are then returned to the circulation but with a shortened life span, resulting in the observed haemolysis. Thus, post-treatment haemolysis is a predictable event related to the life-saving effect of artesunate. Hyperparasitaemic patients must be followed up carefully to identify late-onset anaemia.

Please refer to the *Information note on delayed haemolytic anaemia following treatment with artesunate [235].*

Evidence To Decision

Benefits and harms

Desirable effects:

- In both adults and children, parenteral artesunate prevented more deaths than parenteral quinine (high-quality evidence).
- For intravenous administration, artesunate is given as a bolus, whereas quinine requires slow infusion.
- For intramuscular administration, artesunate is given in a smaller volume than quinine.

Undesirable effects:

- Artesunate is associated with a small increase in neurological sequelae at the time of hospital discharge (moderate-quality evidence). The difference is no longer evident on day 28 after discharge (moderate-quality evidence).

Certainty of the Evidence

High

Overall certainty of evidence for all critical outcomes: high.

Justification

GRADE

In a systematic review of artesunate for severe malaria *[234]*, eight randomized controlled trials with a total of 1664 adults and 5765 children, directly compared parenteral artesunate with parenteral quinine. The trials were conducted in various African and Asian countries between 1989 and 2010.

In comparison with quinine, parenteral artesunate:

- reduced mortality from severe malaria by about 40% in adults (RR, 0.61; 95% CI, 0.50–0.75, five trials, 1664 participants, high-quality evidence);
- reduced mortality from severe malaria by about 25% in children (RR, 0.76; 95% CI, 0.65–0.90, four trials, 5765 participants, high-quality evidence); and
- was associated with a small increase in neurological sequelae in children at the time of hospital discharge (RR, 1.36; 95% CI, 1.01–1.83, three trials, 5163 participants, moderate-quality evidence), most of which, however, slowly resolved, with little or no difference between artesunate and quinine 28 days later (moderate-quality evidence).

Other considerations

The guideline development group considered that the small increase in neurological sequelae at discharge after treatment with artesunate was due to the delayed recovery of the severely ill patients, who would have died had they received quinine. This should not be interpreted as a sign of neurotoxicity. Although the safety of artesunate given in the first trimester of pregnancy has not been firmly established, the guideline development group considered that the proven benefits to the mother outweigh any potential harm to the developing fetus.

Remarks

Parenteral artesunate is recommended as first-line treatment for adults, children, infants and pregnant women in all trimesters of pregnancy.

Rationale for the recommendation

The Guideline Development Group considered the small increase in neurological sequelae at discharge associated with artesunate to be due to prolonged recovery of severely ill patients who would have died if they had received quinine. This should not be interpreted as a sign of neurotoxicity.

Although the safety of artesunate in the first trimester of pregnancy has not been firmly established, the group considered that the proven benefits to the mother outweigh the potential harms to the developing fetus.

Strong recommendation for

Treating severe malaria in children (2015)

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.

*Not evaluated using the GRADE framework; recommendation based on pharmacokinetic modelling

Practical Info

Artesunate is dispensed as a powder of artesunic acid, which is dissolved in sodium bicarbonate (5%) to form sodium artesunate. The solution is then diluted in approximately 5 mL of 5% dextrose and given by intravenous injection or by intramuscular injection into the anterior thigh.

The solution should be prepared freshly for each administration and should not be stored. Artesunate is rapidly hydrolysed in-vivo to dihydroartemisinin, which provides the main antimalarial effect. Studies of the pharmacokinetics of parenteral artesunate in children with severe malaria suggest that they have less exposure than older children and adults to both artesunate and the biologically active metabolite dihydroartemisinin. Body weight has been identified as a significant covariate in studies of the pharmacokinetics of orally and rectally administered artesunate, which suggests that young children have a larger apparent volume of distribution for both compounds and should therefore receive a slightly higher dose of parenteral artesunate to achieve exposure comparable to that of older children and adults.

Artesunate and post-treatment haemolysis
Delayed haemolysis starting >1 week after artesunate treatment of severe malaria has been reported in hyperparasitaemic non-immune travellers. Between 2010 and 2012, there were six reports involving a total of 19 European travellers with severe malaria who were treated with artesunate injection and developed delayed haemolysis. All except one were adults (median age, 50 years; range, 5–71 years). In a prospective study involving African children, the same phenomenon was reported in 5 (7%) of the 72 hyperparasitaemic children studied. Artesunate rapidly kills ring-stage parasites, which are then taken out of the red cells by the spleen; these infected erythrocytes are then returned to the circulation but with a shortened life span, resulting in the observed haemolysis. Thus, post-treatment haemolysis is a predictable event related to the life-saving effect of artesunate. Hyperparasitaemic patients must be followed up carefully to identify late-onset anaemia.

Justification

The dosing subgroup reviewed all available pharmacokinetic data on artesunate and the main biologically active metabolite dihydroartemisinin following administration of artesunate in severe malaria (published pharmacokinetic studies from 71 adults and 265 children) *[236][237]*. Simulations of artesunate and dihydroartemisinin exposures were conducted for each age group. These showed underexposure in younger children. The revised parenteral dose regimens are predicted to provide equivalent artesunate and dihydroartemisinin exposures across all age groups.

Other considerations
Individual parenteral artesunate doses between 1.75 and 4 mg/kg have been studied and no toxicity has been observed. The GRC concluded that the predicted benefits of improved antimalarial exposure in children are not at the expense of increased risk.

5.2.2.2 Parenteral alternatives when artesunate is not available

Conditional recommendation for , Low certainty evidence

Parental alternatives when artesunate is not available (2015)

If artesunate is not available, artemether should be used in preference to quinine for treating children and adults with severe malaria.

Practical Info

Artemether
Artemether is two to three times less active than its main metabolite dihydroartemisinin. Artemether can be given as an oil-based intramuscular injection or orally. In severe falciparum malaria, the concentration of the parent compound predominates after intramuscular injection, whereas parenteral artesunate is hydrolysed rapidly and almost completely to dihydroartemisinin. Given intramuscularly, artemether may be absorbed more slowly and more erratically than water-soluble artesunate, which is absorbed rapidly and reliably after intramuscular injection. These pharmacological advantages may explain the clinical superiority of parenteral artesunate over artemether in severe malaria.

Artemether is dispensed dissolved in oil (groundnut, sesame seed) and given by intramuscular injection into the anterior thigh.

Therapeutic dose: The initial dose of artemether is 3.2 mg/kg bw intramuscularly (to the anterior thigh). The maintenance dose is 1.6 mg/kg bw intramuscularly daily.

Quinine
Quinine treatment for severe malaria was established before the methods for modern clinical trials were developed. Several salts of quinine have been formulated for parenteral use, but the dihydrochloride is the most widely used. The peak concentrations after intramuscular quinine in severe malaria are similar to those after intravenous infusion. Studies of pharmacokinetics show that a loading dose of quinine (20 mg salt/kg bw, twice the maintenance dose) provides therapeutic plasma concentrations within 4 h. The maintenance dose of quinine (10 mg salt/ kg bw) is administered at 8-h intervals, starting 8 h after the first dose. If there is no improvement in the patient's condition within 48 h, the dose should be reduced by one third, i.e. to 10 mg salt/kg bw every 12 h.

Rapid intravenous administration of quinine is dangerous. Each dose of parenteral quinine must be administered as a slow, rate-controlled infusion (usually diluted in 5% dextrose and infused over 4 h). The infusion rate should not exceed 5 mg salt/kg bw per h.

Whereas many antimalarial drugs are prescribed in terms of base, for historical reasons quinine doses are usually recommended in terms of salt (usually sulphate for oral use and dihydrochloride for parenteral use). Recommendations for the doses of this and other antimalarial agents should state clearly whether the salt or the base is being referred to; doses with different salts must have the same base equivalents. Quinine must never be given by intravenous bolus injection, as lethal hypotension may result.

Quinine dihydrochloride should be given by rate-controlled infusion in saline or dextrose solution. If this is not possible, it should be given by intramuscular injection to the anterior thigh; quinine should not be injected into the buttock in order to avoid sciatic nerve injury. The first dose should be split, with 10 mg/kg bw into each thigh. Undiluted quinine dihydrochloride at a concentration of 300 mg/ mL is acidic (pH 2) and painful when given by intramuscular injection, so it is best to administer it either in a buffered formulation or diluted to a concentration of 60–100 mg/mL for intramuscular injection. Gluconate salts are less acidic and better tolerated than the dihydrochloride salt when given by the intramuscular and rectal routes.

As the first (loading) dose is the most important in the treatment of severe malaria, it should be reduced only if there is clear evidence of adequate pre-treatment before presentation. Although quinine can cause hypotension if administered rapidly, and overdose is associated with blindness and deafness, these adverse effects are rare in the treatment of severe malaria. The dangers of insufficient treatment (i.e. death from malaria) exceed those of excessive initial treatment.

Evidence To Decision

Benefits and harms

Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Desirable effects:

- In children > 12 years and adults, parenteral artesunate probably prevents more deaths than intramuscular artemether (moderate-quality evidence).
- No randomized controlled trials have been conducted in children aged ≤ 12 years.

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Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?

Desirable effects:

- In children, artemether is probably equivalent to quinine in preventing death (moderate-quality evidence).
- In children > 5 years and adults, artemether may be superior to quinine (moderate-quality evidence).
- Artemether is easier to administer, requiring a smaller fluid volume for intramuscular injection.

Certainty of the Evidence

Low

Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Overall certainty of evidence for all critical outcomes: moderate.

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Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?

Overall certainty of evidence for all critical outcomes: moderate.

Justification

GRADE

A systematic review of intramuscular artemether for severe malaria comprised two randomized controlled trials in Viet Nam in which artemether was compared with artesunate in 494 adults, and 16 trials in Africa and Asia in which artemether was compared with quinine in 716 adults and 1447 children *[238]*. The trials were conducted between 1991 and 2009.

In comparison with artesunate, intramuscular artemether was not as effective at preventing deaths in adults in Asia (RR, 1.80; 95% CI, 1.09–2.97; two trials, 494 participants, moderate-quality evidence).

Artemether and artesunate have not been directly compared in randomized trials in African children.

In comparison with quinine:

- Intramuscular artemether prevented a similar number of deaths in children in Africa (RR, 0.96; 95% CI, 0.76–1.20; 12 trials, 1447 participants, moderate-quality evidence).
- Intramuscular artemether prevented more deaths in adults in Asia (RR, 0.59; 95% CI, 0.42–0.83; four trials, 716 participants, moderate-quality evidence).

Other considerations

Indirect comparisons of parenteral artesunate and quinine and of artemether and quinine were considered by the guideline development group with what is known about the pharmacokinetics of the two drugs. They judged the accumulated indirect evidence to be sufficient to recommend parenteral artesunate rather than intramuscular artemether for use in all age groups.

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Is parenteral artesunate superior to parenteral quinine in preventing death from severe malaria?

Remarks

Intramuscular artemether should be considered only when parenteral artesunate is not available.

Recommendation

Treat children and adults with severe malaria with parenteral artesunate for at least 24 h.

Strength of recommendation: Strong for.

Rationale for the recommendation

Indirect comparisons of artesunate and quinine and of artemether and quinine were considered by the Guideline Development Group, with what is known about the pharmacokinetics of the two drugs. The group considered that the accumulated indirect evidence is sufficient to recommend artesunate over artemether for all age groups.

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Is intramuscular artemether superior to parenteral quinine in preventing death from severe malaria?

Remarks
Quinine is retained as an option for treating severe malaria when artesunate or artemether is not available or is contraindicated.

Recommendation
If parenteral artesunate is not available, use artemether in preference to quinine for treating children and adults with severe malaria.

Strength of recommendation: conditional for.

Rationale for the recommendation
The Guideline Development Group considered the possible superiority, the ease of administration and the better adverse-event profile of artemether as sufficient to recommend artemether over quinine as a second-line treatment option for severe malaria.

5.2.2.3 Pre-referral treatment options

The risk for death from severe malaria is greatest in the first 24 h, yet, in most malaria-endemic countries, the transit time between referral and arrival at a health facility where intravenous treatment can be administered is usually long, thus delaying the start of appropriate antimalarial treatment. During this time, the patient may deteriorate or die. It is therefore recommended that patients, particularly young children, be treated with a first dose of one of the recommended treatments before referral (unless the referral time is <6 h).

The recommended pre-referral treatment options for children <6 years, in descending order of preference, are intramuscular artesunate; rectal artesunate; intramuscular artemether; and intramuscular quinine. For older children and adults, the recommended pre-referral treatment options, in descending order of preference, are intramuscular injections of artesunate; artemether; and quinine.

Administration of an artemisinin derivative by the rectal route as pre-referral treatment is feasible and acceptable even at community level. The only trial of rectal artesunate as pre-referral treatment showed the expected reduction in mortality of young children but unexpectedly found increased mortality in older children and adults. As a consequence, rectal artesunate is recommended for use only in children aged <6 years and only when intramuscular artesunate is not available.

When rectal artesunate is used, patients should be transported immediately to a higher-level facility where intramuscular or intravenous treatment is available. If referral is impossible, rectal treatment could be continued until the patient can tolerate oral medication. At this point, a full course of the recommended ACT for uncomplicated malaria should be administered.

The single dose of 10 mg/kg bw of artesunate when given as a suppository should be administered rectally as soon as a presumptive diagnosis of severe malaria is made. If the suppository is expelled from the rectum within 30 min of insertion, a second suppository should be inserted and the buttocks held together for 10 min to ensure retention of the dose.

Strong recommendation for , Moderate certainty evidence

Pre-referral treatment options (2015)

Where complete treatment of severe malaria is not possible, but injections are available, adults and children should be given a single intramuscular dose of artesunate, and referred to an appropriate facility for further care. Where intramuscular artesunate is not available, intramuscular artemether or, if that is not available, intramuscular quinine should be used.

Where intramuscular injection of artesunate is not available, children < 6 years should be treated with a single rectal dose (10mg/kg bw) of artesunate, and referred immediately to an appropriate facility for further care. Rectal artesunate should not be used in older children and adults.

Practical Info

Adjustment of parenteral dosing in renal failure of hepatic dysfunction
The dosage of artemisinin derivatives does not have to be adjusted for patients with vital organ dysfunction. However, quinine accumulates in severe vital organ dysfunction. If a patient with severe malaria has persisting acute kidney injury or there is no clinical improvement by 48 h, the dose of quinine should be reduced by one third, to 10 mg salt/kg bw every 12 h. Dosage adjustments are not necessary if patients are receiving either haemodialysis or haemofiltration.

Follow-on treatment
The current recommendation of experts is to give parenteral antimalarial drugs for the treatment of severe malaria for a minimum of 24 h ounce started (irrespective of the patient's ability to tolerate oral medication earlier) or until the patient can tolerate oral medication, before giving the oral follow-up treatment.

After initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial drug by giving a full course of effective ACT (artesunate + amodiaquine, artemether + lumefantrine or dihydroartemisinin + piperaquine). If the patient presented initially with impaired consciousness, ACTs containing mefloquine should be avoided because of an increased incidence of neuropsychiatric complications. When an ACT is not available, artesunate + clindamycin, artesunate + doxycycline, quinine + clindamycin or quinine + doxycycline can be used for follow-on treatment. Doxycycline is preferred to other tetracyclines because it can be given once daily and does not accumulate in cases of renal failure, but it should not be given to children < 8 years or pregnant women. As treatment with doxycycline is begun only when the patient has recovered sufficiently, the 7-day doxycycline course finishes after the artesunate, artemether or quinine course. When available, clindamycin may be substituted in children and pregnant women.

Continuing supportive care
Patients with severe malaria require intensive nursing care, preferably in an intensive care unit where possible. Clinical observations should be made as frequently as possible and should include monitoring of vital signs, coma score and urine output. Blood glucose should be monitored every 4 h, if possible, particularly in unconscious patients.

Please refer to *Rectal artesunate for pre-referral treatment of severe malaria [240]*.

Evidence To Decision

Benefits and harms

Desirable effects:

- No studies of direct comparison of rectal artesunate with parenteral antimalarial drugs for pre-referral treatment.
- In hospital care, parenteral artesunate reduces the number of deaths to a greater extent than parenteral quinine (high-quality evidence) and probably reduces the number of deaths from that with intramuscular artemether (moderate-quality evidence).

Certainty of the Evidence

Moderate

Overall certainty of evidence for all critical outcomes: moderate.

Justification

GRADE
In a systematic review of pre-referral treatment for suspected severe malaria, in a single large randomized controlled trial of 17 826 children and adults in Bangladesh, Ghana and the United Republic of Tanzania, pre-referral rectal artesunate was compared with placebo *[239]*.

In comparison with placebo:

- Rectal artesunate reduced mortality by about 25% in children < 6 years (RR, 0.74; 95% CI, 0.59–0.93; one trial, 8050 participants, moderate- quality evidence).
- Rectal artesunate was associated with more deaths in older children and adults (RR, 2.21; 95% CI, 1.18–4.15; one trial 4018 participants, low- quality evidence).

Other considerations
The guideline development group could find no plausible explanation for the finding of increased mortality among older children and adults in Asia who received rectal artesunate, which may be due to chance. Further trials would provide clarification but are unlikely to be done. The group was therefore unable to recommend its use in older children and adults.

In the absence of direct evaluations of parenteral antimalarial drugs for pre- referral treatment, the guideline development group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for pre-referral situations. When intramuscular injections can be given, the group recommends intramuscular artesunate in preference to rectal artesunate.

Remarks
This recommendation applies to all people with suspected severe malaria, including infants, lactating women and pregnant women in all trimesters.

Where intramuscular artesunate is not available, use rectal artesunate (in children < 6 years), intramuscular artemether or intramuscular quinine.

Rationale for the recommendation
In the absence of direct comparative evaluations of parenteral antimalarial drugs for pre-referral treatment, the Guideline Development Group considered the known benefits of artesunate in hospitalized patients and downgraded the quality of evidence for use in pre-referral situations. When intramuscular injections can be given, the panel recommends intramuscular artesunate in preference to rectal artesunate.

5.2.3 Other considerations in treating malaria

5.2.3.1 Management of malaria cases in special situations

Epidemics and humanitarian emergencies

Environmental, political and economic changes, population movement and war can all contribute to the emergence or re-emergence of malaria in areas where it was previously eliminated or well controlled. The displacement of large numbers of people with little or no immunity within malaria-endemic areas increases the risk for malaria epidemics among the displaced population, while displacement of people from an endemic area to an area where malaria has been eliminated can result in re-introduction of transmission and a risk for epidemics in the resident population.

Climate change may also alter transmission patterns and the malaria burden globally by producing conditions that favour vector breeding and thereby increasing the risks for malaria transmission and epidemics.

Parasitological diagnosis during epidemics

In the acute phase of epidemics and complex emergency situations, facilities for laboratory diagnosis with good-quality equipment and reagents and skilled technicians are often not available or are overwhelmed. Attempts should be made to improve diagnostic capacity rapidly, including provision of RDTs. If diagnostic testing is not feasible, the most practical approach is to treat all febrile patients as suspected malaria cases, with the inevitable consequences of over-treatment of malaria and potentially poor management of other febrile conditions. If this approach is used, it is imperative to monitor intermittently the prevalence of malaria as a true cause of fever and revise the policy appropriately. This approach has sometimes been termed “mass fever treatment”. This is not the same as and should not be confused with “mass drug administration”, which is administration of a complete treatment course of antimalarial medicines to every individual in a geographically defined area without testing for infection and regardless of the presence of symptoms.

Management of uncomplicated falciparum malaria during epidemics

The principles of treatment of uncomplicated malaria are the same as those outlined in section 5.2. Active case detection should be undertaken to ensure that as many patients as possible receive adequate treatment, rather than relying on patients to come to a clinic.

Epidemics of mixed falciparum and vivax or vivax malaria

ACTs (except artesunate + SP) should be used to treat uncomplicated malaria in mixed-infection epidemics, as they are highly effective against all malaria species. In areas with pure *P. vivax* epidemics, ACTs or chloroquine (if prevalent strains are sensitive) should be used.

Anti-relapse therapy for *P. vivax* malaria

Administration of 14-day primaquine anti-relapse therapy for vivax malaria may be impractical in epidemic situations because of the duration of treatment and the difficulty of

ensuring adherence. If adequate records are kept, therapy can be given in the post-epidemic period to patients who have been treated with blood schizontocides.

Malaria elimination settings

Use of gametocytocidal drugs to reduce transmission
ACT reduces *P. falciparum* gametocyte carriage and transmission markedly, but this effect is incomplete, and patients presenting with gametocytaemia may be infectious for days or occasionally weeks, despite ACT. The strategy of using a single dose of primaquine to reduce infectivity and thus *P. falciparum* transmission has been widely used in low transmission settings.

Use of primaquine as a *P. falciparum* gametocytocide has a particular role in programmes to eliminate *P. falciparum* malaria. The population benefits of reducing malaria transmission by
gametocytocidal drugs require that a high proportion of patients receive these medicines. WHO recommends the addition of a single dose of primaquine (0.25 mg base/kg bw) to ACT for uncomplicated falciparum malaria as a gametocytocidal medicine, particularly as a component of elimination programmes. A recent review of the evidence on the safety and effectiveness of primaquine as a gametocytocide of *P. falciparum* indicates that a single dose of 0.25 mg base/kg bw is effective in blocking infectivity to mosquitos and is unlikely to cause serious toxicity in people with any of the G6PD variants. Thus, the G6PD status of the patient does not have to be known before primaquine is used for this indication.

Artemisinin-resistant falciparum malaria
Artemisinin resistance in *P. falciparum* is now prevalent in parts of Cambodia, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam. There is currently no evidence for artemisinin resistance outside these areas. The particular advantage of artemisinins over other antimalarial drugs is that they kill circulating ring-stage parasites and thus accelerate therapeutic responses. This is lost in resistance to artemisinin. As a consequence, parasite clearance is slowed, and ACT failure rates and gametocytaemia both increase. The reduced efficacy of artemisinin places greater selective pressure on the partner drugs, to which resistance is also increasing. This situation poses a grave threat. In the past chloroquine resistant parasites emerged near the Cambodia–Thailand border and then spread throughout Asia and Africa at a cost of millions of lives. In Cambodia, where artemisinin resistance is worst, none of the currently recommended treatment regimens provides acceptable cure rates (> 90%), and continued use of ineffective drug regimens fuels the spread of resistance. In Cambodia use of atovaquone–proguanil instead of ACT resulted in very rapid emergence of resistance to atovaquone.

In this dangerous, rapidly changing situation, local treatment guidelines cannot be based on a solid evidence base; however, the risks associated with continued use of ineffective regimens are likely to exceed the risks of new, untried regimens with generally safe antimalarial drugs. At the current levels of resistance, the artemisinin derivatives still provide significant antimalarial activity; therefore, longer courses of treatment with existing or new augmented combinations or treatment with new partner medicines (e.g. artesunate + pyronaridine) may be effective. Studies to determine the best treatments for artemisinin-resistant malaria are needed urgently.

It is strongly recommended that single-dose primaquine (as a gametocytocide) be added to all falciparum malaria treatment regimens as described in section 5.2.5. For the treatment of severe malaria in areas with established artemisinin resistance, it is recommended that parenteral artesunate and parenteral quinine be given together in full doses, as described in section 5.5.

5.2.3.2 Quality of antimalarial drugs

The two general classes of poor-quality medicines are those that are *falsified* (counterfeit), in which there is criminal intent to deceive and the drug contains little or no active ingredient (and often other potentially harmful substances), and those that are *substandard*, in which a legitimate producer has included incorrect amounts of active drug and/or excipients in the medicine, or the medicine has been stored incorrectly or for too long and has degraded. Falsified antimalarial tablets and ampoules containing little or no active pharmaceutical ingredients are a major problem in some areas. They may be impossible to distinguish at points of care from the genuine product and may lead to under-dosage and high levels of treatment failure, giving a mistaken impression of resistance, or encourage the development of resistance by providing sub-therapeutic blood levels. They may also contain toxic ingredients.

Substandard drugs result from poor-quality manufacture and formulation, chemical instability or improper or prolonged storage. Artemisinin and its derivatives in particular have built-in chemical instability, which is necessary for their biological action but which causes pharmaceutical problems both in their manufacture and in their co-formulation with other compounds. The problems of instability are accelerated under tropical conditions. The requirement for stringent quality standards is particularly important for this class of compounds. Many antimalarial drugs are stored in conditions of high heat and humidity and sold beyond their expiry dates.

In many malaria-endemic areas, a large proportion of the antimalarial drugs used are generic products purchased in the private sector. They may contain the correct amounts of antimalarial drug, but, because of their formulation, are

inadequately absorbed. Antimalarial medicines must be manufactured according to good manufacturing practice, have the correct drug and excipient contents, be proved to have bioavailability that is similar to that of the reference product, have been stored under appropriate conditions and be dispensed before their expiry date.

Tools to assess drug quality at points of sale are being developed, but the capacity of medicines regulatory agencies in most countries to monitor drug quality is still limited. Legal and regulatory frameworks must be strengthened, and there should be greater collaboration between law enforcement agencies, customs and excise authorities and medicines regulatory agencies to deal more effectively with falsified medicines. Private sector drug distribution outlets should have more information and active engagement with regulatory agencies. WHO, in collaboration with other United Nations agencies, has established an international mechanism to prequalify manufacturers of ACTs on the basis of their compliance with internationally recommended standards of manufacture and quality. Manufacturers of antimalarial medicines with prequalified status are listed on the prequalification web site *[241]*.

Good practice statement

Antimalarial drug quality (2015)

National drug and regulatory authorities should ensure that the antimalarial medicines provided in both the public and the private sectors are of acceptable quality, through regulation, inspection and law enforcement.

5.2.3.3 Monitoring efficacy and safety of antimalarial drugs and resistance

When adapting and implementing these guidelines, countries should also strengthen their systems for monitoring and evaluating their national programmes. The systems should allow countries to track the implementation and impact of new recommendations, better target their programmes to the areas and populations at greatest need and detect decreasing antimalarial efficacy and drug resistance as early as possible.

Routine surveillance

WHO promotes universal coverage with diagnostic testing and antimalarial treatment and strengthened malaria surveillance systems. In the “test, track, treat” initiative, it is recommended that every *suspected* malaria case is tested, that every *confirmed* case is treated with a quality-assured antimalarial medicine and that the disease is tracked by timely, accurate surveillance systems. Surveillance and treatment based on confirmed malaria cases will lead to better understanding of the disease burden and enable national malaria control programmes to direct better their resources to where they are most needed.

Therapeutic efficacy

Monitoring of therapeutic efficacy in falciparum malaria involves assessing clinical and parasitological outcomes of treatment for at least 28 days after the start of adequate treatment and monitoring for the reappearance of parasites in blood. The exact duration of post-treatment follow-up is based on the elimination half- life of the partner drug in the ACT being evaluated. Tools for monitoring antimalaria drug efficacy can be found on the WHO website.

PCR genotyping should be used in therapeutic monitoring of antimalarial drug efficacy against *P. falciparum* to distinguish between recrudescence (true treatment failure) and new infections.

An antimalarial medicine that is recommended in the national malaria treatment policy should be changed if the total treatment failure proportion is ≥ 10%, as assessed in vivo by monitoring therapeutic efficacy. A significantly declining trend in treatment efficacy over time, even if failure rates have not yet fallen to the ≥ 10% cut-off, should alert programmes to undertake more frequent monitoring and to prepare for a potential policy change.

Resistance

Antimalarial drug resistance is the ability of a parasite strain to survive and/or multiply despite administration and absorption of an antimalarial drug given in doses equal to or higher than those usually recommended, provided that drug exposure is adequate. Resistance to antimalarial drugs arises because of selection of parasites with genetic changes (mutations or gene amplifications) that confer reduced susceptibility. Resistance has been documented to all classes of antimalarial medicines, including the artemisinin derivatives, and it is a major threat to malaria control.

Widespread inappropriate use of antimalarial drugs exerts a strong selective pressure on malaria parasites to develop high levels of resistance. Resistance can be prevented, or its onset slowed considerably by combining antimalarial drugs with different mechanisms of action and ensuring high cure rates through full adherence to correct dose regimens. If different drugs with different mechanisms of resistance are used together, the emergence and spread of resistance should be slowed.

Clinical and parasitological assessment of therapeutic efficacy should include:

- confirmation of the quality of the antimalarial medicines tested;
- molecular genotyping to distinguish between re-infections and recrudescence and to identify genetic markers of drug resistance;
- studies of parasite susceptibility to antimalarial drugs in culture; and
- measurement of antimalarial drug levels to assess exposure in cases of slow therapeutic response or treatment failure

Pharmacovigilance
Governments should have effective pharmacovigilance systems (such as the WHO pregnancy registry) to monitor the safety of all drugs, including antimalarial medicines. The safety profiles of the currently recommended antimalarial drugs are reasonably well described and supported by an evidence base of several thousand participants (mainly from clinical trials); however, rare but serious adverse drug reactions will not be detected in clinical trials of this size, particularly if they occur primarily in young children, pregnant women or people with concurrent illness, who are usually under-represented in clinical trials. Rare but serious adverse drug reactions are therefore detected only in prospective phase IV post-marketing studies or population-based pharmacovigilance systems. In particular, more data are urgently needed on the safety of ACTs during the first trimester of pregnancy and on potential interactions between antimalarial and other commonly used medicines.

Good practice statement

Monitoring efficacy and safety of antimalarial drugs and resistance (2015)

All malaria programmes should regularly monitor the therapeutic efficacy of antimalarial drugs using the standard WHO protocols.

Practical Info

Routine monitoring of antimalarial drug efficacy is necessary to ensure effective case management and for early detection of resistance. WHO recommends that the efficacy of first- and second-line antimalarial treatments be tested at least once every 24 months at all sentinel sites. Data collected from studies conducted according to the standard protocol inform national treatment policies.

Please refer to the tools for monitoring antimalarial drug efficacy and Methods for surveillance of antimalarial drug efficacy *[242]* which includes tools and materials to conduct routine therapeutic efficacy studies (TES). It is a reference for national programmes and investigators conducting routine surveillance studies to assess the efficacy of medicines that have already been registered.

Additional references include:

- Methods and techniques for clinical trials on antimalarial drug efficacy: Genotyping to identify parasite populations *[243]*
- Report on antimalarial drug efficacy, resistance and response: 10 years of surveillance (2010-2019) *[244]*

5.3 National adaptation and implementation

These guidelines provide a generic framework for malaria diagnosis and treatment policies worldwide; however, national policy-makers will be required to adapt these recommendations on the basis of local priorities, malaria epidemiology, parasite resistance and national resources.

National decision-making
National decision-makers are encouraged to adopt inclusive, transparent, rigorous approaches. Broad, inclusive stakeholder engagement in the design and implementation of national malaria control programmes will help to ensure they are feasible, appropriate, equitable and acceptable. Transparency and freedom from financial conflicts of interest will reduce mistrust and conflict, while rigorous evidence-based processes will ensure that the best possible decisions are made for the population.

Information required for national decision-making
Selection of first- and second-line antimalarial medicines will require reliable national data on their efficacy and parasite resistance, which in turn require that appropriate surveillance and monitoring systems are in place (see Monitoring efficacy and safety of antimalaria drugs). In some countries, the group adapting the guidelines for national use might have to re-evaluate the global evidence base with respect to their own context. The GRADE tables may serve as a starting-point for this

assessment. Decisions about coverage, feasibility, acceptability and cost may require input from various health professionals, community representatives, health economists, academics and health system managers.

Opportunities and risks

The recommendations made in these guidelines provide an opportunity to improve malaria case management further, to reduce unnecessary morbidity and mortality and to contribute to continued efforts towards elimination. Failure to implement the basic principles of combination therapy and rational use of antimalarial medicines will risk promoting the emergence and spread of drug resistance, which could undo all the recent gains in malaria control and elimination.

General guiding principles for choosing a case management strategy and tools

Choosing a diagnostic strategy

The two methods currently considered suitable for routine patient management are light microscopy and RDTs. Different strategies may be adopted in different health care settings. The choice between RDTs and microscopy depends on local circumstances, including the skills available, the patient case-load, the epidemiology of malaria and use of microscopy for the diagnosis of other diseases. When the case-load of patients with fever is high, the cost of each microscopy test is likely to be less than that of an RDT; however, high-throughput, high-quality microscopy may be less operationally feasible. Although several RDTs allow diagnosis of both *P. falciparum* and *P. vivax* infections, microscopy has further advantages, including accurate parasite counting (and thus identification of high parasite density), prognostication in severe malaria, speciation of other malaria parasites and sequential assessment of the response to antimalarial treatment. Microscopy may help to identify other causes of fever. High-quality light microscopy requires well-trained, skilled staff, good staining reagents, clean slides and, often, electricity to power the microscope. It requires a quality assurance system, which is often not well implemented in malaria-endemic countries.

In many areas, malaria patients are treated outside the formal health services, e.g. in the community, at home or by private providers. Microscopy is generally not feasible in the community, but RDTs might be available, allowing access to confirmatory diagnosis of malaria and the correct management of febrile illnesses. The average sensitivity of HRP2-detecting RDTs is generally greater than that of RDTs for detecting *p*LDH of *P. falciparum*, but the latter are slightly more specific because the HRP2 antigen may persist in blood for days or weeks after effective treatment. HRP2-detecting RDTs are not suitable for detecting treatment failure. RDTs are slightly less sensitive for detecting *P. malariae* and *P. ovale*. The WHO Malaria RDT Product Testing programme provides comparative data on the performance of RDT products to guide procurement. Since 2008, 210 products have been evaluated in five rounds of product testing *[172]*.

For the diagnosis of severe malaria, microscopy is preferred, as it provides a diagnosis of malaria and assessment of other important parameters of prognostic relevance in severely ill patients (such as parasite count and stage of parasite development and intra-leukocyte pigment). In severe malaria, an RDT can be used to confirm malaria rapidly so that parenteral antimalarial treatment can be started immediately. Where possible, however, blood smears should be examined by microscopy, with frequent monitoring of parasitaemia (e.g. every 12 h) during the first 2–3 days of treatment in order to monitor the response.

Choosing ACT

In the absence of resistance, all the recommended ACTs have been shown to result in parasitological cure rates of > 95%. Although there are minor differences in the oral absorption, bioavailability and tolerability of the different artemisinin derivatives, there is no evidence that these differences are clinically significant in currently available formulations. It is the properties of the partner medicine and the level of resistance to it that determine the efficacy of a formulation.

Policy-makers should also consider:

- local data on the therapeutic efficacy of the ACT,
- local data on drug resistance,
- the adverse effect profiles of ACT partner drugs,
- the availability of appropriate formulations to ensure adherence,
- cost.

In parts of South-East Asia, artemisinin resistance is compromising the efficacy of ACTs and placing greater selection pressure on resistance to the partner medicines. Elsewhere, there is no convincing evidence for reduced susceptibility to the artemisinins; therefore, the performance of the partner drugs is the determining factor in the choice of ACT, and the following principles apply:

- Resistance to mefloquine has been found in parts of mainland South-East Asia where this drug has been used intensively. Nevertheless, the combination with artesunate is very effective, unless there is also resistance to artemisinin. Resistance to both components has compromised the efficacy of artesunate + mefloquine in western Cambodia, eastern Myanmar and eastern Thailand.
- Lumefantrine shares some cross-resistance with mefloquine, but this has not compromised its efficacy in any of the areas in which artemether + lumefantrine has been used outside South-East Asia.
- Until recently, there was no evidence of resistance to piperaquine anywhere, but there is now reduced susceptibility in western Cambodia. Elsewhere, the dihydroartemisinin + piperaquine combination is highly effective.
- Resistance to SP limits its use in combination with artesunate to the few areas in which susceptibility is retained.
- Amodiaquine remains effective in combination with artesunate in parts of Africa and the Americas, although elsewhere resistance to this drug was prevalent before its introduction in an ACT.

Considerations in use of artemisinin-based combination therapy
Oral artemisinin and its derivatives (e.g. artesunate, artemether, dihydroartemisinin) should not be used alone. In order to simplify use, improve adherence and minimize the availability of oral artemisinin monotherapy, fixed-dose combination ACTs are strongly preferred to co-blistered or co-dispensed loose tablets and should be used when they are readily available. Fixed-dose combinations of all recommended ACT are now available, except artesunate + SP. Fixed-dose artesunate + amodiaquine performs better than loose tablets, presumably by ensuring adequate dosing. Unfortunately, paediatric formulations are not yet available for all ACTs.

The choice of ACT in a country or region should be based on optimal efficacy and adherence, which can be achieved by:

- minimizing the number of formulations available for each recommended treatment regimen
- using, where available, solid formulations instead of liquid formulations, even for young patients.

Although there are some minor differences in the oral absorption and bioavailability of different artemisinin derivatives, there is no evidence that such differences in currently available formulations are clinically significant. It is the pharmacokinetic properties of the partner medicine and the level of resistance to it that largely determine the efficacy and choice of combinations. Outside South-East Asia, there is no convincing evidence yet for reduced susceptibility to the artemisinins; therefore, the performance of the partner drug is the main determinant in the choice of ACT, according to the following principles:

- Drugs used in IPTp, SMC or chemoprophylaxis should not be used as first-line treatment in the same country or region.
- Resistance to SP limits use of artesunate + SP to areas in which susceptibility is retained.Thus, in the majority of malaria-endemic countries, first-line ACTs remain highly effective, although resistance patterns change over time and should be closely monitored.

Choosing among formulations
Use of fixed-dose combination formulations will ensure strict adherence to the central principle of combination therapy. Monotherapies should not be used, except as parenteral therapy for severe malaria or SP chemoprevention, and steps should be taken to reduce and remove their market availability. Fixed-dose combination formulations are now available for all recommended ACTs except artesunate + SP.

Paediatric formulations should allow accurate dosing without having to break tablets and should promote adherence by their acceptability to children. Paediatric formulations are currently available for artemether + lumefantrine, dihydroartemisinin + piperaquine and artesunate + mefloquine.

Other operational issues in managing effective treatment
Individual patients derive the maximum benefit from an ACT if they can access it within 24–48 h of the onset of malaria symptoms. The impact in reducing transmission at a population level depends on high coverage rates and the transmission intensity. Thus, to optimize the benefits of deploying ACTs, they should be available in the public health delivery system, the private sector and the community, with no financial or physical barrier to access. A strategy for ensuring full access (including community management of malaria in the context of integrated case management) must be based on analyses of national and local health systems and may require legislative changes and regulatory approval, with additional local adjustment as indicated by programme monitoring and operational research. To optimize the benefits of effective treatment, wide dissemination of national treatment guidelines, clear recommendations, appropriate information, education and communication materials, monitoring of the deployment process, access and coverage, and provision of adequately packaged antimalarial drugs are needed.

Community case management of malaria
Community case management is recommended by WHO to improve access to prompt, effective treatment of malaria episodes by trained community members living as close as possible to the patients. Use of ACTs in this context is feasible, acceptable and effective *[245]*. Pre-referral treatment for severe malaria with rectal artesunate and use of RDTs are also recommended in this context. Community case management should be integrated into community management of childhood illnesses, which ensures coverage of priority childhood illnesses outside of health facilities.

Health education
From the hospital to the community, education is vital to optimizing antimalarial treatment. Clear guidelines in the language understood by local users, posters, wall charts, educational videos and other teaching materials, public awareness campaigns, education and provision of information materials to shopkeepers and other dispensers can improve the understanding of malaria. They will increase the likelihood of better prescribing and adherence, appropriate referral and reduce unnecessary use of antimalarial medicines.

Adherence to treatment
Patient adherence is a major determinant of the response to antimalarial drugs, as most treatments are taken at home without medical supervision. Studies on adherence suggest that 3-day regimens of medicines such as ACTs are completed reasonably well, provided that patients or caregivers are given an adequate explanation at the time of prescribing or dispensing. Prescribers, shopkeepers and vendors should therefore give clear, comprehensible explanations of how to use the medicines. Co-formulation probably contributes importantly to adherence. User- friendly packaging (e.g. blister packs) also encourages completion of a treatment course and correct dosing.

Good practice statement

National adaptation and implementation (2015)

The choice of ACTs in a country or region should be based on optimal efficacy, safety and adherence.

Practical Info

Pharmacovigilance is the practice of monitoring the effects of medical drugs after they have been licensed for use, especially to identify and evaluate previously unreported adverse reactions. *A practical handbook on the pharmacovigilance of antimalarial medicines [246]* provides a step-by-step approach for antimalarial pharmacovigilance. Designed for health officials, planners, and other health workers, it focuses on active and passive pharmacovigilance, reporting, event monitoring and other key factors.

Good practice statement

National adaptation and implementation (2022)

Drugs used as first line treatment should not be used in IPTp, PMC, SMC, IPTsc or MDA.

Good practice statement

National adaptation and implementation (2015)

When possible:

fixed-dose combinations should be used rather than co-blistered or loose, single-agent formulations; andfor young children and infants, paediatric formulations, with a preference for solid formulations (e.g. dispersible tablets) should be used rather than liquid formulations.

6. INTERVENTIONS IN THE FINAL PHASE OF ELIMINATION AND PREVENTION OF RE-ESTABLISHMENT

The *Global technical strategy for malaria 2016-2030 [5]* urges all malaria-endemic countries to accelerate towards elimination and attainment of malaria-free status. WHO recommends that all countries ensure access to malaria prevention, diagnosis and treatment as part of universal health coverage; recommendations related to these strategies can be found in sections 4 (Prevention) and 5 (Case Management) of these guidelines.

Countries or areas that have attained very low to low levels of transmission require additional interventions in order to eliminate malaria. These interventions should:

- accelerate the decline in malaria transmission to a level at which intensive surveillance, i.e. follow-up of every case, is feasible;
- target specific groups at increased risk of infection that may not be reached adequately through routine prevention and treatment services; and
- respond to individual cases and foci to interrupt transmission.

Activities in settings approaching elimination will be most effective at reducing transmission if they are tailored to the distribution of the reservoir of malaria infection. Recommendations for the final phase of elimination are, therefore, divided into three categories of possible interventions:

- 'mass' strategies applied to the entire population of a delimited geographical area, whether a hamlet, township or district;
- 'targeted' strategies applied to people at increased risk of infection compared to the general population; and
- 'reactive' strategies implemented in response to individual cases.

At very low and low levels of transmission, malaria cases tend to cluster geographically and according to shared risk factors *[247][248]*. The premise behind targeted and reactive strategies is that interventions applied to a small subset of the population or a small area of the community believed to encompass the infectious reservoir of infection could reduce transmission overall. To capture the potential impact of the

intervention on transmission, key outcomes are measured at the community level rather than only among those who actually receive or participate in the intervention.

In post-elimination settings, malaria programmes must continue to actively intervene in order to prevent re-establishment of transmission. Countries will need to ensure that diagnosis and treatment services are available everywhere as part of universal health coverage as imported cases can be identified anywhere and at any time. However, the extent and intensity of additional activities during the post-elimination period will depend on the health system and the malariogenic potential of the area, that is, the degree of receptivity to transmission and the risk or rate of importation of malaria infections. Strategies targeted to specific higher-risk areas or groups, or in response to the identification of an imported or introduced infection, are required in post-elimination settings working to prevent re-establishment of transmission.

6.1 Interventions recommended for mass implementation in delimited geographical areas

In areas approaching elimination where transmission is generalized across the population of a defined geographical area (i.e. a district, village or focus), strategies that cover the whole population may be needed to reduce transmission. These strategies could include mass drug administration (MDA), mass relapse prevention (MRP) or mass testing and treatment (MTaT).

Recommendations on MDA and MRP to reduce transmission of *P. falciparum* and *P. vivax* are presented under section 4.2.4 (Mass drug administration) in the Chemoprevention chapter of the malaria guidelines. Mass strategies are generally not recommended for post-elimination settings unless there is a resumption of local transmission of malaria.

6.1.1 Mass testing and treatment (MTaT)

Mass testing and treatment (MTaT) involves parasitological testing of the entire population of a delimited geographical area and treatment of all positive cases with an appropriate antimalarial medicine at approximately the same time. MTaT is an active case detection strategy that may improve the timeliness and coverage of treatment. MTaT extends malaria diagnosis and treatment to people who experience barriers to care or who do not feel ill. MTaT is generally conducted using point-of-contact malaria rapid diagnostic tests but has also been conducted using microscopy and nucleic acid-based tests. Only people found to be positive receive a full therapeutic course of an effective antimalarial medicine. As a result, the intervention does not provide a population-level prophylactic period as MDA does. However, providing antimalarial medicine only to those who are known to be infected may improve adherence to treatment, population acceptance of the intervention and equity while decreasing the risk of unintended consequences.

Conditional recommendation against , Moderate certainty evidence

Mass testing and treatment to reduce transmission of malaria (2022)

Mass testing and treatment (MTaT) to reduce the transmission of malaria is not recommended.

The GDG noted that there may be exceptional circumstances under which MTaT might be appropriate, such as a transmission focus in a very low transmission or post-elimination setting where MDA is not an acceptable or feasible strategy.

Evidence To Decision

Benefits and harms

Seven studies of MTaT were included in the systematic review: four cRCTs, conducted in Kenya, Indonesia, Zambia and Burkina Faso; and three NRSs in Senegal, Ghana and India (Bhamani *et al* *unpublished evidence*).

Beneficial outcomes

- MTaT does not reduce the prevalence of malaria two months after the last round (RD: -26 per 1000 population; 95% CI [CI] -68 to 15 per 100 persons; one cRCT; high-certainty evidence).
- MTaT does not reduce the incidence of malaria 0–12 months after the start of the intervention (RD: -117 per 1000 p-y (p-y); 95% CI: -303 to 93 per 1000 p-y; one cRCT; high-certainty evidence).
- MTaT probably results in little to no difference in the incidence of malaria (measured only in children) 6–12 months

after the start of the intervention (RD: 4 per 1000 p-y; 95% CI: -2 to 8 per 1000 p-y; two cRCTs; moderate-certainty evidence).
- MTaT reduces the incidence of clinical malaria 0–12 months after the start of the intervention (RD: -44 per 1000 p-y; 95% CI: -70 to -12 per 1000 p-y; two cRCTs; high-certainty evidence).

Adverse events

- Among people treated as part of MTaT, the most common adverse events were fever (0.023/person-day), headache (0.008/person-day, vomiting (0.006/person-day), cough (0.004/person-day), shivering (0.003/person-day) and nasal congestion (0.002/person-day) (one cRCT, not GRADEd because no information was available from the comparator arm).

Judgement of the panel

The GDG judged that the beneficial impact of MTaT on malaria incidence and prevalence at the community level was trivial, as were the potential adverse events.

Certainty of the Evidence

Moderate

The overall certainty of the evidence was judged to be moderate.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified two studies on the cost and cost effectiveness of MTaT in southern Zambia (Bhamani *et al* *unpublished evidence*). The overall cost per test administered was US$ 4.39, whereas the overall cost for treatment with artemether-lumefantrine (AL) was US$ 34.74. Personnel and vehicles were the largest cost drivers, followed by trainings and rapid diagnostic tests. The estimated cost per DALYs averted was US$ 804, which in the context of Zambia was considered a highly cost-effective health intervention.

The GDG judged the resources required to implement MTaT to be large. Although one study found MTaT to be a cost-effective intervention in the context of southern Zambia, the GDG judged the impact of the intervention in general to be likely trivial. Therefore, with high costs, the cost-effectiveness would probably favour not conducting MTaT.

Equity

No studies were identified that addressed the issue of whether MTaT increased or decreased health equity.

The GDG felt that MTaT may favour disadvantaged segments of the population who otherwise might have limited or no access to the health system for diagnostic testing and treatment for malaria. Therefore, the GDG judged that MTaT would probably increase health equity.

Acceptability

The acceptability of MTaT was reported in three qualitative studies identified by the systematic review (Bhamani *et al unpublished evidence*). One study in western Kenya found that the community engaged in an MTaT intervention reported concerns over testing in the absence of symptoms. These concerns were mostly related to the fear of covert HIV testing and some lack of understanding of the possibility of asymptomatic malaria. Other issues related to acceptability were failure to adhere to the full treatment course, treatment effectiveness and the need for intense sensitization activities. In the post-implementation round, although many participants appreciated the intervention and expressed an overall positive experience, some concerns remained, including fear of covert HIV testing and failure to adhere to treatment. One study in Zambia aimed to understand perceptions of community health workers and community members on MTaT. In general, MTaT was perceived very positively by most community health workers and community members. However, some barriers identified by community health workers included difficult transportation to hard-to-reach areas; difficulty charging personal digital assistants for data collection due to unavailability of charging sources; and commodity shortages. Among community participants, most barriers were related to the perceived fears around covert HIV testing and use of blood samples for "Satanism". Lack of community health worker skills and training to conduct testing and treatment was also a perceived barrier among some community members. Lastly, this study also identified the perceived feeling of wellness once symptoms subsided as a barrier to adherence to treatment. One study in Ghana assessed the perception of health workers and community members on MTaT. Overall, the health workers and community participants perceived MTaT as a feasible intervention with many benefits, including reducing incidence in children, increasing sensitization of the community on malaria, reducing hospital admissions, increasing work productivity, reducing expenditure for treatment, providing timely access to treatment at home, and reducing travel to health facilities. However, health care workers were concerned about revenue lost from internally-generated funds at the health facility. Some of the challenges experienced during MTaT were misconceptions and rumours (e.g. fear of being infected with epilepsy by health workers), concerns over the safety of drugs, and a lack of trust in health workers' skills and knowledge.

The GDG judged that MTaT was probably acceptable to key stakeholders.

Feasibility

The systematic review identified two studies reporting on the feasibility of MTaT campaigns in Kenya and Ghana (Bhamani *et al unpublished evidence*). However, one MTaT campaign was implemented within a well developed and well maintained health and demographic surveillance system in Kenya. The other study from Ghana reported on the perception of MTaT as feasible by health workers and community members.

The GDG noted that the type of parasitological test used (rapid diagnostic test, microscopy or nucleic acid based test) would affect the feasibility of implementing the strategy as tests that are not conducted at the point-of-contact would be more difficult to implement, require more staff with more technical training and likely delay identification and treatment of positive cases.

The feasibility of implementing MTaT would also depend on whether radical cure of *P. vivax* using an 8-aminoquinoline medicine was part of the MTaT strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

The GDG judged that MTaT was probably a feasible intervention to implement.

Justification

The GDG judged that there was moderate certainty evidence that MTaT had a trivial impact on malaria prevalence and incidence. Although there may be some benefit to health equity by reaching people who may otherwise have difficulty accessing malaria diagnostic and testing services, and the intervention was found to be acceptable to stakeholders and feasible to implement, the resources required to implement MTaT were considered to be large. The GDG felt that there may be transmission foci in very low transmission settings where an MTaT intervention could be beneficial but decided to provide a conditional recommendation against implementing MTaT to reduce the transmission of malaria.

Research Needs

Further evidence is needed on the impact (prevalence and incidence of malaria infection at the community level) of MTaT when rounds are conducted at more frequent intervals (at least once per month while there is transmission of malaria). This research should include evaluation of the feasibility of implementation and acceptability of the strategy to health care workers and community members. Data on the cost of the strategy and the cost-effectiveness compared to passive

surveillance are needed.

6.2 Interventions targeting infections in people at higher-risk

At any level of malaria transmission, there may be situations that put some individuals at greater risk of infection than the general population. When transmission declines to low or very low levels, malaria infections may be more frequent among people who work or enjoy their leisure where they are more exposed to malaria vectors. Higher-risk situations are often associated with outdoor or night-time activities and include mining, guarding, rubber tapping, forest activities, cattle herding, military and police exercises, night-time sports, socializing outdoors and sleeping outside.

If there are defined situations that that lead to a large proportion of the infections in an area, it may be equally effective but more equitable, acceptable and cost-effective to target interventions to people exposed to these situations rather than to the entire population. While it is clear that those who receive the intervention will benefit from treatment of any extant infections they may have as well as prevention of infection during the prophylactic period, the impact of targeted strategies on community-level transmission of malaria will depend on the extent to which malaria is transmitted in other settings.

The term 'targeted' is used here to differentiate strategies based on defined higher-risk settings from 'mass' strategies that are based on a defined geographical area. Targeted strategies could involve chemoprevention (i.e. targeted drug administration [TDA]) or testing and treatment of confirmed positives (i.e. targeted testing and treatment [TTaT]). There are parallels between different 'targeted' and 'mass' strategies related to the type of intervention and the population included (Table 1).

Table 1. Designation of potential malaria elimination strategies by population and intervention

	Population covered	
Intervention	Every member of the population of a delimited geographical area	Individuals identified by exposure to defined higher-risk situations
Chemoprevention	Mass drug administration	Targeted drug administration
Testing and treatment	Mass testing and treatment	Targeted testing and treatment

A special type of TTaT, border screening, occurs at points of entry into an area. Border screening is a testing and treatment strategy used to detect infections among people crossing by land, sea or air into an area that is post-elimination or with very low to low levels of transmission. Testing may be implemented as routine screening of all consenting individuals passing through a border crossing. Alternatively, organized or identifiable groups may be tested and treated through various approaches in the days immediately following arrival or return.

In post-elimination settings, preventing infections in nonimmune residents travelling to malaria-endemic areas through chemoprophylaxis would likely be a more effective approach than treating them upon return. Chemoprophylaxis is used to reduce infections, severe illness and death in non-immune people who travel to malaria-endemic areas. People living in areas approaching elimination or post-elimination will lose their immunity to malaria over time. Therefore, recommendations related to chemoprophylaxis for travel of nonimmune individuals to malaria-endemic areas are applicable in these settings. Guidance on malaria chemoprophylaxis for travellers can be found in the WHO *International travel and health guidance* [2].

6.2.1 Targeted drug administration (TDA)

Targeted drug administration (TDA) is a form of chemoprevention involving the provision of a full therapeutic course of an antimalarial medicine to individuals at increased risk of malaria infection compared to the general population. Depending on the frequency and duration of exposure, TDA could be provided before, during or after potential exposure to malaria transmission. The antimalarial medicines given during TDA treat all existing infections and prevent new infections over the duration of the drug's post-treatment prophylaxis period. At minimum, a TDA strategy deploys an antimalarial medicine that targets the asexual, blood-stage malaria parasites (e.g. ACTs or chloroquine). TDA interventions may include additional medicines that target hypnozoites in the liver (e.g. primaquine for radical cure of *P. vivax*) or gametocytes in the blood (e.g. single, low-dose primaquine for *P. falciparum*).

TDA, as opposed to MDA, is provided to specific individuals or a subset of the population rather than to everyone present within a delimited geographical area. The premise of the strategy is that providing chemoprevention to individuals whose occupations or behaviours put them at increased risk of malaria infection may reduce transmission in the community if their infections constitute a large proportion of the infectious reservoir. If found to be effective, a targeted strategy is likely to be more resource-efficient, acceptable, feasible and equitable than a mass strategy.

Conditional recommendation for , Very low certainty evidence

Targeted drug administration to reduce transmission of malaria (2022)

In areas with very low to low transmission or post-elimination settings preventing re-establishment of transmission, antimalarial medicine can be given as chemoprevention to people with increased risk of infection relative to the general population to reduce transmission.

- *Persons given antimalarials should be those with increased risk of infection compared to the general population and their infections should constitute a large proportion of the parasite reservoir in the area.*
- *The factors identifying individuals or groups at increased risk of infection should be easy to recognise, thereby improving the acceptability and feasibility of the intervention.*
- *Programmes considering implementing targeted drug administration for P. vivax should carefully consider how to safely and feasibly administer treatment to prevent relapses.*
- *Care should be taken to avoid stigmatizing groups at increased risk of infection.*
- *Additional complementary strategies to eliminate or prevent re-establishment of malaria transmission should be in place.*

Practical Info

TDA depends on detailed, recent knowledge of the epidemiology and ecology of malaria in an area. This knowledge is generally based on a strong passive surveillance system that can detect all suspected cases, diagnose infections, collect and analyse case-based data and characterize cases according to potential risk factors. (The ability to conduct case investigations at the home of the person diagnosed with malaria is not a requirement for a TDA programme but could potentially improve the quality of the data collected.)

The persons given antimalarials in a TDA programme should be those with an increased risk of infection compared to the general population. This could include individuals in key demographic groups or with certain occupations or behaviours that are known to be associated with increased infection rates. Additionally, data from the surveillance system should demonstrate that infections in these individuals are likely to comprise a large proportion of the infectious reservoir in the area. Finally, the characteristics or risk factors that define the group at increased risk of infection should be easily recognizable or identifiable; if not, the TDA programme will be more challenging to implement and possibly less acceptable to stakeholders.

Malaria elimination programmes implementing TDA should recognize that, as areas approach elimination, malaria infections become more concentrated in certain geographies and populations that may already be socially disadvantaged. This includes migrants, displaced persons, ethnic minorities and poor rural communities. A TDA programme should actively seek to prevent further adverse social impact on these groups. Language choices can frame the way that groups are perceived, and TDA programmes should avoid labelling groups of people as “reservoirs" of infection or “hot” populations. Referring to chemoprevention for malaria in higher-risk “situations” rather than higher-risk “groups” can shift the focus away from scapegoating certain populations. By engaging communities affected by malaria in elimination settings, including those that may be socially marginalized, malaria elimination programmes can improve their understanding of local social dynamics and identify strategies to provide better services to people at risk of malaria infection. TDA programmes should monitor the social impact of their interventions to determine if stigma is occurring to any malaria-affected populations and to determine whether their efforts to avoid stigma are working.

Achieving high coverage of the affected population and good adherence to the antimalarial medicine are critical aspects of TDA programmes. TDA programmes ask many asymptomatic, healthy people to take a medicine when they do not feel ill, with the potential for adverse reactions to occur. Improving coverage and adherence requires development of understanding and trust in the institutions implementing the programme. Community engagement is thus a key factor in determining the success of TDA, to improve participation rates and adherence to the full treatment course of the medicine.

A complete therapeutic course of antimalarial medicine, at doses recommended by the manufacturer, should be given to all eligible adults and children. Drug dosage should be determined by weight wherever possible, with dosing according to age only in situations where the person’s weight is unknown. The antimalarial medicines chosen for use in TDA should: a) be WHO recommended and prequalified; b) be efficacious against local parasites; c) be different from the medicine used as first-line treatment, where possible c) have a superior safety and tolerability profile; d) provide a longer duration of post-treatment prophylaxis with component medicines that have closely matched pharmacology to reduce the risk of new infections encountering only a single drug; e) have a positive public reputation and acceptability and f) be available and low-cost. Programmes in areas with *P. falciparum* may consider including a single, low-dose of primaquine in TDA programmes in

order to increase the gametocytocidal effect, although no evidence of an additional benefit from provision of single low-dose primaquine in a TDA programme was reviewed. A drug regimen that can be administered as a directly-observed single dose is preferred to multi-day regimens.

Depending on the medicine chosen, certain population groups may need to be excluded from TDA, such as: pregnant women in their first trimester; infants < 6 months of age or weighing <5kgs; people recently treated with the same medicine; people with a known allergy to the medicine; anyone with severe acute illness or unable to take oral medication; people taking medication known to interact with the medicine used for TDA; and people with specific contraindications to the medicine used. Although rarely implemented in the same area, TDA should not be given to individuals receiving other forms of malaria chemoprevention (e.g. seasonal malaria chemoprevention, perennial malaria chemoprevention, or intermittent preventive treatment during pregnancy) *[141]*.

Programmes contemplating providing medicine for radical cure of *P. vivax* hypnozoites as part of TDA programme should carefully consider whether it is feasible to administer this treatment regimen safely, i.e. with testing for G6PD deficiency prior to treatment, an effective pharmacovigilance system and emergency access to blood transfusion services. Programmes should consider whether sufficient coverage and adherence to the full course of radical cure can be achieved.

Evidence To Decision

Benefits and harms

The systematic review identified two cRCTs in Kenya and Uganda and three NRSs conducted in Ghana, Greece and Sri Lanka assessing the impact of TDA on malaria transmission compared to no TDA (Tusell *et al* *unpublished evidence*). Only one study reported measures of malaria transmission at the community level, while the other studies reported on outcomes only among the individuals targeted by the intervention. Three studies (two cRCTs and one NRS) were conducted in areas of moderate to high transmission and two NRSs were conducted in areas preventing re-establishment of transmission.

The GDG determined that TDA would be most appropriate in very low to low transmission or post-elimination settings. The GDG decided that the PICO question should be modified accordingly (i.e. limited to such settings) and that only the two NRSs conducted in post-elimination settings should be considered as direct evidence of the impact of TDA.

Beneficial outcomes

- The evidence is very uncertain about the effect of TDA on the prevalence of malaria. (Both NRSs found no malaria cases in either the targeted group or the community after use of TDA in migrant workers among whom malaria had been detected prior to the intervention; very low-certainty evidence).

Adverse events

- One NRS monitored adverse events 1–5 months post-intervention and no serious adverse events were reported during or after the treatment.
- One NRS recorded adverse events in 397 out of the 1094 treated individuals; the majority were classified as minor: predominantly dizziness and headache for chloroquine and abdominal pain for primaquine. A single case of primaquine-induced haemolysis was recorded in a person with an incorrect G6PD test result.

Judgement of the panel

With respect to adverse events, the data presented were limited, but the GDG considered the wealth of evidence from other studies on the safety and efficacy of antimalarial medicines as indirect evidence to estimate the level of potential undesirable effects of the strategy.

The GDG judged the potential benefits of the TDA strategy in some settings to be large, particularly if TDA contributes to the prevention of re-establishment of transmission. The potential undesirable effects of TDA were judged to be small. The GDG determined that the balance of effects probably favoured TDA in settings of very low to low transmission or post-elimination of malaria.

Certainty of the Evidence

Very low

The overall certainty of the evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

No studies on the cost or cost-effectiveness of TDA in areas of very low to low transmission or post-elimination settings were found.

The GDG judged that the costs required to implement TDA were moderate, and that cost-effectiveness probably favoured implementation of TDA.

Equity

No studies were identified addressing the issue of whether TDA increased or decreased health equity. However, one article was identified that discussed the potential for strategies such as TDA to lead to social stigmatization if care was not taken to choose terms and descriptions carefully and focus on higher risk situations rather than specific groups *[249]*.

The GDG judged that a targeted strategy that intervenes in a small group of people more affected by malaria than the population surrounding them would likely improve health equity. However, the GDG recognized that, although malaria is not itself a stigmatizing disease, targeting specific groups might raise fears that they were sources of contagion and could lead to social isolation and stigmatization.

Acceptability

No studies were identified addressing the issue of acceptability of TDA in areas of very low to low transmission or post-elimination of malaria.

The GDG judged that TDA was probably acceptable to stakeholders.

Feasibility

No studies were identified that addressed the issue of feasibility of implementing TDA in areas of very low to low transmission or post-elimination of malaria.

The GDG identified several factors likely to affect the feasibility of implementing the strategy, including the choice of drug and the size of the area to be covered. The feasibility of implementing TDA would also vary depending on whether radical cure for *P. vivax* using an 8-aminoquinoline medicine was part of the TDA strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

The GDG judged that implementation of the strategy was feasible with significant planning and agreement of the local authorities.

Justification

Although the quality of evidence was very low, the GDG concluded that the balance of effects probably favoured implementing TDA, particularly in post-elimination settings to prevent re-establishment of transmission. As long as it is relatively simple to identify individuals or groups at increased risk of infection, and care is taken to avoid stigmatizing these

groups, TDA is likely to be more equitable, acceptable and feasible than mass strategies involving the entire population of an area.

Research Needs

- Further evidence is needed on the impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences of TDA for malaria in very low to low transmission or post-elimination settings.
- Evidence is needed on the acceptability, feasibility, impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences (death, hospital admission, severe anaemia or any severe adverse events) of safe provision (including testing for G6PD deficiency and, additionally, an effective pharmacovigilance system and emergency access to blood transfusion services) of an 8-aminoquinoline as part of TDA for radical cure of *P. vivax* infections.
- Investigate approaches to characterizing higher-risk situations with respect to their contribution to the overall human infectious reservoir.
- Evidence is needed to optimize the delivery of TDA with respect to the synchronicity of treatments, time intervals between rounds of treatment, number of rounds needed per year and number of years needed to sustainably reduce malaria transmission.
- Evidence is needed on whether TDA stigmatizes groups that might already be socially isolated, such as migrants or refugee populations.

6.2.2 Targeted testing and treatment (TTaT)

Targeted testing and treatment (TTaT) is the parasitological testing of individuals at increased risk of malaria infection and treatment of all positive cases with an appropriate antimalarial medicine. TTaT is an active case detection strategy that is implemented among people considered to have a higher risk of malaria infection than the general public and whose infections likely constitute a large proportion of the infectious reservoir in an area. TTaT is generally conducted using point of contact malaria rapid diagnostic tests but also has been conducted using microscopy and nucleic acid-based tests.

TTaT, as opposed to MTaT, is provided to specific individuals or to a subset of the population rather than to everyone present in a delimited geographical area. As with TDA, the premise of the TTaT strategy is that diagnosing and treating infections in individuals whose occupations or behaviours put them at increased risk of malaria infection may reduce transmission in the community if their infections constitute a large proportion of the infectious reservoir. Unlike TDA, however, medicine is only provided to the positive cases in TTaT, reducing the number of people who benefit from protection during the drug's prophylactic period. However, providing antimalarial medicine only to those who have confirmed infections may improve adherence to treatment, population acceptance of the intervention and equity while decreasing the risk of unintended consequences.

Conditional recommendation against , Very low certainty evidence

Targeted testing and treatment to reduce transmission of malaria (2022)

Testing and treatment of people with an increased risk of infection relative to the general population to reduce the transmission of malaria is not recommended.

The GDG noted that there may be limited circumstances under which targeted testing and treatment (TTaT) could be beneficial. For example, TTaT could be used when people at a higher risk of infection can be easily identified and chemoprevention is not acceptable to the population. Additionally, TTaT could be used if safe and effective implementation of radical cure to prevent P. vivax relapses is only feasible for those with confirmed infections.

Evidence To Decision

Benefits and harms

The systematic review identified three studies for inclusion: two cRCTs in Ghana and Kenya and one NRS in Malawi (Allen *et al* unpublished evidence). Only one study reported measures of malaria transmission outcomes at the

community level. No studies were conducted in very low to low transmission or post-elimination settings.

The GDG determined that the TTaT strategy would be most relevant in very low to low transmission or post-elimination settings and, therefore, decided that the PICO question should be modified accordingly (i.e. limited to such settings). As a result, the GDG did not consider evidence on benefits from the studies included in the review.

The potential harms (i.e. adverse events) from the intervention were considered likely to be trivial, as people who received treatment would be infected with malaria and, therefore, would receive treatment according to national guidelines.

The judgements of the GDG related to the balance of effects was based on its expert opinions and indirect information from related interventions, such as MTaT and TDA. The GDG judged that the balance of effects probably favoured not implementing TTaT.

Certainty of the Evidence

Very low

The overall certainty of the evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

No studies on the cost or cost-effectiveness of TTaT in very low to low transmission or post-elimination settings were found.

The GDG judged that the costs required to implement TTaT were moderate, and that the cost-effectiveness probably favoured not implementing TTaT.

Equity

No studies were identified that addressed the issue of whether TTaT increased or decreased health equity.

The GDG judged that a targeted strategy that intervenes in a small group of people more affected by malaria than the population surrounding them would improve health equity.

Acceptability

No studies were identified that addressed the issue of acceptability of TTaT in areas of very low to low transmission or post-elimination of malaria.

The GDG judged that TTaT was probably acceptable to stakeholders, as it is a type of active case detection.

Feasibility

No studies were identified that addressed the issue of feasibility of TTaT in areas of very low to low transmission or post-elimination of malaria.

The GDG noted that the type of parasitological test used (rapid diagnostic test, microscopy or nucleic acid-based test)

would affect the feasibility of implementing the strategy as tests that are not point-of-contact would be more difficult to implement, require more technical staff and delay identification and treatment of positive cases.

The feasibility of implementing TTaT would also depend on whether radical cure of *P. vivax* using an 8-aminoquinoline medicine was part of the TTaT strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

The GDG judged that implementation of TTaT was probably feasible.

Justification

The GDG judged that the likely impact of TTaT on malaria transmission in very low to low or post-elimination settings would be trivial, based on experiences with MTaT, challenges with detecting very low parasite densities and a lack of diagnostics for hypnozoites. The GDG felt that there may be specific situations where TTaT could be beneficial, for example, when the parasite reservoir is very clearly limited to a small group of people and infections are detectable. Additionally, TTaT could be used if chemoprevention is either not acceptable to the population or safe and effective implementation of radical cure to prevent *P. vivax* is only feasible for those with confirmed infections, but in most settings, TTaT is not likely to reduce malaria transmission.

Research Needs

While further evidence of the impact (prevalence and incidence of malaria infection at the community level) of TTaT could change the direction or strength of the recommendation given the lack of published studies on the impact of TTaT, the GDG did not judge that this research gap was a priority.

6.2.3 Testing and treatment at points of entry to reduce importation of malaria

Testing and treatment at points of entry (i.e. border screening) is the parasitological testing of individuals crossing a border whether by land, sea or air and treatment of all positive cases with an appropriate antimalarial medicine. Border screening has been used to try to reduce the number of imported cases of malaria into an area in order to eliminate or prevent re-establishment of malaria transmission. Border screening has generally been applied more often at land crossings than air or seaports.

Routine malaria testing and treatment at land crossings is often implemented at the borders between countries approaching elimination and their neighbours with higher levels of malaria transmission. However, many borders are highly porous with uncounted unofficial crossing points, making it difficult to achieve a high coverage of testing and treatment. Rather than attempting to test and treat individuals at a land crossing, several malaria elimination programmes target organized groups, such as the military or pilgrims, or set up testing and treatment at the points where migrant workers will be employed, such as plantations. This latter approach may improve the acceptability and feasibility of the strategy but depends on good multisectoral collaboration and knowledge of travel patterns.

Under the International Health Regulations (IHR) and for public health purposes, national authorities in the country of arrival may require travellers to undertake a non-invasive medical examination that would achieve the public health objective of preventing the international spread of disease, while respecting travellers' dignity, human rights and fundamental freedoms *[250]*. The IHR recommend that countries that share a land border consider entering into agreements concerning the prevention or control of international transmission of disease at ground crossings; public health measures to prevent international transmission of malaria may apply.

Conditional recommendation against , Very low certainty evidence

Routine malaria testing and treatment at points of entry (2022)

Routine malaria testing and treatment of people arriving at points of entry (land, sea or air) to reduce importation is not recommended.

No studies of the impact of testing and treatment at points of entry on the rate of malaria importation were found by the systematic review. Routine testing and treatment for malaria at points of entry is unlikely to be acceptable or feasible to implement.

Evidence To Decision

Certainty of the Evidence

Very low

Conditional recommendation for , Very low certainty evidence

Malaria testing and treatment of organized or identifiable groups arriving or returning from malaria-endemic areas (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, organized or identifiable groups arriving or returning from malaria-endemic areas can be tested and treated soon after entry to reduce importation of malaria.

Relatively easy access to these groups within a short time after entry is required for this strategy to be feasible and acceptable. This strategy may be particularly critical to areas in post-elimination that are working to prevent re-establishment of transmission.

Evidence To Decision

Benefits and harms

The systematic review identified seven NRSs in six countries (Cambodia, China, Equatorial Guinea, Greece, Myanmar and the United Arab Emirates that reported on testing and treatment at points of entry (Coma-Cros *et al* *unpublished evidence*). None of the studies provided information on the outcome considered critical by the GDG, i.e. the number of positive cases identified by the strategy as a proportion of all imported cases found in the country during the same period.

The GDG noted that border screening may take two forms: the traditional approach of testing and treatment of individuals at the time of entry through land crossings, seaports or airports; and the testing and treatment of organized or identifiable groups (e.g. military, migrant workers or religious pilgrims) recently arriving or returning from malaria-endemic areas. Because there are clear differences in the feasibility and acceptability of these two approaches, the GDG developed two separate recommendations.

The benefits of testing and treatment at points of entry could not be assessed as no studies reporting on critical outcomes were identified by the review.

The potential harms (i.e. adverse events) from the intervention were considered likely to be trivial, as people who received treatment would be infected with malaria and, therefore, treated according to national guidelines.

The GDG judged that the balance of effects probably varied depending on the source population, strictness of entry into the area, coverage of the intervention, species of parasite, type of parasitological test and the area's epidemiological profile with respect to malaria.

Certainty of the Evidence

Very low

The certainty of evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified one study with data on the cost of testing and treatment at points of entry (Coma-Cros *et al unpublished evidence*). One NRS study of testing and treatment of recently arrived migrant workers estimated that the programme cost US$ 226 080 annually between 2013 and 2017. No studies of the cost-effectiveness of testing and treatment at points of entry were identified.

The GDG judged the costs required to implement testing and treatment at points of entry to be moderate, and the cost-effectiveness probably varied depending on whether the intervention was applied to individuals at the point of entry or to organized or identifiable groups immediately after arrival. In the latter case, the GDG judged that the intervention was probably cost-effective compared to not testing and treating organized or identifiable groups.

Equity

No studies were identified that addressed the issue of whether testing and treatment at points of entry increased or decreased health equity.

The GDG judged that the testing and treatment of organized or identifiable groups was likely to be more equitable than the routine testing and treatment of individuals at the point of entry.

Acceptability

The systematic review identified two studies of acceptability (Coma-Cros *et al unpublished evidence*). One study assessed the number of refusals for testing at border crossing points between Cambodia and Thailand, Viet Nam and Lao People's Democratic Republic. Out of 4110 people approached, 904 (22%) refused to be tested for malaria. The main reasons for refusal included: not having enough time (51.6%); not perceiving themselves to be at risk of malaria and thus not requiring testing (40.6%); being scared to give blood (34.2%); and having an apparent language or cultural barrier (23.9%) (multiple answers possible). A qualitative study conducted in 2010 in the Solomon Islands on the feasibility and acceptability of testing all travellers using rapid diagnostic tests and offering treatment to those found positive suggested that there was acceptance and support for such an approach.

The GDG judged that acceptance of testing and treatment at points of entry was likely to vary by stakeholder (less acceptable to travellers at the time of entry but potentially more acceptable to organized groups immediately after entry). Among travellers, acceptability is likely to vary considerably depending on factors such as the location of the screening, the time required and the travellers' level of concern regarding possible malaria infection.

Feasibility

No studies on the feasibility of implementing testing and treatment at points of entry were identified.

The GDG noted that the type of parasitological test used (rapid diagnostic test, microscopy or nucleic acid-based test) would affect the feasibility of implementing the strategy as tests that are not administered at point-of-contact would be more difficult to implement, require more technical staff and delay identification and treatment of positive cases.

The GDG judged that the feasibility of implementing routine testing and treatment at points of entry would likely vary. Implementing such an intervention at airports or seaports was considered unlikely to be feasible due to the high volume of travellers and the time required to test and treat. The feasibility of implementing testing and treatment at land crossings was considered to be more feasible but would depend on the volume of travellers. Additionally, the feasibility of covering a high proportion of people crossing into the country through land crossings would depend on the strictness with which entry into the country was controlled and the porosity of the border. In most areas with porous borders, the GDG judged that the feasibility of implementing a testing and treatment with sufficient coverage at land crossings would be low.

However, the feasibility of implementing testing and treatment among organized or identifiable groups arriving or recently returned from malaria-endemic areas was considered to be high. The GDG knew of many reports of military groups, labour migrants and religious groups in countries eliminating malaria or preventing re-establishment who were tested and treated for malaria after returning from periods in malaria-endemic areas.

Justification

With respect to routine testing and treatment at points of entry (land, sea or air), the GDG, in the absence of direct evidence, judged that the impact on importation of malaria was likely to be small except in areas nearing elimination or post-elimination. The GDG felt that the acceptability and feasibility of testing and treating for malaria at points of entry would be low given the likely disruption to travel.

When considering organized or identifiable groups of people (e.g. military, migrant laborers or religious pilgrims) arriving or returning from malaria -endemic areas, the GDG judged that testing these groups for malaria and treating those who are positive could help countries nearing elimination or preventing re-establishment by reducing importation. The acceptability and feasibility of this strategy was considered higher than routine testing and treatment at points of entry but would depend upon the local circumstances.

Research Needs

- Evidence is needed on the efficiency (number of imported cases identified as a proportion of all imported cases identified during the same period) of testing and treating organized or identifiable groups of people arriving or returning from malaria-endemic areas in terms of the importation of malaria.
- Investigate novel approaches to improving the efficiency of identifying and implementing testing and treatment among organized or identifiable groups, such as the plantation ambassador programme in Malaysia.

6.3 Interventions in response to detection of confirmed malaria cases

As transmission declines and approaches zero, there is evidence that malaria cases tend to cluster more than at higher levels of transmission *[247]*. This clustering could occur geographically, in small areas such as households and neighbourhoods, or socially, among people exposed at the same time and place, such as through a common occupation or shared travel to endemic areas *[248]*. If clusters can be identified and targeted with effective interventions, malaria transmission at the community level may be reduced.

Follow-up of confirmed cases of malaria at very low levels of transmission is one approach to identifying and targeting potential clusters of cases. A confirmed case of malaria, usually identified through passive case detection, is investigated to determine the likely location of infection. Interventions are subsequently implemented in and around the likely location of infection as well as among any people co-exposed with the index case. These strategies are called 'reactive' interventions because they are triggered 'in reaction' to the identification of a confirmed case of malaria.

The radius of implementation of interventions around the index case will need to be determined according to the strategy implemented, the likelihood that malaria cases could be afebrile and the degree of clustering of cases. For reactive drug administration (RDA) and reactive case detection and treatment (RACDT), programmes could begin with a larger radius of implementation and then evaluate their data to determine whether scaling back the size of the area or limiting activity to just the household of the index case is likely to be the most efficient. For reactive IRS, information on the behaviors and likely flight range of local vector mosquitoes will be needed to determine a reasonable radius of implementation.

Because cases of malaria, whether imported or local, may be identified in post-elimination settings, reactive strategies are also relevant to areas working to prevent re-establishment of malaria. Although data on the effectiveness of strategies in these settings will be extremely rare, evidence from areas with ongoing transmission can serve as indirect evidence for the likely impact in post-elimination settings.

Recommendations related to three reactive strategies, i.e. RDA, RACDT and reactive IRS, are reported below.

6.3.1 Reactive drug administration (RDA)

RDA is the provision of antimalarial medicine as chemoprevention to every person living with or near a person with a confirmed malaria infection, or to every person who was likely exposed to infection at the same time and place as the index case. The antimalarial medicines given during RDA aim to treat all existing infections and prevent new infections over the duration of the drug's post-treatment prophylaxis period. At minimum, an RDA strategy deploys an antimalarial medicine that targets the asexual, blood-stage malaria parasites (e.g. ACTs or chloroquine). RDA interventions may include additional medicines that target hypnozoites in the liver (e.g. primaquine for radical cure of *P. vivax*) or gametocytes in the blood (e.g. single, low-dose primaquine for *P. falciparum*).

Reactive interventions should target the likely location of infection of the index case. The likely location of infection is determined through a case investigation, using the date of symptom onset and knowledge of the incubation period of the specific parasite species to determine the location of the person during the likely period of infection. If the likely location of infection is a residence, RDA can be administered to at least the household of the confirmed case, but could also

be extended to neighbours. If the infection was imported from elsewhere, RDA can be administered to individuals who may have had the same exposure as the index case, such as co-travellers and co-workers.

Conditional recommendation for , Low certainty evidence

Reactive drug administration for reducing malaria transmission (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, antimalarial medicine can be given as chemoprevention to all people residing with or near a confirmed malaria case and all people who share the same risk of infection (e.g. co-travellers and co-workers) to prevent or reduce malaria transmission.

- *Programmes implementing reactive drug administration (RDA) should have the capacity to conduct case investigations at the residence to determine the likely location of infection and to identify those individuals co-exposed with the index case.*
- *Programmes implementing RDA should have the capacity to enumerate and provide antimalarials to the people residing with or near a confirmed malaria case and others that share the same risk of infection.*
- *The people given antimalarial medicine in an RDA intervention should share the same risk of having acquired infection as the index case or be at risk of acquiring infection from the index case. This includes residents in the same household or neighborhood, co-travellers and co-workers. However, if the infection was imported and the residence is not located in a receptive area, there may be no benefit from RDA.*
- *Programmes contemplating implementation of RDA for P. vivax should carefully consider how to safely and feasibly administer treatment to prevent relapses.*

Practical Info

When used, RDA should be one of several components of a programme to eliminate or prevent re-establishment of malaria, including intensive follow-up of every case as described in the *Framework for malaria elimination [10]*.

RDA depends on a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a quality-assured parasitological test and investigates all cases at their residence. If these elements are not in place, it is unlikely that an RDA intervention will have any effect on transmission.

It is essential to determine the likely location of infection through a case investigation that identifies the location of the person during the likely period of infection in order to understand where or in what group of people the RDA intervention should take place. RDA should be administered to other residents of the same house if the person is determined to have been infected locally. Programmes may consider extending the radius of RDA to neighbours depending on the local epidemiology and ecology of malaria. If the index infection is not likely to have been acquired at the residence, programmes should administer RDA to all people identified as having the same exposure to infection as the index case. People with the same risk of infection are likely to be those who travelled, worked or engaged in leisure activities with the index case. If the infection was classified as imported from elsewhere and the household is not located in a receptive area, there may be no benefit to RDA.

Countries that are at very low or low transmission but not yet close to achieving zero indigenous cases should prioritize implementation of RDA and reactive IRS over RACDT. However, RACDT should be added on top of RDA when countries are closer to elimination to strengthen the sensitivity of the surveillance system to monitor progress towards elimination and, post-elimination, to provide additional evidence of a malaria-free status.

RDA should be implemented according to standardized operating procedures (SOPs). A household listing of all people residing within the limits of RDA as specified by the SOPs should be developed and verified, along with a list of all people who may have been co-exposed. The RDA programme should seek to provide antimalarial medicine to everyone listed, using different approaches as needed to reach everyone at risk.

Achieving high coverage of the targeted population and good adherence to the antimalarial medicine are critical aspects of RDA programmes. RDA programmes ask many asymptomatic, healthy people to take a medicine when they do not feel ill, with the potential for adverse reactions to occur. Improving coverage and adherence requires development of understanding and trust in the institutions implementing the programme. Community engagement is thus a key factor in determining the success of RDA, to improve participation rates and adherence to the full treatment course of the medicine.

A complete therapeutic course of antimalarial medicine, at doses recommended by the manufacturer, should be given to all eligible adults and children. Drug dosage should be determined by weight wherever possible, with dosing according to age

only in situations where the person's weight is unknown. The antimalarial medicines chosen for use in RDA should: a) be WHO recommended and prequalified; b) be efficacious against local parasites; c) be different from the medicine used as first-line treatment, where possible c) have a superior safety and tolerability profile; d) provide a longer duration of post-treatment prophylaxis with component medicines that have closely matched pharmacology to reduce the risk of new infections encountering only a single drug; e) have a positive public reputation and acceptability and f) be available and low-cost. Programmes in areas with *P. falciparum* may consider including a single, low-dose of primaquine in an RDA programmes in order to increase the gametocytocidal effect, although there is no evidence of additional benefit from provision of of single low-dose primaquine in an RDA programme. A drug regimen that can be administered as a directly-observed single dose is preferred to multi-day regimens.

Depending on the medicine chosen, certain population groups may need to be excluded from RDA, such as: pregnant women in their first trimester; infants < 6 months of age or weighing < 5kgs; people recently treated with the same medicine; people with a known allergy to the medicine; anyone with severe acute illness or unable to take oral medication; people taking medication known to interact with the medicine used for RDA; and people with specific contraindications to the medicine used *[141]*. Although rarely implemented in the same area, RDA should not be given to individuals receiving other forms of malaria chemoprevention (e.g. seasonal malaria chemoprevention, perennial malaria chemoprevention, or intermittent preventive treatment during pregnancy).

Programmes contemplating providing medicine for radical cure of *P. vivax* hypnozoites as part of RDA should carefully consider whether it is feasible to administer this treatment regimen safely, i.e. with testing for G6PD deficiency prior to treatment, an effective pharmacovigilance system and emergency access to blood transfusion services. Programmes should consider whether sufficient coverage and adherence to the full course of radical cure can be achieved.

Evidence To Decision

Benefits and harms

The systematic review identified six cRCTs in four countries of sub-Saharan Africa (Eswatini, Gambia, Namibia and Zambia) and one NRS from Peru assessing the impact of RDA (Steinhardt *et al unpublished evidence (c)*). Almost all infections from the cRCTs in Africa were due to *P. falciparum* while the NRS in Peru included mainly *P. vivax* infections. The NRS from Peru provided chloroquine plus seven days of primaquine at a dosage of 0.5mg/kg. All studies except for the study from Zambia were from low-transmission settings. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- RDA may reduce malaria prevalence (RD: -5 per 1000 persons; 95% CI: -9 to 2 per 1000 persons; four cRCTs; low-certainty evidence).
- RDA probably reduces the incidence of parasitaemia (RD: -7 per 1000 p-y; 95% CI: -17 to 13 per 1000 p-y; two cRCTs; moderate-certainty evidence).
- RDA probably results in little to no difference in the incidence of clinical malaria (RD: -2 per 1000 p-y; -4 to 1 per 1000 p-y; six cRCTs; moderate-certainty evidence).
- The evidence is very uncertain about the effect of RDA on the incidence of clinical malaria. (RD: -2 per 1000 p-y; -3 to -1 per 1000 p-y; one NRS; very low-certainty evidence).

Adverse events

Four cRCTs reported on adverse events; however, only two studies reported adverse events from the RDA arm and the comparator arm. In RDA arms with DP:

- 123 (6.9%) mild adverse events were reported from 1775 participants receiving DP; all were resolved.
- 75 (7.6%) adverse events were reported from 979 participants receiving DP; 69 were rated as mild and six as moderate.
- 68 (3.8%) adverse events reported from 1776 participants receiving DP; 54 were rated as mild and 14 as moderate.

In RDA arms using AL:

- 17 (0.4%) adverse events were reported from 4247 participants.

The NRS in Peru that used chloroquine plus seven days of primaquine for radical cure of *P. vivax* hypnozoites reported no adverse events but there was no active pharmacovigilance system.

Judgement of the panel
The GDG judged both the benefits and undesirable effects of RDA to be small and the overall certainty of evidence to be low. The GDG noted that the comparator in several studies was RACDT rather than no RDA. As a result, the GDG judged that the systematic review likely underestimated the impact of RDA. Overall, the balance of effects was determined to favour neither the intervention nor the comparison.

Certainty of the Evidence

Low

The overall certainty of the evidence was judged to be low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified one study from Zambia with data on the financial and economic costs of RDA (Steinhardt *et al* *unpublished evidence* *(c)*). The study identified index cases through active rather than passive surveillance. The total cost of two rounds of RDA (with DP) conducted between 2014 and 2015, covering a total population of 132 393 was US$ 912 767 (all figures in 2015 US$). The mean cost per person reached was US$ 85.69 (interquartile range [IQR] US$39.92).

The overall incremental costs per infection and case averted (vs. standard of care) for RDA were US$ 810 and US$ 6 353, respectively. In high transmission settings, the incremental costs per infection and case averted were US$ 429 and US$ 5951, respectively; in low transmission settings, they were US$ 1119 and US$ 6755, respectively. Incremental cost per DALY averted for infections and cases were US$ 4889 and US$ 38 344, respectively.

The GDG judged the resources required for RDA to be large but dependent on the number of index cases.

Equity

No studies were identified that addressed the issue of whether RDA increased or decreased health equity.

The GDG was unable to determine a judgement on equity.

Acceptability

The systematic review identified six studies in four countries (Eswatini, Gambia, Namibia and Zambia) with information on acceptability (Steinhardt *et al* *unpublished evidence* *(c)*). Community acceptance of RDA was high (refusal rate of 2% or lower) in Namibia and Zambia. However, in Eswatini, the overall refusal rate was about 4%, with refusal rates of 1.4% (11/776) and 5.3% (65/1232) in seasons 1 and 2, respectively. In Namibia, participants expressed concern over having “to take medicine without feeling sick”. Similarly, participants in Gambia “generally considered it unnecessary to take medicine without having any symptoms”. Continued community sensitization has been recommended to mitigate these stigmas. In the systematic review, no studies reporting on the acceptability of RDA to health care workers or policymakers were found.

The GDG judged that RDA was probably acceptable to key stakeholders given the high rate of participation in RDA programmes.

Feasibility

Data on the feasibility of implementing RDA were summarized from five studies in four countries (Eswatini, Gambia, Namibia and Zambia) (Steinhardt *et al* *unpublished evidence* (c)). All countries used a three-day regimen of an ACT. RDA coverage, defined as the proportion of index cases followed up, varied between countries with a low of 62.4% in Eswatini to about 97% in Gambia.

RDA adherence data were abstracted from three studies in three countries (Eswatini, Gambia and Zambia). Full adherence, defined as taking all three doses of an ACT and verifying that no tablets remained in the blister pack, was above 90% in all the countries.

The feasibility of implementing RDA would also depend on whether radical cure of *P. vivax* using an 8-aminoquinoline medicine was part of the RDA strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

The GDG judged that RDA was likely feasible to implement.

Justification

While the GDG concluded that the balance of effects favoured neither RDA nor the comparison, the panel judged that the intervention would likely have been more effective if studies had compared RDA to no RDA rather than to RACDT. The GDG judged that RDA was probably an acceptable, feasible and potentially cost-effective strategy when numbers of cases are low enough to permit programmes to conduct case investigations, including in post-elimination settings working to prevent re-establishment of infection. The GDG concluded that a conditional recommendation for RDA as a component of an elimination programme should be issued.

Research Needs

- Further evidence is needed on the impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences of RDA.
- Evidence is needed on the acceptability, feasibility, impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences (death, hospital admission, severe anaemia or any severe adverse event) of safe provision (including testing for G6PD deficiency and, additionally, an effective pharmacovigilance system and emergency access to blood transfusion services) of an 8-aminoquinoline as part of RDA for radical cure of *P. vivax* infections.
- Investigate the optimal approach to delimiting the target area for implementation of RDA around an index case in order to maximize reductions in transmission of malaria.
- Determine the optimal time interval between index case detection and RDA to maximize reductions in transmission of malaria.
- Determine whether additional rounds of RDA should be repeated in the same residences or neighborhood to prevent subsequent generations of transmission.

6.3.2 Reactive case detection and treatment (RACDT)

RACDT is the parasitological testing of every person living with or near a person who has a confirmed malaria case, or every person who was likely exposed to infection at the same time and place as the index case, and treatment of those who are positive for malaria. RACDT is an active case detection strategy that may improve the timeliness and coverage of treatment. RACDT is generally conducted using point-of-contact malaria rapid diagnostic tests but has also been conducted using microscopy and nucleic acid-based tests. Only people found to be positive receive a full therapeutic course of an effective antimalarial medicine. As a result, the intervention does not provide a population-level prophylactic period as RDA does.

In an RACDT strategy, individuals are provided with antimalarials only if they are round to be infected. As a result, the proportion of the population that is protected from new infections over the duration of the post-treatment prophylaxis period is substantially lower than the population that would be protected in an RDA intervention. However, providing

antimalarial medicine only to those who are known to be infected may improve adherence to treatment, population acceptance of the intervention and equity while decreasing the risk of unintended consequences and depleting stocks of medicines.

Reactive interventions that are applied geographically should target the likely location of infection of the index case. The likely location of infection is determined through a case investigation, using the date of symptom onset and knowledge of the incubation period for the specific parasite species to determine the location of the person during the likely period of infection. If the likely location of infection is a residence, RACDT can be conducted at least in the household of the person with the confirmed case, but could also be extended to neighbours. The radius of the intervention should be determined based on an understanding of the epidemiology of malaria in the area. If the index infection was imported from elsewhere, RACDT should be conducted among individuals who may have the same exposure as the index case, such as co-travellers and co-workers.

As an active case detection strategy, RACDT is an essential component of the final phase of elimination as it improves the sensitivity of the surveillance system while maintaining specificity; RACDT accomplishes this by increasing testing in areas more likely to experience transmission of malaria. RACDT provides important information to countries close to elimination by identifying any additional cases around the index case that could suggest gaps in the surveillance system. Once countries have reached zero indigenous cases, RACDT provides additional evidence to the Malaria Elimination Certification Panel that the country has interrupted indigenous transmission.

Conditional recommendation for , Very low certainty evidence

Reactive case detection and treatment to reduce transmission of malaria (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, all people residing with or near a confirmed malaria case and all people who share the same risk of infection (e.g. co-travellers and co-workers) can be tested for malaria and treated if positive.

Until an area is nearing elimination or is post-elimination, it is unlikely that reactive case detection and treatment (RACDT) will have any effect on malaria transmission. However, RACDT becomes an essential component of surveillance when countries are nearing interruption of transmission to monitor progress towards elimination. When countries are post-elimination and working towards certification, RACDT can strengthen a country's claim that it has reached and maintained zero indigenous cases. RACDT is an essential part of surveillance and response to prevent re-establishment of malaria.

Practical Info

RACDT should be implemented when areas are nearing interruption of transmission and malaria cases are rare. When used, RACDT should be one of several components of a programme to eliminate or prevent re-establishment of malaria, including intensive surveillance as described in the *Framework for malaria elimination [10]*.

RACDT depends on a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a parasitological test and investigates all cases at their place of residence. RACDT complements this surveillance system through active case finding around index cases.

It is essential to determine the likely location of infection through a case investigation that identifies the location of the person during the likely period of infection in order to understand where or in what group of people an RACDT intervention should take place. RACDT should be administered to other residents of the same house if the person is determined to have been infected locally. Programmes may consider extending the radius of RACDT to neighbours depending on the local epidemiology and ecology of malaria. If a person was not likely to have been infected at the residence, programmes should administer RACDT to all people identified as having the same risk of acquiring infection as the index case. People with the same risk of infection are likely to be those who travelled, worked or engaged in leisure activities with the index case.

Countries that are at very low or low transmission but not yet close to achieving zero indigenous cases should prioritize implementation of RDA and reactive IRS over RACDT. However, RACDT may be added on top of RDA when countries are closer to elimination to strengthen the sensitivity of the surveillance system to monitor progress towards elimination and, post-elimination, to provide additional evidence of a malaria-free status. When RACDT and RDA are jointly implemented, chemoprevention is provided to everyone, irrespective of the results of the parasitological test. However, testing results are used to monitor progress towards elimination or demonstrate that the country has reached zero indigenous cases.

RACDT should be implemented according to SOPs. A household listing of all people residing within the limits of RDA as

specified by the SOPs should be developed and verified, along with a list of all individuals who may have been co-exposed. The RACDT programme should seek to test everyone listed, using different approaches as needed to reach everyone at risk.

Malaria cases detected during RACDT should be treated with antimalarial medicine according to the national treatment protocol if not already provided chemoprevention through RDA.

Evidence To Decision

Benefits and harms

The systematic review identified three cRCTs in three countries of sub-Saharan Africa (Eswatini, Namibia and Zambia) (Steinhardt *et al* *unpublished evidence* *(d)*). However, all three studies were intended to evaluate the impact of RDA, and RACDT was used as the comparator. The two NRSs identified from Brazil and Zambia reported on outcomes among those receiving the intervention, but did not evaluate impact at the community level. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- The evidence is very uncertain about the effect of RACDT on the prevalence of malaria (RD: 25 per 1000 persons; 95% CI [95% CI] -1 to 72 per 1000 persons; one cRCT; very low-certainty evidence).
- The evidence is very uncertain about the effect of RACDT on the incidence of clinical malaria (RD: 3 per 1000 p-y; 95% CI: -1 to 7 per 1000 p-y; three cRCTs; very low-certainty evidence).
- The evidence is very uncertain about the effect of RACDT on parasite prevalence among people who participate in RACDT (two NRSs; very low-certainty evidence).

Adverse events

Three cRCTs reported on adverse events. All trials used AL in the RACDT arms while DP was provided for the RDA arms.

- In Zambia, no events were reported from the RACDT arm compared to 123 (6.9%) adverse events reported from 1 775 persons administered DP in the RDA arm;
- In Namibia, 1 (1.0%) participant out of 96 reported an adverse event compared to 17 (0.4%) out of 4 247 in the RDA arm using DP;
- In Eswatini, no adverse events were reported from the RACDT arm while 68 (3.8%) of 1 776 participants reported adverse events in the RDA arm provided with DP.

Judgement of the panel

The GDG judged that the undesirable effects of RACDT were likely trivial. However, the GDG was unable to judge the benefit of RACDT as the cRCTs compared results with RDA rather than no intervention. The NRS studies provided results only for those who received the intervention, and as a result, could not provide evidence for the impact of RACDT on transmission. As a result, the GDG concluded that they could not judge whether the balance of effects favoured RACDT or not.

Certainty of the Evidence

Very low

The overall certainty of the evidence was judged to be very low.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies

Resources

The systematic review identified four studies with information on the costs of RACDT (Steinhardt *et al* *unpublished evidence (d)*). The average cost of RACDT varied across different regions – from US$ 5.21 in Thailand to US$ 27.60 in Indonesia. In Senegal, the cost per person screened by RACDT was US$ 14.00. Costing models developed based on the experience of implementing partners, operational documents and costing studies from Ethiopia, Senegal and Zambia found that the average annual financial cost per capita (total population of 360 000 based on one region, three districts, 20 health facility catchment areas [HFCAs] each, and 6000 population per HFCA) were US$ 1.07 for the first year of RACDT, and US$ 0.65 per year for the subsequent five years (2014 US$) and the per capita economic cost was US$ 1.27 in first year of RACDT, and US$ 0.75 per year for the subsequent five years (2014 US$).

Total costs for RACDT varied between study areas ranging from US$ 3469 in Indonesia to US$ 10 486 in Thailand for total personnel and US$ 257 (Indonesia) to US$13 969 (Thailand) for commodities, services and other costs. The variations in personnel, commodity, service and other costs specific to case investigation and RACDT activities are likely due to differences in programme structure and the level of integration of malaria-related activities into the broader healthcare system.

In Zambia, the mean annual cost of RACDT per HFCA was US$ 1177 (median = US$ 923, IQR US$ 651–1417). The variation in costs was driven by the number of community health workers and index cases detected. Costs related to community health workers and data review meetings accounted for the largest share of total costs. Rapid diagnostic tests and medicines accounted for less than 10% of total costs.

Cost models based on studies from Ethiopia, Senegal, and Zambia showed that targeted search radius and per diems paid to community health workers dominated intervention parameters. In Indonesia, at 0.4% prevalence of infection, the cost per infection detected was US$ 7070, which declined to US$ 1767 when the prevalence was 1.6%. Cost declines began to plateau thereafter.

The GDG judged the resources required for RACDT to be moderate, depending on the number of index cases.

Equity

No studies were identified that addressed the issue of whether RACDT increased or decreased health equity.

The GDG was unable to determine a judgement on equity.

Acceptability

The systematic review identified community acceptability data from three studies conducted in Namibia, Senegal and Zambia (Steinhardt *et al* *unpublished evidence (d)*). Community acceptance of RACDT was high (refusal rate 2% or lower). In Namibia, some “hesitation/resistance” during pre-trial was reported but community engagement and sensitization appear to have helped participation. Similarly, in Senegal, the high RACDT participation has been attributed to advanced cascade sensitization, making follow-up appointments to follow up absent members, and conducting return visits to the compound on the same or next day. Lack of community confidence in community health workers’ ability to address diseases other than malaria and community unwillingness to visit community health workers for malaria testing were reported in Zambia.

There were no studies reporting data directly on health care workers’ acceptance of RACDT. Related information was abstracted from two studies. In Zambia, community health workers reported lack of motivation to conduct RACDT, which was in part linked to community health workers feeling their community service went unrecognized. The lack of stipend or financial support was the biggest problem noted by community health workers, who were volunteers.

The GDG judged that RACDT was probably acceptable to key stakeholders.

Feasibility

The systematic review identified feasibility and health systems considerations data from 17 studies, of which seven were from sub-Saharan Africa and eight from the Asia-Pacific region (Steinhardt *et al* *unpublished evidence (d)*). The proportion

of households reached by RACDT varied across different geographical locations – from 49% of index case households investigated in Zanzibar to 100% in Jiangsu, China. Similarly, the proportion of households reached in a timely manner also varied across different locations – from about 20% in Zanzibar to 100% in China. Barriers and challenges to RACDT implementation were identified along all three steps of RACDT.

First, index case detection and notification from private health facilities was low and these cases were largely reported to be missed by RACDT in Cambodia and Zanzibar. Collaborating and engaging the private sector in malaria surveillance systems has been identified as critical, particularly in areas where many patients resort to private providers, facilities including drug shops, and pharmacies. Within the public health sector, delayed presentation of malaria patients to health facilities, poor preparation of village clinics to participate in surveillance programmes, and the lack of adequate human resources and malaria rapid diagnostic tests haves been reported as barriers and challenges to effective implementation of RACDT. Second, the complexity of case investigation procedures and lack of standard operating procedures have been identified as barriers to effective case investigation. Difficulty with case classification (imported vs. local) due to incomplete travel histories has also been reported. During peak malaria transmission seasons, the proportions of case investigations conducted were lower than in other times mainly because community health workers were overwhelmed by patient volumes and there were insufficient numbers of malaria rapid diagnostic tests. To overcome these barriers, authors from a study in Zambia suggested that the programme would benefit from additional community health workers or the suspension of RACDT during the high-transmission season. Third, difficulty accessing mountainous terrains, flooded areas, and border areas with highly mobile populations were reported as barriers to timely follow up during the RACDT intervention. To overcome the barriers posed by flooding during the rainy season, study authors from Zambia recommended that community health workers, particularly those serving flood-prone areas, be provided with rain gear and access to boats.

Another barrier to effective implementation of RACDT was identified as the large numbers of households to screen, particularly in high-density areas of the Asia-Pacific region. Incomplete case investigation forms also limited follow-up and the lack of household-level listings of all individuals in the RACDT area meant that those conducting RACDT did not always know which households to include in the RACDT. Imported cases posed a major challenge for RACDT interventions. District-level responses alone were unlikely to be effective in interrupting transmission when most malaria cases were imported from outside the district. Communication and surveillance linkages with other operational districts and their malaria response teams were considered necessary. In the case of Bhutan, RACDT buffer zones sometimes extended beyond international borders, limiting implementation of adequate RACDT activities. Strengthened cross-border collaborations are needed to ensure adequate coverage of households across borders, as well as migrant and mobile populations. Other barriers to conducting effective RACDT were stockouts of malaria rapid diagnostic tests, which prevented testing around index cases, the limit of detection of most rapid diagnostic tests, and the inability of *P. falciparum*-only rapid diagnostic tests to detect other species and low-density infections. In Botswana, malaria microscopy was used as the gold standard for malaria diagnosis, so all RDT-positive malaria cases were re-examined by microscopy; however, it was challenging to ensure a high quality of malaria microscopy slides prepared by health centre staff in these settings. A lack of health care workers to conduct malaria activities and lack of surveillance officers at the district level were reported to result in inadequate supervision, case investigation and follow-up. Lack of motivation among health care workers to pursue case investigation and contact testing, particularly on weekends and public holidays, was also reported. Maintaining workforce motivation and providing consistent support, supervision and incentives were recommended to overcome these challenges.

The feasibility of implementing RACDT would also depend on whether radical cure of *P. vivax* using an 8-aminoquinoline medicine was part of the RACDT strategy, which would necessitate testing for G6PD deficiency, an effective pharmacovigilance system and emergency access to blood transfusion services.

The GDG judged that RACDT was likely feasible to implement.

Justification

Although the GDG was not presented with any relevant evidence for the benefit of RACDT in reducing transmission of malaria, RACDT is considered an essential surveillance strategy for countries nearing elimination in order to ensure that there are no cases remaining around or associated with a confirmed case. The GDG concluded that a conditional recommendation for RACDT as a component of the end-stage of an elimination programme should be issued.

Research Needs

No research needs were identified by the GDG.

6.3.3 Reactive indoor residual spraying

Indoor residual spraying (IRS) is the application of a residual insecticide to the interior surfaces of dwellings (i.e. walls, ceilings, windows and doors) to kill resting mosquitoes and reduce malaria transmission. IRS is generally conducted campaign-style across a large geographical area or a higher-risk area prior to the start of a malaria transmission season (i.e. proactive spraying). By contrast, reactive IRS is the use of IRS in the houses of a confirmed case and neighbours at approximately the same time.

Reactive IRS should be implemented in the likely location of infection of the index case. The likely location of infection is determined through a case investigation by using the date of symptom onset and knowledge of the incubation period for the specific parasite species in order to determine the location of the person during the likely period of infection. If the likely location of infection was a residence, reactive IRS should be deployed to the dwelling of the confirmed case and extended to neighbouring houses. If the index infection was imported, reactive IRS at the residence of the index case may still have some effect on reducing onward transmission. The size of the radius of implementation of reactive IRS should be determined by the behaviours and likely flight range of local vector mosquitoes.

Conditional recommendation for , Moderate certainty evidence

Reactive indoor residual spraying (2022)

In areas approaching elimination or post-elimination settings preventing re-establishment of transmission, indoor residual spraying of insecticide can be conducted in in the houses of confirmed cases and neighbours to prevent or reduce transmission of malaria.

- *In areas approaching elimination or post-elimination settings where proactive indoor residual spraying (IRS) is occurring, programmes can consider switching to reactive IRS only, depending on the receptivity of the area.*
- *Programmes considering adding reactive IRS on top of proactive IRS should balance the potential added benefit with increasing cost and the risk of insecticide resistance.*
- *In areas approaching elimination or post-elimination settings where no IRS is occurring, initiating reactive IRS may be beneficial, depending on whether IRS is a suitable vector control strategy. IRS is most effective where the vector population is susceptible to the insecticide(s) being applied, the majority of mosquitoes feed and rest indoors and where most structures are suitable for spraying.*
- *If the index infection was imported and the residence is not located in a receptive area, there may be no benefit from reactive IRS.*

Practical Info

Please refer to the Practical Info section for IRS (4.1.1) for more information on operational issues related to IRS.

When used, reactive IRS should be one among several components of a programme to eliminate or prevent re-establishment of malaria, including intensive surveillance as described in the *Framework for malaria elimination [10]*.

Reactive IRS depends on a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a parasitological test and investigates all cases at their place of residence. If these elements are not in place, it is unlikely that an reactive IRS intervention can be effectively implemented.

It is essential to determine the likely location of infection through a case investigation that identifies the location of the person during the likely period of infection in order to understand where the reactive IRS intervention should take place. Reactive IRS should be applied to the residence if the person is determined to have been infected locally. Programmes should extend RIRS to neighbours, with the radius of implementation depending on the local epidemiology and ecology of malaria. If the index infection is not likely to have been acquired at the residence, reactive IRS might still reduce the chances of onward transmission. However, if the infection was classified as imported and the household is not located in a receptive area, there may be no benefit to reactive IRS.

In very low to low transmission settings where standard IRS is occurring (proactive spraying), there may be advantages to programmes from switching to reactive IRS. Decisions to switch from standard IRS to reactive IRS should be based on assessments that include:

- the potential risk of increasing malaria transmission by scaling back proactive IRS;

- the potential cost savings;
- the potential for increased acceptance and equity; and
- the potential for reducing insecticide resistance.

In settings where no standard IRS is occurring, reactive IRS may be beneficial, depending on the factors listed below.

- The programme has the capacity to conduct case investigations at the residences of cases to determine whether the case is imported or local.
- The capacity of the vector control programme to respond quickly to conduct reactive IRS after identification of a confirmed case.
- The population living in the houses where RIRS is applied are at risk of infection.
- The majority of the vector population feeds and rests indoors.
- The vectors are susceptible to the insecticide that is being deployed.
- People mainly sleep indoors at night.
- The majority of structures are suitable for spraying.

Programmes considering adding reactive IRS on top of proactive IRS should balance the potential added benefit with the risk of insecticide resistance and increased cost, and develop protocols that take into account the time since the dwelling was last sprayed. Reactive IRS depends upon a strong passive surveillance system that detects suspected cases, tests all suspected cases for malaria with a parasitological test and investigates all cases at the residence. If these elements are not in place, it is unlikely that an reactive IRS intervention will have an impact on malaria transmission.

Evidence To Decision

Benefits and harms

The systematic review identified two cRCTs in Namibia and South Africa (Gimnig *et al* *unpublished evidence*). The study from Namibia (superiority trial design) was conducted as a 2x2 factorial design with RACDT alone, RDA alone, RACDT plus reactive IRS, and RDA plus reactive IRS. The study from South Africa was designed as a non-inferiority trial comparing reactive IRS to proactive IRS (used in defined priority areas) that reached one third of houses. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- Reactive IRS reduces the prevalence of malaria (RD: -27 per 1000 persons; 95% CI: -35 to -8 per 1000 persons; one cRCT [superiority design]; high-certainty evidence).
- Reactive IRS may have little to no effect on the incidence of clinical malaria. (RD: -14 per 1000 p-y; 95% CI: -32 to 4 per 1000 p-y; one cRCT [superiority design]; moderate-certainty evidence).
- Reactive IRS probably results in little to no difference in incidence of clinical malaria compared with proactive IRS (mean difference: 0.1 per 1000 p-y; 95% CI: -0.38 to 0.59 per 1000 p-y; one cRCT [non-inferiority design]; moderate-certainty evidence).

Adverse events

- Reactive IRS results in little to no difference in reported adverse events (RD: 2 per 1000 persons; 95% CI: -2 to 1 per 1000 persons; one cRCT [superiority design]; high-certainty evidence).
- Reactive IRS results in little to no difference in serious adverse events (deaths) compared with proactive IRS (one cRCT [non-inferiority design]; high-certainty evidence).

Judgement of the panel

The GDG judged the benefits of reactive IRS to be moderate, undesirable effects to be trivial and the overall certainty of evidence to be moderate. The GDG noted that studies were only available from southern Africa. The variability of mosquito and human ecology may influence the effectiveness of the strategy where vectors differ from those in the trial areas. Additionally, the different designs (superiority vs. non-inferiority) and different comparators (no reactive IRS or proactive IRS) complicated the GDG's judgement. However, the GDG judged that the balance of effects probably favoured reactive IRS.

Certainty of the Evidence

Moderate

The overall certainty of the evidence was judged to be moderate.

Values and preferences

No studies were identified regarding preferences and values.

The GDG judged that there may be important uncertainty or variability in preferences or values that could not be determined due to the lack of studies.

Resources

The systematic review identified one study from South Africa with data on cost and cost-effectiveness of reactive IRS compared to proactive IRS (non-inferiority trial) (Gimnig *et al* *unpublished evidence*). Over the two-year study, the average annual economic cost was US$ 184 319 per 100 000 population in the proactive IRS arm compared to US$ 88 258 per 100 000 population in the reactive IRS arm, a 52% cost savings. Using the cost per DALY, the incremental cost-effectiveness ratios were estimated overall and for each year of the study. It was estimated that per additional DALY averted, reactive IRS saved US$ 7845 (95% CI: US$ 2902–64 907) over proactive IRS. During year 1, when the incidence of malaria was low, the savings per additional DALY averted in the RIRS arm was estimated at US$ 35 149. The lower bound of the 95% CI was US$ 6481, while at the higher bound, RIRS was both less expensive and more effective. In year 2, when incidence was higher, the savings per additional DALY averted in the reactive IRS arm was US$ 3869 (95% CI: US$ 1371–50 689). The cost-effectiveness thresholds were set at US$ 2637 (43% of GDP per capita) and US$ 3557 (58% of GDP per capita). At the incidence observed during the trial, reactive IRS would have a 94–98% probability of being the cost-effective choice at either threshold. It was estimated that reactive IRS would remain the preferred strategy up to an incidence of 2.0–2.7 cases per 1000 person-years using the higher and lower cost-effectiveness thresholds.

The GDG judged that the resources required for reactive IRS are likely to vary depending on whether the programme is moving from proactive IRS to reactive IRS or starting an RIRS programme from scratch. The resource requirements are also likely to vary depending on the number of index cases. However, the GDG judged that cost-effectiveness probably favours reactive IRS.

Equity

No studies were identified that addressed the issue of whether reactive IRS increased or decreased health equity.

Because reactive IRS focuses resources where they are needed, the GDG judged that reactive IRS probably increased health equity.

Acceptability

The systematic review identified one study from Namibia with information on the acceptability of reactive IRS (Gimnig *et al* *unpublished evidence*). Refusals of households to participate in reactive IRS were due to lack of notification before arrival and reluctance to move furniture at short notice. In year two of the study, advance notification was provided to households and < 1% refused reactive IRS. Community participants generally considered reactive IRS to be a useful tool for malaria prevention, and participants in the study arms that did and did not receive reactive IRS indicated a desire to have their houses sprayed. Participants specifically referenced IRS's effectiveness, noting reductions in both flies and mosquitoes. In the endline survey, 616 of 624 respondent (98.7%) from the reactive IRS arm indicated that they would participate in the same intervention again.

The GDG noted that reactive IRS would likely be more accepted by households than proactive IRS because residents would know that a malaria case had been detected in or near their home. The GDG judged that reactive IRS was probably acceptable to key stakeholders.

Feasibility

The systematic review identified two case studies from China that reported on their implementation of reactive IRS (Gimnig *et al unpublished evidence*).

The GDG judged that reactive IRS was likely feasible to implement.

Justification

Proactive IRS applied campaign-style across a geographical area has long been a staple of malaria vector control and is currently recommended by WHO for large-scale deployment in areas of ongoing transmission. Reactive IRS uses the same intervention (application of a residual insecticide to the interior surfaces of a dwelling) as does proactive IRS; however, reactive IRS is triggered by a single case of malaria and applied in a limited geographical area around the likely location of infection of the index case. When transmission is low and cases are clustered, the GDG noted that RIRS might be more cost-effective than proactive IRS as the area at risk of transmission is more limited. However, the benefits gained by introducing RIRS are likely to depend on whether the programme already has a proactive IRS programme or not; whether the programme intends to scale back proactive IRS to reactive IRS or add reactive IRS on top of proactive IRS; and the characteristics of the vector and human populations. As a result, the GDG provided a conditional recommendation for reactive IRS.

Research Needs

- Further evidence is needed on the impact (prevalence and incidence of malaria infection at the community level) and potential harms/unintended consequences of reactive IRS.
- Determine the impact (prevalence and incidence of malaria infection at the community level) of reactive IRS in areas with different mosquito behaviours.
- Determine the impact (prevalence and incidence of malaria infection at the community level) of reactive IRS in areas where *P. vivax* is transmitted.
- Investigate the optimal approach to delimiting the target area for implementation of reactive IRS around an index case.
- Determine the optimal time interval between case detection and reactive IRS.
- Determine whether additional rounds of reactive IRS should be repeated in the same households to prevent subsequent generations of transmission.
- Determine the benefit and acceptability of switching from IRS to reactive IRS or adding reactive IRS on top of proactive IRS.

7. SURVEILLANCE

Surveillance is “the continuous and systematic collection, analysis and interpretation of disease-specific data, and the use of that data in the planning, implementation and evaluation of public health practice” *[251]*.

Pillar 3 of the *Global technical strategy for malaria 2016–2030 [5]* is to transform malaria surveillance into a key intervention in all malaria-endemic countries and in those countries that have eliminated malaria but remain susceptible to re-establishment of transmission.

Although surveillance guidance is not evaluated using the GRADE framework, surveillance forms is the basis of operational activities in settings at any level of transmission and is therefore included in these Guidelines for reference. The objective of surveillance is to support reduction of the burden of malaria, eliminate the disease and prevent its re-establishment. In settings where transmission remains relatively high and the aim of national programmes is to reduce the burden of morbidity and mortality, malaria surveillance is often integrated into broader routine health information systems to provide data for overall analysis of trends, stratification and planning of resource allocation. In settings where malaria is being eliminated, the objectives of surveillance are to identify, investigate and eliminate foci of continuing transmission, prevent and cure infections, and confirm elimination. After elimination has been achieved, the role of surveillance becomes that of preventing re-establishment of malaria.

A malaria surveillance system comprises the people, procedures, tools and structures necessary to generate information on malaria cases and deaths. The information is used for planning, implementing, monitoring and evaluating malaria programmes. An effective malaria surveillance system enables programme managers to:

- identify and target areas and population groups most severely affected by malaria, to deliver the necessary interventions effectively and to advocate for resources;
- regularly assess the impact of intervention measures and progress in reducing the disease burden and help countries to decide whether adjustments or combinations of interventions are required to further reduce transmission;

- detect and respond to epidemics in a timely way;
- provide relevant information for certification of elimination; and
- monitor whether the re-establishment of transmission has occurred and, if so, guide the response.

Please refer to the WHO *Malaria surveillance, monitoring & evaluation: a reference manual [30]*.

Subnational stratification

WHO has made guidance available on the strategic use of data to inform subnational stratification (see chapter 2 of *WHO technical brief for countries preparing malaria funding requests for the Global Fund (2020-2022)*) *[252]*. This guidance was developed in recognition of the increasing heterogeneity of malaria risk within countries as malaria control improves and the need to use problem-solving approaches to identify appropriate, context-specific packages of interventions to target different sub-populations. For example, case management should be accessible wherever there is a possibility of malaria cases seeking treatment. How case management is delivered will vary according to factors such as health-seeking behaviour, the accessibility and functioning of the public health infrastructure, availability of the private retail sector and the potential for community services. Local data are essential to complete the malaria stratification and select the optimal mixes of interventions. The guidance explains how to undertake a comprehensive multi-indicator stratification process to define sub-national intervention mixes that are optimized to achieve strategic goals. As countries will rarely have all the resources they need to fully implement their ideal plan, a careful resource prioritization process is then required to maximize the impact of available resources. Prioritization should be based on the expected impact of interventions and consider value for money across the whole country, driven by local evidence.

8. METHODS

The consolidated *WHO Guidelines for malaria* were prepared in accordance with WHO standards and methods for guideline development and originally published as the *Guidelines for the treatment of malaria* (3rd edition, 2015) and the *Guidelines for malaria vector control* (1st edition, 2019). Details of the approach can be found in the WHO *Handbook for guideline development [1]*. Here we provide an overview of the standards, methods, processes and platforms applied by the Global Malaria Programme across the topics covered in this guideline *[103][253][254]* and a description of the joint process (with WHO Immunization, Vaccination and Biologicals department) used to develop the malaria vaccine recommendation.

Organization and process

The WHO guideline development process involved planning; conducting a "scoping" and needs assessment; establishing an internal WHO Guidelines Steering Groups and external Guidelines Development Groups (GDGs); formulating key recommendation questions using the PICO (Population, Intervention, Comparison, Outcome) format; commissioning evidence reviews or where a recent review was already available, commissioning an independent assessment of the review using the AMSTAR checklist *[114]*; applying GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to assess the certainty of evidence; and using evidence-to-decision (EtD) frameworks to take the GRADE results and contextual factors into account in developing recommendations. This methodology ensures that the link between the evidence base and the recommendations is transparent. The Guidelines have been consolidated and will be continuously updated in the online MAGICapp publication platform (www.magicapp.org) as new evidence becomes available and published in user-friendly formats available on all electronic devices.

Technical leads in the Global Malaria Programme established Guidelines Steering Groups for each technical area to support drafting the scope of the Guidelines and preparing the planning proposal, including formulating key questions, as well as suggesting potential members for the GDGs. Technical leads then obtained declarations of interest from GDG members, assessed these and oversaw the management of any potential conflicts of interest, as well as the finalization and submission of a planning proposal to the Guidelines Review Committee (GRC) for review and approval.

The GDGs - external bodies of experts and stakeholders - were responsible for the development of the evidence-based recommendations contained in the Guidelines. As well as providing expert opinion, the specific tasks of the GDGs included:

- providing inputs on the scope of the Guidelines;
- building on the work of the Guidelines Steering Groups to finalize the key recommendation questions in PICO format;
- choosing and ranking priority outcomes to guide the evidence reviews and focus the recommendations;
- reviewing eligibility criteria for the inclusion of studies in the evidence reviews;
- providing input on appropriate measures of outcomes of interest to be included in the evidence reviews;
- validating the list of included and excluded studies;
- reviewing the meta-analyses, GRADE evidence profiles or other assessments of the certainty of evidence used to inform the recommendations;
- interpreting the evidence, considering different factors included in the EtD framework and judging how these factors may impact the direction and strength of a recommendation, particularly in terms of the overall balance of benefits and harms;
- formulating recommendations, taking into account benefits, harms, values and preferences, feasibility, equity, acceptability, resource requirements, cost and cost-effectiveness and other factors, as appropriate;
- identifying methodological shortcomings and evidence gaps in the available body of evidence, and providing guidance on

how to address these as part of future research;
- reviewing and approving the final recommendations prior to submission to the GRC; and
- contributing to the dissemination of the final recommendations.

Different GDGs were used to develop the *WHO Guidelines for malaria* (see Section 10: Contributors and interests), each with experts in that particular field. The composition of each GDG was balanced according to geographical representation and gender. Potential interests we identified and managed appropriately within the Global Malaria Programme (see section below). Membership included the following categories of stakeholders:

- relevant technical experts (e.g. clinicians with relevant expertise; epidemiologists; entomologists)
- intended end-users (programme managers and health professionals responsible for adopting, adapting and implementing the Guidelines)
- patients and/or other representatives from malaria-endemic countries.

In selecting the chair of each GDG, each Steering Group ensured that the individual had content expertise, had no conflicts of interest and was able to approach the recommendations with an open mind, i.e. having no preconceptions about the final recommendations. Chairs of the GDGs and/or members were sensitized to ensure that equity, human rights, gender and social determinants were taken into consideration in efforts to improve public health outcomes.

External Review Groups (ERGs) (see Section 10: Contributors and interests) were identified by the respective Steering Group for each technical area for malaria. Each ERG was composed of people interested in the subject of the Guidelines and included members of the Malaria Policy Advisory Group (MPAG; formerly the Malaria Policy Advisory Committee [MPAC]) and individuals affected by or interested in the recommendations, such as technical experts, end-users, programme managers, implementing partners, advocacy groups and funders. The ERGs reviewed the draft Guidelines prior to their submission to the GRC for approval. The role of each group was to identify any errors or missing evidence and to provide comment on clarity, context-specific issues, and implications for implementation. The groups were not expected to change the recommendations formulated by the GDGs. In cases where external reviewers raised major concerns related to the recommendations, these were taken back to the GDG for discussion. Comments from external reviewers were incorporated into the revised Guidelines as appropriate. The final drafts were circulated to the GDGs.

Guideline methodologists
Experts in guideline development processes complemented the technical expertise of the GDG members. Different methodologists supported the development of recommendations and guidance for each technical area. Methodologists were identified by the Steering Groups based on their experience, ensuring they had expertise in the prioritization of questions and outcomes, evidence synthesis, GRADEing of evidence, translation of evidence into recommendations, and guideline development processes. The methodologists supported the planning, scoping and development of key questions and assisted the GDG in formulating evidence-informed recommendations in a transparent and explicit manner. The methodologists served as the methodological co-chairs of some GDG meetings.

Evidence synthesis methods
Following the initial GDG meeting, existing systematic reviews already published were identified or new systematic reviews were commissioned to systematically assess the certainty of the evidence for each priority question across the guideline topics. Where there was an existing published review, the review was assessed independently using the AMSTAR-2 checklist *[114]*.

The reviews involved extensive searches for published and unpublished trials using highly sensitive searches of established registers such as the Cochrane Infectious Diseases Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE®, Embase and LILACS. Types of outcome measures for consideration in the evidence reviews included: rate of all-cause child mortality; rate of severe malaria episodes; rate of clinical malaria; rate of uncomplicated episodes of *P. falciparum* illness; parasite prevalence (also specifically *P. falciparum* and *P. vivax* prevalence); anaemia prevalence; and, in the case of vector control interventions, entomological inoculation rate (EIR); mosquito mortality and blood-feeding success; density of immature vector stages; and number of larval sites positive for immature vector stages. Harms and undesirable outcomes such as adverse events, development of antimalarial drug resistance, reduced use of other malaria interventions or changes in mosquito behaviour were also assessed, where appropriate, to permit determination of the balance of benefits and harms. Epidemiological outcomes, namely, demonstration that an intervention has proven protective efficacy to reduce, prevent or eliminate infection and/or disease in humans, were prioritized over entomological outcomes, given that the correlation between the effect of interventions on entomological outcomes and the effect of interventions on public health outcomes has not been well established. Depending on the question posed, outcomes were measured at the individual and/or community level. The specific search methods, inclusion criteria, data collection and analysis plans for each evidence review were detailed in the published review protocols. Systematic review teams were encouraged to publish their protocols in an online register of systematic reviews and to write their final reports using the 2020 PRISMA reporting guidelines.

When limited evidence was available from randomized trials, some systematic reviews included non-randomized studies such as quasi-experimental designs, including controlled before-and-after studies, interrupted time series (controlled and uncontrolled), and stepped wedge designs. As per WHO guidelines, the GDGs also considered systematically collected evidence on contextual factors to develop the EtD frameworks. The GDGs used GRADEPro software and/or the MAGICapp platform, and the interactive EtD framework to assist in the process of evidence review and recommendation-setting.

The EtD framework considered several criteria to arrive at a

recommendation for or against an intervention; these were *[103]*:

1. How substantial are the desirable anticipated effects?
2. How substantial are the undesirable anticipated effects?
3. What is the overall certainty of the evidence of effects?
4. Is there important uncertainty about or variability in how much people value the main outcomes?
5. How large are the resource requirements (costs)?
6. Does the cost-effectiveness of the intervention favour the intervention or the comparison?
7. What would be the impact on health equity?
8. Is the intervention acceptable to key stakeholders?
9. Is the intervention feasible to implement?

While criteria 1-3 relate to the health effects of recommendations, criteria 4-9 relate to contextual factors. In some cases, the GDG opted to omit factors or add factors as deemed relevant. Recommendations formulated before 2021 may not have included assessment of all factors. In MAGICapp, the EtD framework summaries for each of the recommendations contained in the *WHO Guidelines for malaria* are presented in a tab below the recommendation alongside the GRADE tables in the evidence profile tab.

Subgroup and sensitivity analysis
Where the data was available, several potential effect modifiers were assessed through subgroup analyses. These included:

- Insecticides used for both active ingredients and manufacturer
- Malaria vector species
- Setting (Urbanicity, classed as rural/ urban/ peri-urban)

Subgroups were assessed on their credibility of being a genuine effect modifier using the Instrument for assessing the Credibility of Effect Modification (ICEMAN)*[255]*. This is a tool that reviewers can use based on answering a series of questions that address specific criteria that can be used to evaluate whether an effect modification is likely. ICEMAN credibility assessment statements are expressed as very low (very likely no effect modification), low (likely no effect modification), moderate (likely effect modification), and high (very likely effect modification).

Certainty of evidence
The certainty of evidence in the systematic reviews was rated for each outcome using a four-level categorization (Table 1). The certainty of evidence considered the study design, factors that would lead to rating down the certainty (the risk of bias, inconsistency, indirectness, imprecision of the effect estimates, and publication bias) as well as factors that would lead to rating up the certainty (large effect size and dose-response effect). The terms used in the certainty assessments refer to the level of certainty in the estimate of effect relative to the recommendation question, and not necessarily to the scientific quality of the investigations reviewed. Informative statements of results for each outcome were aligned to the certainty of evidence based on standard GRADE methodology *[256]*.

Table 1. The four categories of certainty of evidence used in GRADE

Certainty of evidence	Interpretation
High	The Group is very confident in the estimate of effect and considers that further research is very unlikely to change this confidence.
Moderate	The Group has moderate confidence in the estimate of effect and considers that further research is likely to have an important impact on that confidence and may change the estimate.
Low	The Group has low confidence in the estimate of effect and considers that further research is very likely to have an important impact on that confidence and is likely to change the estimate.
Very Low	The Group is very uncertain about the estimate of effect.

Formulation of recommendations
The systematic reviews, GRADE tables and other relevant materials were provided to all members of the GDG prior to meeting to discuss particular key questions. Recommendations were formulated after considering the criteria included in the EtD framework listed above. Values and preferences, acceptability, feasibility and resource needs were important considerations. Given that these contextual factors are important in setting national policies and are broadly considered in the recommendation formulation process, efforts were made to collect information about these factors in preparation for the GDG meeting. This was achieved through systematic reviews of the literature, survey of stakeholders, or directly from the GDG. Expanded evidence-based recommendations on resource implications for malaria interventions, deployed alone or in combination, are a focus of ongoing work and guidance and will be developed where possible and incorporated into the Guidelines.

After reviewing and judging the different criteria, the GDG discussed and reached a consensus on the final recommendation at in-person or online meetings, or through e-mail correspondence. Typically, the GDG was presented with a 'neutral' recommendation and decided on its direction and strength. The guideline development process aimed to generate group consensus through open and transparent discussion. In most cases, anonymous voting was used to judge the different criteria and develop the final recommendation in order to reduce peer pressure. Voting was used as a starting point to build consensus or to reach a final decision when no consensus was reached.

Types of guidance
Two types of guidance are presented in the Guidelines:.

- GRADEd recommendations: These recommendations were formulated by the GDG using the GRADE approach described above, supported by systematic reviews of the evidence, with formal assessment of the certainty of evidence.
- Good practice statements: These statements reflect a consensus within the GDG that the net benefits of adhering

to the statement are large and unequivocal, and that the implications of the statement are common sense. These statements were not usually supported by a systematic review of evidence. In some cases, good practice statements were taken or adapted from existing recommendations or guidance initially developed through broad consultation, such as through the WHO Vector Control Technical Expert Group (VCTEG) or MPAG. These statements are made to reinforce the basic principles of good management practice for implementation.

Strength of recommendations

Each intervention recommendation was classified as strong or conditional, for or against an intervention, according to the GRADE system *[254]*. A strong recommendation is one for which the GDG was confident that the desirable effects of adhering to the recommendation outweighed the undesirable effects. A conditional recommendation is one for which the GDG concluded that the desirable effects of adhering to the recommendation probably outweighed the undesirable effects, but the GDG was not confident about these trade-offs. In addition to considering certainty of evidence regarding the benefits and harms and their relative effect, the strength of the recommendation was influenced by the contextual factors considered in the EtD framework. The reasons that favoured making a conditional recommendation included lower certainty evidence; smaller effect sizes and/or a tight balance between benefits and harms; variability or uncertainty in the values and preferences of individuals regarding the outcomes of interventions; high costs; equity-related concerns; feasibility issues; and acceptability issues. The implications of strong and conditional recommendations for various groups are given in Tables 2a and 2b.

Table 2a. Interpretations of recommendations

Strength of recommendation	Interpretation	
	For Policy-makers and Programme Managers	For End-users
Strong for	This recommendation can be adopted as policy in most situations.	Most people in this situation would want the recommended intervention, and only a small proportion would not.
Conditional for	The recommended intervention can be adopted as a policy after relevant stakeholders judge its positive consequences to outweigh its negative ones based on a careful assessment of the contextual factors.	The majority of people in this situation would want the recommended intervention, but many would not.

Table 2b. Interpretations of recommendations against an intervention

Strength of recommendation	Interpretation	
	For Policy-makers and Programme Managers	For End-users
Strong against	This recommendation should not be adopted as policy in most situations.	Most people in this situation would not want the intervention, and only a small proportion would.
Conditional against	The recommended intervention should not be adopted as a policy unless relevant stakeholders judge its positive consequences to outweigh its negative ones based on a careful assessment of the contextual factors.	The majority of people in this situation would not want the intervention, but many would.

Presentation of evidence and recommendations

For clarity, the recommendations are presented in individual boxes on the MAGICapp platform, colour-coded and labelled by strength and certainty of evidence based on the evidence reviewed. Strong recommendations for are green, conditional recommendations for are yellow, conditional recommendations against are orange, strong recommendations against are red, and best practice statements are blue. More information on how to interpret the strength of a recommendation can be obtained by clicking on the label in the online platform. By expanding the tabs directly below the recommendation, further detail can be obtained on the research evidence; the EtD framework; the justification including judgements by the GDG; practical information, including dosing and contextual factors; and related references. Details about the evidence can be found by clicking on the outcomes included in the evidence (e.g. the “Summary of findings” tables show the estimates of effects and relevant literature).

Management of conflicts of interest

All members of the GDGs were requested to make declarations of interest, which were managed in accordance with WHO

procedures and summarized at the beginning of each meeting to all participants. Where necessary, GDG members were excluded from the discussion and/or decision-making on topics for which they had declared interests. The members of the GDGs and a summary of their declarations of interest are listed in Section 10: Contributors and Interests.

Link to WHO prequalification

When a recommendation is linked to the introduction of a new tool or product, there is a parallel process managed by the WHO Prequalification Team to ensure that diagnostics, medicines, vaccines and vector control products meet global standards of quality, safety and efficacy, in order to optimize use of health resources and improve health outcomes. The prequalification process consists of a transparent, scientifically sound assessment that, includes dossier review, consistency testing or performance evaluation, and site visits to manufacturers. This information, in conjunction with other procurement criteria, is used by United Nations and other procurement agencies to make purchasing decisions regarding these health products. This parallel process aims to ensure that recommendations are linked to prequalified products and that prequalified products are linked to a recommendation for their use.

Joint process for developing the malaria vaccine recommendation

In order to enable joint decision-making on a malaria vaccine, the different guideline development processes of the Global Malaria Programme and the WHO Department for Immunization, Vaccines and Biologicals (IVB) were harmonized following discussion with the WHO Department of Quality, Norms and Standards. The standard process for the development of WHO vaccine recommendations was used as the basis for developing the malaria vaccine recommendation. The process employed by the Strategic Group of Experts (SAGE) on Immunization, described here, complies with the principles and requirements of the standard GRC process which is described above and used for the development of the *WHO Guidelines for malaria.* MPAG members exceptionally participated in the guideline development process given their previous role in developing the malaria vaccine recommendation in 2015 and because both advisory groups had been kept up to date with the progress of the Malaria Vaccine Implementation Programme (MVIP).

A SAGE/MPAG Working Group was established with Terms of Reference and an open call for members. The SAGE/MPAG Working Group members (biographies are publicly accessible on the WHO Malaria Vaccine Implementation Programme website) were required to complete a Declaration of Interest (DOI) form prior to their appointment in advance of each meeting. Review of DOI forms revealed no relevant conflicts and all members participated in all discussions. Support for the closed sessions of the SAGE/MPAG Working Group's full evidence review was provided by a restricted WHO Secretariat - known as the SAGE/MPAG Working Group Secretariat - composed of the IVB and GMP Directors, and other staff who were not involved in the generation or synthesis of evidence being reviewed by the MVIP Programme Advisory Group (see Section 10.2 Contributors – malaria vaccine).

The SAGE/MPAG Working Group performed the following functions: developed relevant and answerable question(s) in PICO format, reviewed and interpreted the evidence, with explicit consideration of the overall balance of benefits and harms; examined and provided input to the GRADE evidence profiles developed by the Cochrane Response; and formulated the proposed recommendations for SAGE/MPAG in alignment with the 2019 RTS,S Framework for WHO recommendation (*unpublished evidence*), taking into account benefits, harms, values and preferences, feasibility, equity, acceptability, resource requirements and other factors, as appropriate.

SAGE and MPAG were jointly convened on 6 October 2021 to review the work of the SAGE/MPAG Working Group, to consider the malaria vaccine evidence and to reach consensus on their vaccine recommendations to the Director-General of WHO *[257][258].*

Following the Director General's endorsement of the SAGE/MPAG recommendations, the evidence and deliberations that informed the WHO malaria vaccine position paper were put into the format required for the Weekly Epidemiological Record by the WHO Secretariat and reviewed by the a WHO Editorial Board as per the standard SAGE process. The draft was subject to broad peer review. Reviewers included members of SAGE, WHO Regional Offices, external subject matter experts, selected national immunization and malaria control programme managers, other interested parties (who had not been involved in the process to that point) and industry. Request for peer review from industry was coordinated through the International Federation of Pharmaceutical Manufacturers Association and the Developing Country Vaccine Manufacturer Network.

The final recommendation, GRADE and evidence-to-decision frameworks, and other relevant components were included in the *WHO Guidelines for malaria* and submitted for GRC review in parallel with the development of the WHO position paper in the Weekly Epidemiologic Record.

9. GLOSSARY

The Glossary lists the terms contained in the *WHO malaria terminology 2021 update [259]* which is reviewed and agreed by the Drafting Committee on Malaria Terminology first convened in 2015. Please refer to that document for additional information on the Drafting Committee and the process to review and update malaria terminology and for more detailed notes on the glossary contained here.

adherence	Compliance with a regimen (chemoprophylaxis or treatment) or with

	procedures and practices prescribed by a health care worker
adverse drug reaction	A response to a medicine that is harmful and unintended and which occurs at doses normally used in humans
adverse event	Any untoward medical occurrence in a person exposed to a biological or chemical product, which does not necessarily have a causal relationship with the product
adverse event, serious	Any untoward medical occurrence in a person exposed to a biological or chemical product, which is not necessarily causally related to the product, and results in death, requirement for or prolongation of inpatient hospitalization, significant disability or incapacity or is life-threatening
aestivation	A process by which mosquitoes at one or several stages (eggs, larvae, pupae, adults) survive by means of behavioural and physiological changes during periods of drought or high temperature
age group	Subgroup of a population classified by age. The following grouping is usually recommended: • 0–11 months • 12–23 months • 2–4 years • 5–9 years • 10–14 years • 15–19 years • ≥ 20 years
age, physiological	Adult female mosquito age in terms of the number of gonotrophic cycles completed: nulliparous, primiparous, 2-parous, 3-parous et seq.
age-grading, of female adult mosquitoes	Classification of female mosquitoes according to their physiological age (number of gonotrophic cycles) or simply as nulliparous or parous (parity rate)
age-grading, of mosquito larvae	Classification of mosquito larvae as instars (development stages) 1, 2, 3 and 4
annual blood examination rate	The number of people receiving a parasitological test for malaria per unit population per year
Anopheles, infected	Female *Anopheles* mosquitoes with detectable malaria parasites
Anopheles, infective	Female *Anopheles* mosquitoes with sporozoites in the salivary glands
anopheline density	Number of female anopheline mosquitoes in relation to the number of specified shelters or hosts (e.g. per room, per trap or per person) or to a given period (e.g.

	overnight or per hour), specifying the method of collection
anthropophilic	Description of mosquitoes that show a preference for feeding on humans, even when non-human hosts are available
antimalarial medicine	A pharmaceutical product used in humans for the prevention, treatment or reduction of transmission of malaria
artemisinin-based combination therapy	A combination of an artemisinin derivative with a longer-acting antimalarial drug that has a different mode of action
basic reproduction number	The number of secondary cases that a single infection (index case) would generate in a completely susceptible population (referred to as R0)
bioassay	In applied entomology, experimental testing of the biological effectiveness of a treatment (e.g. infection, insecticide, pathogen, predator, repellent) by deliberately exposing insects to it
biting rate	Average number of mosquito bites received by a host in a unit time, specified according to host and mosquito species (usually measured by human landing collection)
capture site	Site selected for periodic sampling of the mosquito population of a locality for various purposes
case, confirmed	Malaria case (or infection) in which the parasite has been detected in a diagnostic test, i.e. microscopy, a rapid diagnostic test or a molecular diagnostic test
case, fever	The occurrence of fever (current or recent) in a person
case, imported	Malaria case or infection in which the infection was acquired outside the area in which it is diagnosed
case, index	A case of which the epidemiological characteristics trigger additional active case or infection detection. The term “index case” is also used to designate the case identified as the origin of infection of one or a number of introduced cases
case, indigenous	A case contracted locally with no evidence of importation and no direct link to transmission from an imported case
case, induced	A case the origin of which can be traced to a blood transfusion or other form of parenteral inoculation of the parasite but not to transmission by a natural mosquito-borne inoculation

case, introduced	A case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first-generation local transmission)
case, locally acquired	A case acquired locally by mosquito-borne transmission
case, malaria	Occurrence of malaria infection in a person in whom the presence of malaria parasites in the blood has been confirmed by a diagnostic test
case, presumed	Case suspected of being malaria that is not confirmed by a diagnostic test
case, recrudescent	Malaria case attributed to the recurrence of asexual parasitaemia after antimalarial treatment, due to incomplete clearance of asexual parasitaemia of the same genotype(s) that caused the original illness. A recrudescent case must be distinguished from reinfection and relapse, in the case of *P. vivax* and *P. ovale*
case, relapsing	Malaria case attributed to activation of hypnozoites of *P. vivax* or *P. ovale* acquired previously
case, suspected malaria	Illness suspected by a health worker to be due to malaria, generally on the basis of the presence of fever with or without other symptoms
case detection	One of the activities of surveillance operations, involving a search for malaria cases in a community
case detection, active	Detection by health workers of malaria cases at community and household levels, sometimes in population groups that are considered at high risk. Active case detection can consist of screening for fever followed by parasitological examination of all febrile patients or as parasitological examination of the target population without prior screening for fever
case detection, passive	Detection of malaria cases among patients who, on their own initiative, visit health services for diagnosis and treatment, usually for a febrile illness
case follow-up	Periodic re-examination of patients with malaria (with or without treatment)
case investigation	Collection of information to allow classification of a malaria case by origin of infection, i.e. imported, indigenous, induced, introduced, relapsing or recrudescent
case management	Diagnosis, treatment, clinical care, counselling and follow-up of symptomatic malaria infections
case notification	Compulsory reporting of all malaria cases by medical units and medical practitioners to either the health department or the malaria control programme, as prescribed by national laws or regulations
catchment area	A geographical area defined and served by a health programme or institution, such as a hospital or community health centre, which is delineated on the basis of population distribution, natural boundaries and accessibility by transport
cerebral malaria	Severe *P. falciparum* malaria with impaired consciousness (Glasgow coma scale < 11, Blantyre coma scale < 3) persisting for > 1 hour after a seizure
certification of malaria-free status	Certification granted by WHO after it has been proved beyond reasonable doubt that local human malaria transmission by Anopheles mosquitoes has been interrupted in an entire country for at least three consecutive years and a national surveillance system and a programme for the prevention of reintroduction are in place
chemoprevention, seasonal malaria	Intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness. The objective is to maintain therapeutic concentrations of an antimalarial drug in the blood throughout the period of greatest risk for malaria.
chemoprophylaxis	Administration of a medicine, at predefined intervals, to prevent either the development of an infection or progression of an infection to manifest disease
cluster	Aggregation of relatively uncommon events or diseases in space and/or time in numbers that are considered greater than could be expected by chance
combination therapy	A combination of two or more classes of antimalarial medicine with unrelated mechanisms of action
coverage	A general term referring to the fraction of the population of a specific area that receives a particular intervention
coverage, optimal	Optimal coverage is the outcome of an explicit prioritization process guiding resource allocation decisions. The process combines the analysis of impact and value for money with extensive stakeholder engagement and discussion that explicitly outlines the trade-offs involved in the selection of interventions and combining

	them in an intervention package. The process should take into account a country's programmatic goals, context-specific factors, and should consider equity implications of the resource allocation decisions.
coverage, universal health	Ensuring all individuals and communities receive the health services they need without suffering financial hardship. It includes the full spectrum of essential quality health services from health promotion to prevention, treatment, rehabilitation, and palliative care.
cure	Elimination from an infected person of all malaria parasites that caused the infection
cure, radical	Elimination of both blood-stage and latent liver infection in cases of *P. vivax* and *P. ovale* infection, thereby preventing relapses
cure rate	Percentage of treated individuals whose infection is cured
cyto-adherence	Propensity of malaria-infected erythrocytes to adhere to the endothelium of the microvasculature of the internal organs of the host
diagnosis	The process of establishing the cause of an illness (for example, a febrile episode), including both clinical assessment and diagnostic testing
diagnosis, molecular	Use of nucleic acid amplification-based tests to detect the presence of malaria parasites
diagnosis, parasitological	Diagnosis of malaria by detection of malaria parasites or *Plasmodium*-specific antigens or genes in the blood of an infected individual
diapause	Condition of suspended animation or temporary arrest in the development of immature and adult mosquitoes
dosage regimen (or treatment regimen)	Prescribed formulation, route of administration, dose, dosing interval and duration of treatment with a medicine
dose	Quantity of a medicine to be taken at one time or within a given period
dose, loading	One or a series of doses that may be given at the start of therapy with the aim of achieving the target concentration rapidly
drug efficacy	Capacity of an antimalarial medicine to achieve the therapeutic objective when administered at a recommended dose, which is well tolerated and has minimal toxicity
drug resistance	The ability of a parasite strain to survive and/or multiply despite the absorption of a medicine given in doses equal to or higher than those usually recommended
drug safety	(see Medicine safety)
drug, gametocytocidal	A drug that kills male and/or female gametocytes, thus preventing them from infecting a mosquito
drug, schizontocidal	A drug that kills schizonts, either in the liver or the blood
endemic area	An area in which there is an ongoing, measurable incidence of malaria infection and mosquito-borne transmission over a succession of years
endemicity, level of	Degree of malaria transmission in an area
endophagy	Tendency of mosquitoes to blood-feed indoors
endophily	Tendency of mosquitoes to rest indoors
entomological inoculation rate (EIR)	Number of infective bites received per person in a given unit of time, in a human population
epidemic	Occurrence of a number of malaria cases highly in excess of that expected in a given place and time
epidemiological investigation	Study of the environmental, human and entomological factors that determine the incidence or prevalence of infection or disease
erythrocytic cycle	Portion of the life cycle of the malaria parasite from merozoite invasion of red blood cells to schizont rupture. The duration is approximately 24 h in *P. knowlesi*, 48 h in *P. falciparum*, *P. ovale* and *P. vivax*, and 72 h in *P. malariae*.
exophagy	Tendency of mosquitoes to feed outdoors
exophily	Tendency of mosquitoes to rest outdoors
experimental huts	For vector investigations, simulated house with entry and exit traps for sampling mosquitoes entering and exiting, blood-feeding indoors (when a host is present), and surviving or dying in each sub-sample, per day or night
fixed-dose combination	A combination in which two antimalarial medicines are formulated together in the same tablet, capsule, powder, suspension or granule
focus, malaria	A defined circumscribed area situated in a currently or formerly malarious area that

	contains the epidemiological and ecological factors necessary for malaria transmission
gametocyte	Sexual stage of malaria parasites that can potentially infect anopheline mosquitoes when ingested during a blood meal
gametocyte rate	Percentage of individuals in a defined population in whom sexual forms of malaria parasites have been detected
geographical reconnaissance	Censuses and mapping to determine the distribution of the human population and other features relevant for malaria transmission in order to guide interventions
gonotrophic cycle, mosquito	The period of reproductive development in the female mosquito, including host-seeking, blood feeding, digestion of a blood meal, ovarian development, search for a breeding site and oviposition.
gonotrophic discordance (dissociation)	Female mosquitoes that take more than one blood meal per gonotrophic cycle
hibernation	Process in which mosquitoes at one or several stages (eggs, larvae, pupae, adults) survive by means of behavioural or physiological changes during cold periods
house	Any structure other than a tent or mobile shelter in which humans sleep
household	The ecosystem, including people and animals occupying the same house and the accompanying vectors
house-spraying	Application of liquid insecticide formulation to specified (mostly interior) surfaces of buildings
human landing catch	A method for collecting vectors as they land on individuals
hyperparasitaemia	A high density of parasites in the blood, which increases the risk that a patient's condition will deteriorate and become severe malaria
hypnozoite	Persistent liver stage of *P. vivax* and *P. ovale* malaria that remains dormant in host hepatocytes for variable periods, from three weeks to one year (exceptionally even longer), before activation and development into a pre-erythrocytic schizont, which then causes a blood-stage infection (relapse)
importation rate	Rate of influx of parasites via infected individuals or infected *Anopheles* spp. mosquitoes
importation risk	Probability of influx of infected individuals and/or infective anopheline mosquitoes
incidence, malaria	Number of newly diagnosed malaria cases during a defined period in a specified population
incubation period	Period between inoculation of malaria parasites and onset of clinical symptoms
index, host preference	Proportion of blood-fed female *Anopheles* mosquitoes that feed on the host species and/or individual of interest
index, human blood	Proportion of mosquito blood meals from humans
index, parasite-density	Mean parasite density on slides examined and found positive for a sample of the population; calculated as the geometric mean of individual parasite density counts
indoor residual spraying	Operational procedure and strategy for malaria vector control involving spraying interior surfaces of dwellings with a residual insecticide to kill or repel endophilic mosquitoes
indoors	Inside any shelter likely to be used by humans or animals, where mosquitoes may feed or rest
infection, chronic	Long-term presence of parasitaemia that is not causing acute or obvious illness but could potentially be transmitted
infection, mixed	Malaria infection with more than one species of *Plasmodium*
infection, reservoir of	Any person or animal in which *Plasmodium* species live and multiply, such that they can be transmitted to a susceptible host
infection, submicroscopic	Low-density blood-stage malaria infections that are not detected by conventional microscopy
infectious	Capable of transmitting infection, a term commonly applied to human hosts
infective	Capable of producing infection, a term commonly applied to parasites (e.g., gametocytes, sporozoites) or to the vector (mosquito)
infectivity	Ability of sporozoites of a specific strain of *Plasmodium* to be injected by *Anopheles* mosquitoes into susceptible humans and develop through the liver stage to infect red blood cells ("infectivity to humans") and the ability of competent *Anopheles* mosquitoes to ingest human *Plasmodium* gametocytes which undergo development until the mosquito has infective sporozoites in its salivary glands ("infectivity to mosquitoes").
insecticide	Chemical product (natural or synthetic) that

	kills insects. Ovicides kill eggs; larvicides (larvacides) kill larvae; pupacides kill pupae; adulticides kill adult mosquitoes. Residual insecticides remain active for an extended period
insecticide, cross-resistance	Resistance to one insecticide by a mechanism that also confers resistance to another insecticide, even when the insect population has not been selected by exposure to the latter
insecticide discriminating dose, or diagnostic dose for resistance	Amount of an insecticide (usually expressed as the concentration per standard period of exposure), which, in a sample of mosquitoes containing resistant individuals, distinguishes between susceptible and resistant phenotypes and determines their respective proportions
insecticide, dose	Amount of active ingredient of insecticide applied per unit area of treatment (mg/m^2) for indoor residual spraying and treated mosquito nets, or per unit of space (mg/m^3) for space spraying and per unit area of application (g/ha or mg/m^2) or per volume of water (mg/L) for larvicides
insecticide, mixture	Insecticide product consisting of two or more active ingredients mixed as one formulation so that, when applied, the mosquito will contact both simultaneously
insecticide mosaic	Strategy for mitigating resistance, whereby insecticides with different modes of action are applied in different parts of an area under coverage (usually in a grid pattern), so that parts of the mosquito populations are exposed to one insecticide and others to another
insecticide resistance	Property of mosquitoes to survive exposure to a standard dose of insecticide; may be the result of physiological or behavioural adaptation
insecticide rotation	Strategy involving sequential applications of insecticides with different modes of action to delay or mitigate resistance
insecticide tolerance	Less-than-average susceptibility to insecticide but not inherited as resistance
insecticide, contact	Insecticide that exerts a toxic action on mosquitoes when they rest on a treated surface; the insecticide is absorbed via the tarsi (feet).
insecticide, fumigant	Insecticide that acts by releasing vapour from a volatile substance
insecticide, residual	Insecticide that, when suitably applied onto a surface, maintains its insecticidal activity for a considerable time by either contact or fumigant action
integrated vector management (IVM)	Rational decision-making for optimal use of resources for vector control
intermittent preventive treatment of malaria in school-aged children	Administration of a full treatment course of an antimalarial medicine at predefined intervals to school children, in order to prevent illness in areas with moderate to high malaria transmission
intermittent preventive treatment in infants (IPTi)	Please see ‘perennial malaria chemoprevention’
intermittent preventive treatment in pregnancy (IPTp)	A full therapeutic course of antimalarial medicine given to pregnant women at routine prenatal visits, regardless of whether the woman is infected with malaria
invasive species	A non-native species that establishes in a new ecosystem, and causes, or has the potential to cause, harm to the environment, economy, or human health
larval source management	Management of aquatic habitats (water bodies) that are potential habitats for mosquito larvae, in order to prevent completion of development of the immature stages
larvicide	Substance used to kill mosquito larvae
latent period	For *P. vivax* and *P. ovale* infections, the period between the primary infection and subsequent relapses. This stage is asymptomatic; parasites are absent from the bloodstream but present in hepatocytes.
long-lasting insecticidal net (LLIN)	A factory-treated mosquito net made of material into which insecticide is incorporated or bound around the fibres. The net must retain its effective biological activity for at least 20 WHO standard washes under laboratory conditions and three years of recommended use under field conditions.
malaria case	(See Case, malaria)
malaria, cerebral	(See Cerebral malaria)
malaria control	Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts. Continued interventions are required to sustain control.
malaria	Interruption of local transmission (reduction

elimination	to zero incidence of indigenous cases) of a specified malaria parasite in a defined geographical area as a result of deliberate activities. Continued measures to prevent re-establishment of transmission are required.
malaria eradication	Permanent reduction to zero of the worldwide incidence of infection caused by human malaria parasites as a result of deliberate activities. Interventions are no longer required once eradication has been achieved.
malaria infection	Presence of *Plasmodium* parasites in blood or tissues, confirmed by diagnostic testing
malaria mortality rate	Number of deaths from malaria per unit of population during a defined period
malaria pigment (haemozoin)	A brown-to-black granular material formed by malaria parasites as a by-product of haemoglobin digestion. Pigment is evident in mature trophozoites and schizonts. It may also be phagocytosed by monocytes, macrophages and polymorphonuclear neutrophils.
malaria prevalence (parasite prevalence)	Proportion of a specified population with malaria infection at one time
malaria rebound	Increased malaria incidence following time-limited reduction of malaria transmission (through effective interventions such as chemoprevention, vaccination or vector control), when the population becomes exposed to more transmission
malaria receptivity	Degree to which an ecosystem in a given area at a given time allows for the transmission of *Plasmodium* spp. from a human through a vector mosquito to another human.
malaria reintroduction	The occurrence of introduced cases (cases of the first-generation local transmission that are epidemiologically linked to a confirmed imported case) in a country or area where the disease had previously been eliminated
malaria risk stratification	Classification of geographical areas or localities according to factors that determine receptivity and vulnerability to malaria transmission
malaria stratification	Classification of geographical areas or localities according to epidemiological, ecological, social and economic determinants for the purpose of guiding malaria interventions
malaria, cross-border	Malaria transmission associated with the movement of individuals or mosquitoes across borders
malaria-free	Describes an area in which there is no continuing local mosquito-borne malaria transmission and the risk for acquiring malaria is limited to infection from introduced cases
malariogenic potential	Potential level of transmission in a given area arising from the combination of malaria receptivity, importation rate of malaria parasites and infectivity
malariometric survey	Survey conducted in a representative sample of selected age groups to estimate the prevalence of malaria and coverage of interventions
malarious area	Area in which transmission of malaria is occurring or has occurred during the preceding three years
mass drug administration (MDA)	Administration of full treatment course of an antimalarial to all age groups of a population in a defined geographical area (except those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals
mass screening	Population-wide assessment of risk factors for malaria infection to identify subgroups for further intervention, such as diagnostic testing, treatment or preventive services
mass screening, testing and treatment	Screening of an entire population for risk factors, testing individuals at risk and treating those with a positive test result
mass testing and focal drug administration	Testing a population and treating groups of individuals or entire households in which one or more infections is detected
mass testing and treatment	Parasitological screening of the entire population of a delimited geographical area and treating those with a positive test result at approximately the same time
medicine safety	Characteristics of a medicine that reflects its potential to cause harm, including the important identified risks of a drug and important potential risks
merozoite	Extracellular stage of a parasite released into host plasma when a hepatic or erythrocytic schizont ruptures; the merozoites can then invade red blood cells.
moderate to high perennial transmission	Persistent *P. falciparum* transmission at rates which result in a parasite prevalence greater than 10%, or an annual parasite incidence greater than 250 per 1000.

monotherapy	Antimalarial treatment with a single active compound or a synergistic combination of two compounds with related mechanisms of action
national focus register	Centralized database of all foci of malaria infection in a country, which includes relevant data on physical geography, parasites, hosts and vectors for each focus
national malaria case register	Centralized database with individual records of all malaria cases registered in a country
net, insecticide-treated (ITN)	Mosquito net that repels, disables or kills mosquitoes that come into contact with the insecticide on the netting material. Insecticide treated nets (ITNs) include those that require treatment and retreatment (often referred to as conventional nets) and those that are "long-lasting" (see definition of long-lasting insecticidal net).
oocyst	The stage of malaria parasite that develops from the ookinete; the oocyst grows on the outer wall of the midgut of the female mosquito.
oocyst rate	Percentage of female *Anopheles* mosquitoes with oocysts on the midgut
ookinete	Motile stage of malaria parasite after fertilization of macrogamete and preceding oocyst formation
parasitaemia	Presence of parasites in the blood
parasitaemia, asymptomatic	The presence of asexual parasites in the blood without symptoms of illness
parasite clearance time	Time between first drug administration and the first examination in which no parasites are present in the blood by microscopy
parasite density	Number of asexual parasites per unit volume of blood or per number of red blood cells
parasite density, low	Presence of *Plasmodium* parasites in the blood at parasite density below 100 parasites/µl
patent period	Period during which malaria parasitaemia is detectable
perennial malaria chemoprevention	Administration of a full treatment course of an antimalarial medicine at predefined intervals to children at risk of severe malaria, in order to prevent illness in moderate to high perennial malaria transmission settings.
Plasmodium	Genus of protozoan blood parasites of vertebrates that includes the causal agents of malaria. *P. falciparum*, *P. malariae*, *P. ovale* and *P. vivax* cause malaria in humans. Human infection with the monkey malaria parasite *P. knowlesi* and very occasionally with other simian malaria species may occur in tropical forest areas.
population at risk	Population living in a geographical area where locally acquired malaria cases have occurred in the past three years
population, target	An implementation unit targeted for activities or services (e.g., prevention, treatment)
post-discharge malaria chemoprevention	Administration of a full treatment course of an antimalarial medicine to children hospitalized for severe anemia, starting at time of discharge from hospital and continuing at predefined intervals.
pre-erythrocytic development	Development of the malaria parasite from the time it first enters the host and invades liver cells until the hepatic schizont ruptures
pre-patent period	Period between inoculation of parasites and the first appearance of parasitaemia
prequalification	Process to ensure that health products are safe, appropriate and meet stringent quality standards for international procurement
preventive chemotherapy	Use of medicines either alone or in combination to prevent malaria infections and their consequences
prophylaxis	Any method of protection from or prevention of disease; when applied to chemotherapy, it is commonly termed "chemoprophylaxis".
prophylaxis, causal	Complete prevention of erythrocytic infection by destroying the pre-erythrocytic forms of the parasite
rapid diagnostic test (RDT)	Immunochromatographic lateral flow device for rapid detection of malaria parasite antigens
rapid diagnostic test, combination	Malaria rapid diagnostic test that can detect a number of different malaria species
rapid diagnostic test positivity rate	Proportion of positive results among all rapid diagnostic tests performed
reactive case detection and treatment	Parasitological screening of every person living with or near a person who has a confirmed malaria case, and/or every person who was likely exposed to infection at the same time and place as the index case, and treating those with a malaria positive test result
reactive drug administration	Administration of a full treatment course of an antimalarial medicine as

	chemoprevention to every person living with or near a person with a confirmed malaria infection, and/or to every person who was likely exposed to infection at the same time and place as the index case
reactive indoor residual spraying	Application of residual insecticide to the interior surfaces of dwellings in the location of the index case and neighboring houses at approximately the same time
receptivity	Receptivity of an ecosystem to transmission of malaria
recrudescence	Recurrence of asexual parasitaemia of the same genotype(s) that caused the original illness, due to incomplete clearance of asexual parasites after antimalarial treatment
recurrence	Reappearance of asexual parasitaemia after treatment, due to recrudescence, relapse (in *P. vivax* and *P. ovale* infections only) or a new infection
reinfection	A new infection that follows a primary infection; can be distinguished from recrudescence by the parasite genotype, which is often (but not always) different from that which caused the initial infection
reintroduction risk	The risk that endemic malaria will be re-established in a specific area after its elimination
relapse	Recurrence of asexual parasitaemia in *P. vivax* or *P. ovale* infections arising from hypnozoites
repellent	Any substance that causes avoidance in mosquitoes, especially substances that deter them from settling on the skin of the host (topical repellent) or entering an area or room (area repellent, spatial repellent, excito-repellent)
resistance	(See Drug resistance, Insecticide resistance)
ring form (ring stage, ring-stage trophozoite)	Young, usually ring-shaped malaria trophozoites, before pigment is evident by microscopy
schizont	Stage of the malaria parasite in host liver cells (hepatic schizont) or red blood cells (erythrocytic schizont) that is undergoing nuclear division by schizogony and, consequently, has more than one nucleus
screening	Identification of groups at risk that may require further intervention, such as diagnostic testing, treatment or preventive services
seasonal malaria	Intermittent administration of full treatment courses of an antimalarial medicine to children at risk of severe malaria, to prevent malarial illness in areas with seasonal malaria. The objective is to maintain therapeutic concentrations of an antimalarial drug in the blood throughout the period of greatest risk for malaria.
selection pressure	The force of an external agent that confers preferential survival; examples are the pressure of antimalarial medicines on malaria parasites and of insecticides on anopheline mosquitoes
sensitivity (of a test)	Measured as the proportion of people with malaria infection (true positives) who have a positive result
serological assay	Procedure used to measure antimalarial antibodies in serum
severe anaemia	Haemoglobin concentration of < 5 g/100 mL (haematocrit < 15%)
severe falciparum malaria	Acute falciparum malaria with signs of severe illness and/or evidence of vital organ dysfunction
single-dose regimen	Administration of a medicine as a single dose to achieve a therapeutic objective
slide positivity rate	Proportion of blood smears found to be positive for *Plasmodium* among all blood smears examined
specificity (of a test)	Measured as the proportion of people without malaria infection (true negatives) who have a negative result
sporozoite	Motile stage of the malaria parasite that is inoculated by a feeding female anopheline mosquito and may cause infection
sporozoite rate	Percentage of female *Anopheles* mosquitoes with sporozoites in the salivary glands
spray round	Spraying of all sprayable structures in an area designated for coverage in an indoor residual spraying programme during a discrete period
sprayable	In the context of a malaria vector control programme, a unit (dwelling, house, room, shelter, structure, surface) suitable for spraying or required to be sprayed
spraying cycle	Repetition of spraying operations at regular intervals, often designated in terms of the interval between repetitions, e.g., a 6-month spraying cycle when spraying is repeated after a 6-month interval
spraying frequency	Number of regular applications of insecticide per house per year, usually by

	indoor residual spraying
spraying interval	Time between successive applications of insecticide
spraying, focal	Spray coverage by indoor residual spraying and/or space spraying of houses or habitats in a limited geographical area
spraying, residual (IRS)	Spraying the interior walls and ceilings of dwellings with a residual insecticide to kill or repel endophilic mosquito vectors of malaria
surveillance	Continuous, systematic collection, analysis and interpretation of disease-specific data and use in planning, implementing and evaluating public health practice
surveillance, entomological	The regular, systematic collection, analysis and interpretation of entomological data for risk assessment, planning, implementation, monitoring and evaluation of vector control interventions
targeted drug administration	Administration of a full treatment course of an antimalarial medicine to individuals at increased risk of malaria infection compared to the general population.
targeted testing and treatment	Parasitological screening of individuals at increased risk of malaria infection compared to the general population and treating those with a malaria positive test result.
testing, malaria	Use of a malaria diagnostic test to determine whether an individual has malaria infection
tolerance	A response in a human or mosquito host to a given quantum of infection, toxicant or drug that is less than expected
transmission intensity	The frequency with which people living in an area are bitten by anopheline mosquitoes carrying human malaria sporozoites
transmission season	Period of the year during which most mosquito-borne transmission of malaria infection occurs
transmission, re-establishment of	Renewed presence of a measurable incidence of locally acquired malaria infection due to repeated cycles of mosquito-borne infections in an area in which transmission had been interrupted
transmission, interruption of	Cessation of mosquito-borne transmission of malaria in a geographical area as a result of the application of antimalarial measures
transmission, perennial	Transmission that occurs throughout the year with no great variation in intensity
transmission, residual	Persistence of malaria transmission following the implementation in time and space of a widely effective malaria programme
transmission, seasonal	Transmission that occurs only during some months of the year and is markedly reduced during other months
transmission, stable	Epidemiological type of malaria transmission characterized by a steady prevalence pattern, with little variation from one year to another except as the result of rapid scaling up of malaria interventions or exceptional environmental changes that affect transmission
transmission, unstable	Epidemiological type of malaria transmission characterized by large variation in incidence patterns from one year to another
trap, mosquito	Device designed for capturing mosquitoes with or without attractant components (light, CO_2, living baits, suction)
treatment failure	Inability to clear malarial parasitaemia or prevent recrudescence after administration of an antimalarial medicine, regardless of whether clinical symptoms are resolved
treatment, anti-relapse	Antimalarial treatment designed to kill hypnozoites and thereby prevent relapses or late primary infections with *P. vivax* or *P. ovale*
treatment, directly observed (DOT)	Treatment administered under the direct observation of a health care worker
treatment, first-line	Treatment recommended in national treatment guidelines as the medicine of choice for treating malaria
treatment, second-line	Treatment used after failure of first-line treatment or in patients who are allergic to or unable to tolerate the first-line treatment
treatment, presumptive	Administration of an antimalarial drug or drugs to people with suspected malaria without testing or before the results of blood examinations are available
treatment, preventive	Intermittent administration of a full therapeutic course of an antimalarial either alone or in combination to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk
treatment, radical	Treatment to achieve complete cure. This applies only to vivax and ovale infections and consists of the use of medicines that

	destroy both blood and liver stages of the parasite.
trophozoite	The stage of development of malaria parasites growing within host red blood cells from the ring stage to just before nuclear division. Trophozoites contain malaria pigment that is visible by microscopy.
uncomplicated malaria	Symptomatic malaria parasitaemia without signs of severity or evidence of vital organ dysfunction
vector	In malaria, adult females of any mosquito species in which *Plasmodium* undergoes its sexual cycle (whereby the mosquito is the definitive host of the parasite) to the infective sporozoite stage (completion of extrinsic development), ready for transmission when a vertebrate host is bitten
vector competence	For malaria, the ability of the mosquito to support completion of malaria parasite development after zygote formation and oocyst formation, development and release of sporozoites that migrate to salivary glands, allowing transmission of viable sporozoites when the infective female mosquito feeds again
vector control	Measures of any kind against malaria-transmitting mosquitoes, intended to limit their ability to transmit the disease
vector susceptibility	The degree to which a mosquito population is susceptible (i.e., not resistant) to insecticides
vector, principal	The species of *Anopheles* mainly responsible for transmitting malaria in any particular circumstance
vector, secondary or subsidiary	Species of *Anopheles* thought to play a lesser role in transmission than the principal vector; capable of maintaining malaria transmission at a reduced level
vectorial capacity	Number of new infections that the population of a given vector would induce per case per day at a given place and time, assuming that the human population is and remains fully susceptible to malaria
vigilance	A function of the public health services for preventing reintroduction of malaria. Vigilance consists of close monitoring for any occurrence of malaria in receptive areas and application of the necessary measures to prevent re-establishment of transmission.

10. CONTRIBUTORS AND INTERESTS

The Guideline was consolidated for the first time in February 2021, building on previously published guidelines. The consolidation and coordination between the technical areas and GDGs was driven by Dr Pedro Alonso, Director and Erin Shutes, Programme Manager of the Global Malaria Programe to ensure consistency in approach and harmonization in the recommendations. The many contributors to the development of recommendations are acknowledged in the sub-sections below according to the evidence reviews of the intervention areas.

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10.1 Recommendations for vector control

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Declaration of interests (2019)

Participants in the technical consultations or sessions for development of the Guidelines reported relevant interests. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat, with support from the Office of Compliance, Risk Management and Ethics as needed. WHO was of the opinion that these declarations did not constitute conflicts of interest and that the considered experts could participate in the consultations on the Guidelines subject to the public disclosure of their interests, which was conducted.

The relevant declared interests are summarized as follows:

Dr T. Burkot reported several potential conflicts of interest related to consulting payments, research support and non-monetary support, as follows: 1) consulting with Intellectual Ventures Global Good Fund (IVGGF), the non-profit arm of Intellectual Ventures Laboratory. Work was conducted from October 2014 to March 2015 through James Cook University; 2) consulting with IVGGF for a secondment in 2017 to develop a vector control strategy on mosquitoproof housing and methods to age-grade mosquitoes through James Cook University; 3) consulting with the non-profit Programme for Appropriate Technology in Health (PATH) in 2017 to support grant applications to evaluate new vector control tools in Africa; 4) consulting with IVGGF from 2017 to February 2018 to provide technical support on developing guidelines for testing new vector control strategies, paid directly to Dr Burkot; 5) consulting with PATH from 2017 to February 2018 to provide technical advice on field trials for mosquito-proof housing products paid, directly to Dr Burkot; 6) research support in a supervisory role provided to James Cook University for evaluation of a new malaria diagnostic test from October 2015 to March 2017; 7) research support in a supervisory role provided to James Cook University to undertake a malaria serologic survey in the Solomon Islands until June 2018; and 8) non-monetary support to Vestergaard in a supervisory role to evaluate the impact of insecticide netting on malaria in Solomon Islands.

Dr M. Coetzee reported a potential conflict of interest related to a family member's consulting work with AngloGold Ashanti in 2016 to carry out mosquito surveys and determine insecticide resistance in order to inform vector control strategies by gold mining companies in Africa.

Professor M. Coosemans reported receiving a grant from the Bill & Melinda Gates Foundation for studying the impact of repellents for malaria prevention in Cambodia and also reported receiving repellent products for the study from SC Johnson for work conducted in 2012–2014. He also reported receiving six grants for the evaluation of public health pesticides from WHOPES from 2007, some of which continued until 2018.

Dr J. Hii reported receiving remuneration for consulting services from WHO and from the Ministry of Health of Timor-Leste for work conducted in 2017. He reported holding a grant from SC Johnson that ceased in 2017 for the evaluation of transfluthrin, and receiving travel and accommodation support from Bayer Crop Science to attend the 4th Bayer Vector Control Expert Meeting in 2017. He reported holding a WHO/TDR research grant that focused on studying the magnitude and identifying causes for residual transmission in The Kingdom of Thailand and Viet Nam (completed in 2018), and reported a plan to study the impact of socio-ecological systems and resilience (SESR)-based strategies on dengue vector control in schools and neighbouring household communities in Cambodia, which in November 2017 was awaiting ethical approval.

Members of the Guidelines Development Group (GDG) (2021)

- Dr Dorothy Achu, Programme manager, National Malaria Control Programme, Yaoundé, the Republic of Cameroon
- Prof Basil Brooke, Associate professor, University Witwatersrand/National Institute for Communicable Disease, Johannesburg, Republic of South Africa
- Prof Ahmad Ali Enayati, Head, Medical Entomology Department, School of Public Health, Mazandaran University of Medical Sciences, Sari, Islamic Republic of Iran
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- Prof Fang Jing, Director, Institute for Health Sciences, Kunming Medical University, Yunnan Province, People's

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- Dr Kui Muraya, Social scientist, KEMRI-Wellcome Trust, Nairobi, Republic of Kenya
- Prof Martha Quiñones, Professor, Universidad Nacional de Colombia, Bogotá, the Republic of Colombia
- Dr Christina Rundi, Health director, Sabah Health Department, Ministry of Health, Sabah, Malaysia
- Dr Tanya Russell, Research fellow, James Cook University, Cairns, Australia
- Dr Lucy Tusting, Assistant professor, Faculty of Infectious Tropical Disease, LSHTM, London, United Kingdom of Great Britain and Northern Ireland
- Dr Josh Yukich, Associate professor, Department of Tropical Medicine Tulane University School of Public Health and Tropical Medicine, New Orleans, United States of America

Members of the Guidelines Development Group (GDG) (2022)

- Dr Dorothy Achu, Programme manager, National Malaria Control Programme, Yaoundé, the Republic of Cameroon
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- Prof Martha Quiñones, Professor, Universidad Nacional de Colombia, Bogotá, the Republic of Colombia
- Dr Tanya Russell, Research fellow, James Cook University, Cairns, Australia
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Members of the Guidelines Steering Group (2021 & 2022)

- Dr Samira Al-Eryani, WHO Regional Office for the Eastern Mediterranean, Cairo, Arab Republic of Egypt
- Dr Haroldo Bezerra, WHO Regional Office for the Americas, Washington DC, United States of America
- Dr Maurice Bucagu, Family, Women, Children and Adolescents, World Health Organization, Geneva, Swiss Confederation
- Dr Emmanual Chanda, WHO Regional Office for Africa, Brazzaville, Republic of the Congo
- Dr Florence Fouque, Special Programme for Research and Training in Tropical Diseases, Geneva, Swiss Confederation
- Dr Riffat Hossain, Programme for Health and Migration, World Health Organization, Geneva, Swiss Confederation
- Dr Tessa Knox, WHO Country Office, Vanuatu
- Dr Jan Kolaczinski, Global Malaria Programme, World Health Organization, Geneva, Swiss Confederation
- Mrs Marion Law, Prequalification Team for Vector Control, Departments of Essential Medicines of Health Products, World Health Organization, Geneva, Swiss Confederation
- Dr Kim Lindblade, Global Malaria Programme, World Health Organization, Geneva, Swiss Confederation
- Dr Katherine Littler, Department of Research for Health, World Health Organization, Geneva, Swiss Confederation
- Dr Ramona Ludolph, Environment, Climate Change and Health, World Health Organization, Geneva, Swiss Confederation
- Dr Edith Patouillard, Global Malaria Programme, World Health Organization, Geneva, Swiss Confederation
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- Dr Jennifer Stevenson, Global Malaria Programme, World Health Organization, Geneva, Swiss Confederation
- Dr Raman Velayudhan, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Swiss Confederation

Members of the External Review Group (ERG) (2021 & 2022)

- Dr Jenifer Armistead, Malaria Division, United States Agency for International Development (USAID), Unites States of America
- Prof Maureen Coetzee, University of the Witwatersrand, Republic of South Africa
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Republic of the Gambia
- Dr Scott Filler, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Swiss Confederation
- Dr Caroline Jones, Senior Social Scientist, KEMRI Wellcome Trust Research Programme, Republic of Kenya
- Prof Neil Lobo, University of Notre Dame, United States of America
- Dr Melanie Renshaw, African Leaders Malaria Alliance

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- Prof Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Ms Katherine Gleave, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Jo Leonardi-Bee, University of Nottingham, United Kingdom of Great Britain and Northern Ireland
- Prof Jo Lines, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Elisa Martello, University of Nottingham, United Kingdom of Great Britain and Northern Ireland
- Dr Louisa Messenger, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Lucy Paintain, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Ms Laura Paris, The MENTOR Initiative, Crawley, United Kingdom of Great Britain and Northern Ireland
- Ms Bethanie Pelloquin Department of Disease Control, Faculty of Infectious Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland; School of Tropical Medicine and Global Health, University of Nagasaki, Nagasaki, Japan
- Prof Mark Rowland, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Rebecca Thomas, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Gowsika Yogeswaran, University of Nottingham, United Kingdom of Great Britain and Northern Ireland

Systematic review team members (2022)

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- Ms Carrie Price, Albert S. Cook Library, Towson University, Towson, Maryland, United States
- Dr Alinune Kabaghe, Training and Research Unit of Excellence, Blantyre, Malawi
- Professor Zachary Munn, JBI Adelaide GRADE Centre, Faculty of Health and Medical Sciences, The University of Adelaide, SA 5005, Australia

Guidelines methodologist and co-chair (2021 & 2022))

Dr Elie Akl, American University of Beirut, Lebanese Republic

Declaration of interests (2021)

Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

One member of the GDG reported interests related to housing improvements for malaria and it was decided that she be recused from discussions on decision-making regarding housing modifications to prevent malaria.

The relevant declared interests for the GDG are summarized as follows:

Dr Lucy Tusting: declared receiving research funding exceeding GBP 5000 within the last 4 years towards studies related to the impact of housing improvements on malaria from the UK Medical Research Council, a topic which was discussed at the GDG meeting. She declared being the principal investigator of this study and the project supports 100% of her income. This support continues to 2022. She also has some unpaid roles relating to housing and malaria, for which she receives travel expenses. She works with a project in the Republic of Uganda, funded by the NIH, analysing data exploring the relationship between housing and malaria. She is also the co-director of the BOVA network (Building Out Vector-Borne Diseases in Africa) from 2017 to date which is an interdisciplinary network focusing on preventing vector-borne diseases such as malaria, dengue and zika disease through improving the built environment. From 2017-2020 she was co-chair of the RBM VCWG's 'Vector-Borne Diseases and the Built Environment Workstream' (formerly 'Housing and Malaria'). She has led key reviews on housing type or improvement and the impact on malaria. The first was a systematic review of housing improvements for malaria control, published in Malaria Journal 2015: Tusting , L.S., Ippolito, M.M., Willey, B.A. *et al.* The evidence for improving housing to reduce malaria: a systematic review and meta-analysis. *Malar J* 14, 209 (2015). https://doi.org/10.1186/s12936-015-0724-1. The second and third were analyses of DHS data, studying the relationship between house type and malaria infection in children. Both were published in PLOS Med in 2017 and 2020: Tusting LS, Bottomley C, Gibson H, Kleinschmidt I, Tatem AJ, et al. (2017) Housing Improvements and Malaria Risk in Sub-Saharan Africa: A Multi-Country Analysis of Survey Data. PLOS Medicine 14(2): e1002234. https://doi.org/10.1371/journal.pmed.1002234; Tusting LS, Gething PW, Gibson HS, Greenwood B, Knudsen J, et al. (2020) Housing and child health in sub-Saharan Africa: A cross-sectional analysis. PLOS Medicine

17(3): e1003055. https://doi.org/10.1371/journal.pmed.100305. She was also a guest editor for a Malaria Journal thematic series on Housing and Malaria between 2015 and 2016.

Dr Tusting also was involved in studies and reviews related to larval source management (LSM) as a vector control tool but all these date to 2015 or earlier and she has not received any support towards work on this topic since and so it was concluded that this did not constitute a conflict of interest.

It was determined that Dr Tusting could participate in all parts of the meeting except for decision-making with respect to recommendations related to housing improvements.

Five members of the External Review Group reported relevant interests; it was assessed that all members could fully participate as the remit of the Review Group was limited to identifying factual errors, providing clarity and commenting on implications for implementation not changing the recommendations formulated by the GDG. It was concluded that their expertise in some of these areas would be valuable, particularly on implementation considerations and factors to be considered associated with gender and social determinants, equity, and human rights.

The relevant declared interests for the ERG are summarized as follows:

Umberto D'Alessandro: reported receiving remuneration for the following activities which were topics of the meeting. He declared receiving research funding exceeding USD 5000 in the last 4 years on three projects titled 'Can improved housing provide additional protection against clinical malaria over current best practice? A household-randomised controlled study. Supported by the Joint Global Health Trial Scheme (Medical Research Council (MRC), Welcome Trust (WT), Department for International Development (DfID)) and 'Will raised buildings reduce malaria transmission in sub-Saharan Africa and keep buildings cool?' which is a collaboration with Durham University; and 'Towards the end game: operational research on improving rural housing in sub-Saharan Africa as a strategy to support malaria elimination' also a collaboration with Durham University.

Jennifer Armistead: reported the following projects that she had been involved in in the past 4 years, where funding exceeded GBP 5000 and which concerned topics for discussion during the meeting; Monitoring the deployment of PBO synergist ITNs in Ebonyi State, the Federal Republic of Nigeria, estimating coverage, and impact, funded by PMI; Impact of housing modifications combined with piperonyl butoxide (PBO) long-lasting insecticidal nets (LLINs) on malaria burden in the Republic of Uganda, a collaboration between CDC, London School of Hygiene & Tropical Medicine, UK and Infectious Disease Research Collaboration, Kampala, The Republic of Uganda; Determining the feasibility and effectiveness of larviciding, funded by PMI collaboration with PATH.

Maureen Coetzee: reported acting as supervisor for a PhD project to investigate whether integrated spatial information tools could enable targeted urban planning interventions to control malaria and lymphatic filariasis in Dar es Salaam, Tanzania. This was a collaboration with Ifakara Health Institute, United Republic of Tanzania; Swiss Tropical & Public Health Institute, Swiss Confederation; Liverpool School of Tropical Medicine, UK. This project investigated housing characteristics that were associated with risk of mosquito biting but did not evaluate the impact of housing modifications on malaria

Caroline Jones: reported being a co-Investigator on a Wellcome Trust Collaborative Award: Improving the efficacy of malaria prevention in an insecticide resistant Africa which aimed to investigate the factors limiting the efficacy of current tools to prevent malaria, largely insecticide-treated nets, and to identify the most cost effective, complementary interventions that would drive malaria transmission towards zero. Although this project could consider interventions under discussion by the ERG, it did not seek to systematically evaluate a particular tool. She also reported being a co-investigator on a DfID/MRC/Wellcome Trust Joint Global Health Trials funded project: Can improved housing provide additional protection against clinical malaria over current best practice? A household-randomised controlled trial.

Neil Lobo: reported being a co-principal investigator on 'Screening mosquito entry points into houses with novel long lasting insecticidal netting to reduce indoor vector densities and mitigate pyrethroid resistance' in collaboration with Durham University.

No interests related to the topics of the meetings were disclosed by the methodologist or systematic review teams.

Declaration of interests (2022)
Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

The relevant declared interests for the GDG are summarized as follows:

Dr Lucy Tusting declared receiving remuneration for consulting services exceeding USD 5000 for WHO that ended in October 2022. This agreement was for providing support and input into the development of the WHO Urban Malaria Framework. She also received research funding exceeding USD 5000 for a Medical Research Council (UK) fellowship that will continue until November 2023. The fellowship is on the role of improved housing on malaria. She has also received a grant from the NovoNordisk Foundation that involves risk mapping of malaria and Aedes-borne diseases in Tanzania. The grant runs until 2026.

Charles Wondji declared receiving research support, including grants, collaborations, sponsorships, and other funding from the Innovative Vector Control Consortium (IVCC) exceeding USD 5000. Ongoing studies aim to evaluate the entomological impact of more recently developed indoor residual spraying (IRS) products, dual active ingredient nets and pyrethroid-PBO nets

against insecticide-resistant mosquitoes.

Dr Josh Yukich declared receiving salary support from his university through a project titled 'New Nets' to investigate the cost and cost effectiveness of dual active ingredient nets and pyrethroid- PBO nets. He also declared supervising students engaged in the analysis of the effectiveness of IRS and he has been engaged in similar analyses over the past several years whilst being employed by Tulane university. He is acting as a consultant for the University of California San Francisco to design and develop data collection tools for a cost effectiveness and willingness to pay study that involves topical repellents.

In summary, three members of the GDG declared potential interests. Based on the detailed assessment of the information provided to WHO it was decided that Dr Lucy Tusting could participate in all sessions, while Dr Josh Yukich was to be recused from the decision-making processes where the impact of dual active ingredient nets and topical repellents against malaria were be determined and from the sessions where recommendations were formulated. It was also concluded that Prof Wondji was to be recused from the decision-making processes where the impact of IRS and dual active ingredient nets against malaria were determined and from the sessions where recommendations are formulated.

The relevant declared interests for the ERG are summarized as follows:

Dr Umberto D'Alessandro reported receiving renumeration for being a member of the external scientific advisory board for Medicines for Malaria Venture until December 2018, travel support for a meeting in Geneva in Sept 2017 and Oct 2018, and a donation of dihydroartemisinin piperaquine treatments for malaria for a cluster randomized trial on mass drug administration from Guilin Pharma in 2018. He was also an investigator in a trial on the safety and efficacy of pyronaridine artesunate in asymptomatic malaria-infected individuals.

Jennifer Armistead reported being employed by the US President's Malaria Initiative, who in turn has supported a number of projects in the past 4 years for which funding exceeded USD 5000 but for which she did not receive any personal funding. The projects focused on the effect of indoor residual spraying on Anopheles vector behaviors and their impact on malaria transmission in the northern region of Ghana, an evaluation of pirimiphos-methyl efficacy in experimental huts when sprayed on half the usual surface against natural populations of Anopheles gambiae in Ghana, a small-scale field pilot of Partial IRS with pirimiphos-methyl in households in northern Ghana for Malaria Vector Control and evaluating the impact of attractive targeted sugar baits (ATSBs) and indoor residual spraying (IRS) in experimental huts.

Caroline Jones reported receiving research support within the last 4 years that exceeded USD 5000 for being a co-investigator on UNITAID funded project: Broad One Health Endectocide-based Malaria Intervention in Africa, for being a co-investigator on Wellcome Trust Collaborative Award: Improving the efficacy of malaria prevention in an insecticide resistant Africa, for being a co-investigator on DfID/MRC/Wellcome Trust Joint Global Health Trials funded project: Can improved housing provide additional protection against clinical malaria over current best practice? A household-randomised controlled trial and lastly for being a co-investigator on the Program for Appropriate Technology in Health (PATH) funded project: Dynamics of health care utilization strategies in the context of RTS,S/AS01vaccine introduction: a qualitative longitudinal study [in Kenya].

Neil Lobo reported receiving research funding exceeding USD 5000 and/or non-monetary support valued at over USD 1000 overall within the last 4 years towards a project investigating Spatial Repellent Products for Control of Vector-borne Diseases by SC Johnson, and a project on innovative intervention for reducing outdoor malaria transmission by Widder Bros.

Melanie Renshaw reported receiving salary support exceeding USD 5000 from the African Leaders Malaria Alliance.

In summary, five members of the ERG reported interests; it was, however, judged that none of these were relevant to the recommendations under review and it was decided that all members could fully participate particularly as the remit of the review group was limited to identifying factual errors, providing clarity and commenting on implications for implementation not changing the recommendations formulated by the GDG. It was concluded that their expertise in some of these areas would be valuable, particularly on implementation considerations and factors to be considered associated with gender and social determinants, equity, and human rights.

No interests related to the topics of the meetings were disclosed by the methodologist or systematic review teams.

10.2 Recommendations for chemoprevention

The following outlines the constitution of the Guideline Development Group, Guideline Steering Group, and External Review Group for the chemoprevention recommendations listed below and published in 2022. Also indicated are the contributors to systematic reviews, summaries of contextual factors, AMSTAR-2 Checklist assessments and background papers, as well as the guidelines methodologist. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Recommendations

- Intermittent preventive treatment of malaria in pregnancy (4.2.1)
- Perennial malaria chemoprevention (4.2.2)
- Seasonal malaria chemoprevention (4.2.3)
- Intermittent preventive treatment of malaria in school-aged children (4.2.4)
- Post-discharge malaria chemoprevention (4.2.5)
- Mass drug administration for burden reduction (4.2.6.1)
- Mass drug administration for burden reduction in

emergency settings (4.2.6.2)

Members of the Guideline Development Group (2022)

- Professor Salim Abdulla, Chief Scientist, Ifakara Health Institute, United Republic of Tanzania (Male – Expertise: Malaria research & policy-making)
- Dr Dorothy Achu, Manager, National Malaria Control Programme, Cameroon (Female – Expertise: Malaria control, end-user perspective, service-user, case management & chemoprevention)
- Professor Joseph Amon, Director, Office of Global, Dornsife School of Public Health, Drexel University, United States of America (Male – Expertise: Human rights, epidemiology)
- Dr Anup Anvikar, Scientist, ICMR-National Institute of Malaria Research, India (Male – Expertise: Malaria research, drug resistance/AMR, malaria prevention)
- Dr Matthew Coldiron (PDMC only), Medical Epidemiologist, Epicentre / Médecins Sans Frontières (MSF), USA / France (Male – Expertise: Malaria control in emergency / fragile situations)
- The late Dr Martin De Smet, Senior Health Advisor, Médecins Sans Frontières (MSF), Belgium (Male – Expertise: Malaria control in emergency/fragile situations)
- Dr Corine Karema, Independent Consultant, African Leaders Malaria Alliance (ALMA), Rwanda (Female – Expertise: Malaria control)
- Professor Miriam Laufer, Director, Office of Student Research, University of Maryland School of Medicine, United States of America (Female – Expertise: Malaria drug resistance)
- Mrs Olivia Ngou, Executive Director, Impact Santé Afrique, Cameroon (Female – Expertise: Civil society)
- Professor Melissa Penny, Professor and Unit Head, Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland (Female – Expertise: Mathematical modelling for malaria)
- Dr Francisco Saute, Scientific Director, Manhiça Health Research Center (CISM), Mozambique (Male – Expertise: Malaria control programming & research)
- The late Dr Samuel Smith, Manager, National Malaria Control Programme, Sierra Leone (Male – Expertise: Malaria control programming)
- Dr Allan Schapira, Visiting Consultant, Bicol University College of Medicine, Phillippines (Male – Expertise: Malaria control and research)
- Professor Robert Snow, Scientist, KEMRI-Wellcome Trust collaboration, Kenya (Male – Expertise: Malaria epidemiology & control)

Members of the Guideline Steering Group (2022)

- Sheick Oumar Coulibaly, Technical Officer, Diagnostic and Laboratory Services, World Health Organization Regional Office for Africa, Brazzaville, Congo
- Mary Hamel, Senior Technical Officer, Immunization, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
- James Kelley, Technical Officer, Malaria and Neglected Tropical Diseases, World Health Organization Regional Office for the Western Pacific, Manila, Philippines
- Kim Lindblade, Team Lead, Elimination, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Özge Tuncalp Mingard, Scientist, Sexual and Reproductive Health and Research, World Health Organization, Geneva, Switzerland
- Laura Nic Lochlainn, Technical Officer, Immunizations, Vaccines and Biologicals, World Health Organization, Geneva, Switzerland
- Sarah Marks, Consultant for the World Health Organization supporting the Responsible Technical Officer
- Abdisalan Noor, Team Leader, Information for Response, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Lynda Ozor, Malaria National Programme Officer, World Health Organization Country Office, Nigeria
- Charlotte Rasmussen, Technical Officer, Diagnostics, Medicines & Resistance, World Health Organization, Geneva, Switzerland
- Lisa Rogers, Technical Officer, Nutrition and Food Safety, World Health Organization, Geneva, Switzerland
- Anthony Solomon, Medical Officer, Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland
- David Schellenberg (Responsible Technical Officer), Science Advisor, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Jackson Sillah, Medical Officer, Tropical and Vector Borne Diseases, World Health Organization Regional Office for Africa, Brazzaville, Congo
- Neena Valecha, Regional Malaria Adviser, World Health Organization Regional Office for South-East Asia, New Delhi, India
- Wilson Were, Medical Officer, Child Health and Development, World Health Organization, Geneva, Switzerland

Members of the External Review Group (2022)

- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia (Malaria Policy Advisory Group [MPAG] member)
- Mrs Valentina Buj de Lauwerier, Global Malaria and Health Partnerships Advisor, Health Section, Programme Division, UNICEF, New York, United States of America
- Professor Graham Brown, Professor Emeritus (MDA, PMC and SMC only), University of Melbourne, Australia
- Dr Caroline Jones, Senior Social Scientist, KEMRI-Wellcome Trust Research Programme, Kenya (MPAG member)
- Dr Estrella Lasry (MDA, PMC, IPTp, IPTsc, and PDMC only), Senior Disease Advisor Malaria, Technical Advice and Partnerships Department, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland
- Dr Sussann Nasr (SMC only), Senior Malaria Advisor, Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland

- Dr Harriet Pasquale, HIV/AIDS and STI Program Director, National Ministry of Health, Republic of South Sudan
- Dr Richard Steketee, Deputy Coordinator, U.S. President's Malaria Initiative (PMI), United States of America

Contributors to systematic reviews, summaries of contextual factors and AMSTAR-2 Checklist assessments (2022)

Intermittent preventive treatment of malaria in pregnancy (IPTp)

- Jordan Ahn, Emory University, Atlanta, United States of America
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Eva Rodriguez, Emory University, Atlanta, United States of America
- Professor Feiko ter Kuile, Chair in Tropical Epidemiology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
- Dr Anna Maria van Eijk, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

Perennial Malaria Chemoprevention (PMC) (formerly Intermittent Preventive Treatment in infants or IPTi)

- Dr Christina Carlson, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Laura Steinhardt, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

Seasonal malaria chemoprevention (SMC)

- Dr Achuyt Bhattarai, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Irene Cavros, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Julie Thwing, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr John Williamson, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

Intermittent preventive treatment of malaria in school-aged children (IPTsc)

- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Rose Zulliger, President's Malaria Initiative, United States Agency for International Development, Washington DC, United States of America

Post-discharge malaria chemoprevention (PDMC)

- Dr Kalifa Bojang, Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, Fajara, Gambia
- Dr Aggrey Dhabangi, Makerere University College of Health Sciences, Kampala, Uganda
- Professor Brian Greenwood, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
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- Carole Khairallah, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland
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- Dr Bjarne Robberstad, Section for Ethics and Health Economics, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
- Dr Kasia Stepniewska, Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland
- Sarah Svege, Centre for International Health and Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
- Professor Feiko ter Kuile, Chair in Tropical Epidemiology, Liverpool School of Tropical Medicine, Liverpool, United Kingdom of Great Britain and Northern Ireland

- Dr Julie Thwing, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

MDA for burden reduction

- Marisa Boily, Rollins School of Public Health, Emory University, Atlanta, United States of America
- Alexandra Busbee, Rollins School of Public Health, Emory University, Atlanta, United States of America
- Dr Julie Gutman, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Jimee Hwang, U.S. President's Malaria Initiative, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Monica Shah, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Zachary Schneider, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

MDA for burden reduction in emergency settings

- Dr Alaine Knipes, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Leah Moriarty, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Dean Sayre, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Monica Shah, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America
- Dr Nelli Westercamp, Malaria Branch, Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention, Atlanta, United States of America

Preparation of background papers (2022)

- Mr Emmanuel Bache-Bache, Centre for Tropical Medicine and Travel Medicine, Amsterdam UMC, University of Amsterdam, The Netherlands
- Professor Martin Grobusch, Head, Centre for Tropical Medicine and Travel Medicine, Amsterdam UMC, University of Amsterdam, The Netherlands
- Dr Jasper Littmann, Associate Professor, Bergen Centre for Ethics and Priority Setting, University of Bergen, Norway
- Dr Christopher Plowe, University of Maryland School of Medicine, Baltimore, United States of America

Guidelines methodologist (2022)
Dr Joseph Okebe, Senior Research Associate, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland

Declaration of interests (2022)
Members of the Guideline Development Group (GDG) were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

The relevant declared interests for the GDG are summarized as follows:

Professor Salim Abdulla declared two chemoprevention research support grants his institute receives; he is involved in one of the studies as a technical advisor. The interests were assessed as related to the overall topic of discussion on malaria chemoprevention, with one interest directly related to the topic of PMC. One interest was considered non-personal in nature, academic and financially significant, and the other was considered personal in nature, academic and financially insignificant. Professor Abdulla was allowed to join the discussions as a full member of the GDG.

Professor Joseph Amon declared a research support grant a previous employer received to fund activities related to MDA/chemoprevention for other diseases. This interest was not current and of a non-personal nature. He was allowed to join the discussions as a full member of the GDG.

The late Dr Martin De Smet declared his employment with an organization that is involved in the use of chemoprevention. This interest was of a non-personal nature and financially significant. He was allowed to join the discussions as a full member of the GDG.

Professor Miriam Laufer declared four research grants. The interests were assessed as related to the overall topic of discussion on malaria chemoprevention, with one interest directly related to the topic of IPT during pregnancy and another interest directly related to the topic of IPT in school children. The four interests were considered non-personal in nature, academic, and financially significant. Professor Laufer was also senior author for the systematic review on IPT in school children that was considered by the GDG, although she did not contribute empirical data to the review. The systematic review on IPT in school children was subjected to a third-party AMSTAR assessment and found to be of good quality. Professor Laufer was allowed to join all GDG discussions as a full member, but was a non-voting and non-chairing participant in discussions on IPT in school children.

Professor Melissa Penny declared financial research support received by her institute related to the overall topic of discussion on malaria chemoprevention, and grants that she held on the broader subject of malaria. These interests were assessed as financially significant, of a non-personal nature and academic. She was able to join the discussions as a full member of the GDG.

Dr Francisco Saute declared involvement in a relevant research project and that his employer is involved in related research

studies on malaria. This interest was considered non-personal in nature, academic and financially significant. He was allowed to join the discussions as a full member of the GDG.

Dr Allan Schapira declared his role as Member of a Board of Trustees for an organization working on malaria. He did not receive any remuneration for this role. This interest was assessed as financially insignificant and of a personal nature. Dr Schapira's position on the Board of Trustees was not seen to interfere with the discussions on malaria chemoprevention. He was allowed to join the discussions as a full member of the GDG.

Professor Robert Snow declared his employment and funding for studies on various aspects of malaria but not specifically chemoprevention. This interest was considered non-personal in nature, academic and financially significant. He was allowed to join the discussions as a full member of the GDG.

10.3 Malaria vaccine recommendation

The following outlines the constitution of MPAG, SAGE, the RTS,S/AS01 MPAG/SAGE Working Group, and the External Review Group for the recommendations drafted in 2021. Also indicated are members of the systematic review production and management team and GRADE analysis subgroup, as well as the guidelines methodologists. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Members of MPAG:

- Dr Samira Abdelrahman, Professor of Community Medicine, Faculty of Medicine, University of Gezira, Sudan
- Professor Ahmed Adeel, Professor of Medical Parasitology, College of Medicine, King Saud University, Saudi Arabia
- Emeritus Professor Graham Brown, University of Melbourne, Australia
- Professor Tom Burkot, Professor and Tropical Leader, Australian Institute for Topical Health and Medicine, James Cook University, Cairns, Australia
- Dr Gabriel Carrasquilla, Director of ASIESALUD for consultancy and research in epidemiology and public health
- Professor Maureen Coetzee, Professor and Director, Wits Research Institute for Malaria, University of the Witwatersrand, Johannesburg, South Africa
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia
- Professor Abdoulaye Djimde, Head, Molecular Epidemiology and Drug Resistance Unit, Faculty of Medicine, University of Mali, Mali
- Professor Gao Qi, Senior Professor, Jiangsu Institute of Parasitic Diseases, Wuxi, China
- Professor Azra Ghani, Chair in Infectious Disease Epidemiology, Faculty of Medicine, School of Public Health, Imperial College, London, United Kingdom of Great Britain and Northern Ireland
- Dr Caroline Jones, Senior Social Scientist, KEMRI-Wellcome Trust Research Programme, Kenya
- Dr S. Patrick Kachur, Columbia University Irving Medical Center, United States of America
- Professor Evelyn Ansah, Director, Center for Malaria Research, University of Health and Allied Sciences, Ghana
- Dr Nilima Kshirsagar, Emeritus Scientist, Indian Council of Medical Research, India
- Dr Fedros Okumu, Public Health Researcher and Director of Science at Ifakara Health Institute, United Republic of Tanzania
- Dr Arantxa Roca Feltrer, Head of Surveillance, Monitoring and Evaluation, Malaria Consortium, Madagascar
- Professor Dyann Wirth, Director, Harvard Life Sciences, Harvard T.H. Chan School of Public Health, United States of America (MPAG Chair)

Members of SAGE:

- Professor Rakesh Aggarwal, Director, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), India
- Professor Alejandro Cravioto, Professor Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico (SAGE Chair)
- Dr Ilesh Jani, Director General, National Institute of Health, Ministry of Health, Mozambique
- Dr Jaleela Jawad, Head of the Immunization Group, Public Health Directorate, Ministry of Health, Bahrain
- Dr Sonali Kochhar, Clinical Associate Professor, Department of Global Health, University of Washington, United States of America
- Professor Noni MacDonald, Professor of Paediatrics, Division of Paediatric Infectious Diseases, Dalhousie University, Canada
- Professor Shabir Madhi, Professor of Vaccinology, University of the Witwatersrand, South Africa
- Professor Peter McIntyre, Professor, Department of Women's and Children's Health, Dunedin School of Medicine, University of Otago, New Zealand
- Dr Ezzeddine Mohsni, Senior Technical Adviser, Global Health Development (GHD), The Eastern Mediterranean Public Health Network (EMPHNET), Jordan
- Professor Kim Mulholland, Murdoch Children's Research Institute, University of Melbourne, Australia
- Professor Kathleen Neuzil, Director, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, United States of America
- Dr Hanna Nohynek, Chief Physician, Finnish Institute for Health and Welfare (THl), Finland
- Dr Folake Olayinka, USAID Immunization Team Lead, United States of America
- Professor Punnee Pitisuttithum, Head, Department of Clinical Tropical Medicine, Mahidol University, Thailand
- Professor Andrew J. Pollard, Professor, Department of Paediatrics, University of Oxford, United Kingdom of Great Britain and Northern Ireland

Members of the RTS,S/AS01 MPAG/SAGE Working Group

- Professor Ifedayo Adetifa, KEMRI-Wellcome Trust Research Programme, Kenya
- Professor Nick Andrews, Public Health England, United Kingdom of Great Britain and Northern Ireland
- Dr Dafrossa Cyrily Lyimo, Independent consultant (and former National Immunization and Vaccine Development Programme Manager), United Republic of Tanzania
- Dr Corine Karema, Independent consultant (and former Director of the Rwanda National Malaria Control Programme), Rwanda
- Dr Eusebio Macete, Centro de Investigação em Saúde de Manhiça, Mozambique (Co-Chair)
- Professor Kim Mulholland, Murdoch Children's Research Institute, Australia
- Professor Kathleen Neuzil, Center for Vaccine Development and Global Health (CVD), University of Maryland School of Medicine, United States of America
- The late Ms Adelaide Shearley, John Snow Inc., Zimbabwe
- Professor Peter Smith, London School of Hygiene & Tropical Medicine, United Kingdom of Great Britain and Northern Ireland (Chair)
- Professor S. Patrick Kachur, Mailman School of Public Health, Columbia University, United States of America

Members of the RTS,S/AS01 MPAG/SAGE Working Group Secretariat

- Dr Pedro Alonso, Global Malaria Programme
- Dr Tracey Goodman, Expanded Programme on Immunization
- Mr John Grove, Quality Assurance / Norms & Standards
- Dr Joachim Hombach, Agenda, Policy & Strategy
- Dr Melanie Marti, Agenda, Policy & Strategy
- Dr Kate O'Brien, Immunization, Vaccines and Biologicals
- Dr Vaseeharan Sathiyamoorthy, Research for Health
- Rapporteur: Ms Cynthia Bergstrom, Consultant for WHO

Members of the WHO Editorial Board

- Dr Madhava Ram Balakrishnan
- Dr Shalini Desai, Expanded Programme on Immunization
- Ms Eliane Furrer, Immunization, Vaccines and Biologicals
- Ms Tracey Goodman, Expanded Programme on Immunization
- Dr Mary Hamel, Immunization, Vaccines and Biologicals
- Dr Joachim Hombach, Immunization, Vaccines and Biologicals
- Dr Dianliang Lei, Norms, Standards and Biologicals
- Dr Melanie Marti, Immunization, Vaccines and Biologicals
- Dr Marie-Perre Preziosi, Immunization, Vaccines and Biologicals
- Dr David Schellenberg, Global Malaria Programme
- Ms Erin Shutes, Global Malaria Programme

Members of the Peer review group (External review group)

Members of the Peer review group include SAGE, MPAG, WHO Regional Offices, external subject matter experts, selected national immunization and malaria programme managers, other interested parties (who have not been involved in the process to that point) and industry. Request for peer-review from industry is coordinated through the International Federation of Pharmaceutical Manufacturers Association and the Developing Country Vaccine Manufacturer Network. The list of external reviewers is available upon request from the SAGE secretariat.

Guidelines methodologist and systematic review team

Two methodologists from the Cochrane Response – Gemma Villanueva and Nicholas Henschke – were commissioned to support the development of the malaria vaccine recommendations. They provided a systematic review of evidence, applied the PICO framework to conduct evidence assessments using GRADE, and supported the SAGE/MPAG Working Group in the transparent formulation of evidence-informed recommendations.

Designated writer/editor

Dr Laurence Slutsker drafted and consolidated a full evidence review for the SAGE/MPAG Working Group. WHO contracted Dr Slutsker under an Agreement for Performance of Work (APW).

Declaration of interests

All nine SAGE/MPAG Working Group members updated their Declarations of Interest in advance of the meeting. These were assessed by the WHO Secretariat. Six members reported interests; it was assessed that all members could fully participate. The full summary of interests for the SAGE/MPAG Working Group is available on the WHO Malaria Vaccine Implementation Programme website.

All 15 SAGE members participating in the meeting updated their Declarations of Interest in advance of the meeting. These were assessed by the WHO Secretariat. Eleven SAGE members reported interests and zero SAGE members recused themselves from the discussion and decision-making during the malaria vaccine session. The full summary of interests for SAGE members is available on the meeting website.

All 17 MPAG members participating in the meeting updated their Declarations of Interest in advance of the meeting. These were assessed by the WHO Secretariat. Thirteen members reported interests and five MPAG members reported relevant interests. Three members (Evelyn Ansah, Abdoulaye Djimde and Azra Ghani) recused themselves from the discussion and decision-making during the malaria vaccine session. It was assessed that the remaining members could fully participate in all sessions. The full summary of interests for MPAG members is available on the meeting website.

- Professor Evelyn Ansah, University of Health & Allied Sciences, Ghana: declared research support and her role as

the Ghana Co-Investigator on funding from PATH for the Health Utilization Study on a qualitative assessment of the pilot implementation of RTS,S. This interest was assessed as non-personal, specific and financially significant.

- Professor Abdoulaye Djimde, Head, Molecular Epidemiology Drug Resistance Unit, University of Mali, Mali: declared his role as a sub-investigator on the RTS,S – SMC trial which contributed minimal salary support through the London School of Tropical Medicine & Hygiene. Professor Djimde was a co-author on: Chandramohan D, Zongo I, Sagara I, Cairns M, Yerbanga RS, Diarra M, Nikièma F, Tapily A, Sompougdou F, Issiaka D, Zoungrana C, Sanogo K, Haro A, Kaya M, Sienou AA, Traore S, Mahamar A, Thera I, Diarra K, Dolo A, Kuepfer I, Snell P, Milligan P, Ockenhouse C, Ofori-Anyinam O, Tinto H, Djimde A, Ouédraogo JB, Dicko A, Greenwood B. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. N Engl J Med. 2021 Sep 9;385(11):1005-1017. doi: 10.1056/NEJMoa2026330. Epub 2021 Aug 25. PMID: 34432975. This interest is assessed as non-personal, specific and financially significant.
- Professor Azra Ghani, Infectious Diseases Epidemiology, Imperial College, UK: declared research support to Imperial College from the Global Fund on different projects related to modelling impact estimates for malaria including global scenarios that incorporate RTS,s from 2016 to 2019 and in 2021. This interest is assessed as non-personal, specific and financially significant; and research support funding from multiple organizations for work on malaria and COVID-19 research including Bill & Melinda Gates Foundation (BMGF), MVI, MMV, IVCC, MRC, Wellcome Trust, NIH over three years (current). Included data analysis and modelling of public health impact of routine implementation and assessment of seasonal implementation related to RTS,s. This interest is assessed as non-personal, specific and financially significant.
- Professor Caroline Jones, Senior Social Scientist, KEMRI-Wellcome Trust Research, Kenya: declared her role as a mentor for a post-doctorate student on the study conducted in collaboration with PATH entitled “Dynamics of health care utilization strategies in the context of RTS,S/AS01 vaccine introduction: a qualitative longitudinal study in Kenya” (2018- 2020). The institution received support for the post-doc who has now left the institution. This interest is assessed as non-personal, specific and non-financially significant.* Although specific to the malaria vaccine, the interest was assessed as that of the post-doc, not Professor Jones as the mentor.
- Professor Dyann Wirth, Richard Pearson Strong Professor and Chair, Harvard T.H. Chan School of Public Health, USA: declared a research grant to Harvard University received from PATH and her role as the Principal Investigator for Mal095 using RTS,S to look at the issue of allele specific immunity. This interest is assessed as non-personal, specific and financially significant.* Although related to the malaria vaccine, this work is to understand gaps in immunity provided by RTS,S and will inform the development of future malaria vaccines. This research is not being considered as evidence for the decision on the malaria vaccine and the work will continue regardless of the outcome.

10.4 Recommendations for treatment

Since the first and second editions of the Guidelines were issued in 2006 and 2010, respectively, WHO's methods for preparing guidelines have continued to evolve. The third edition of the *Guidelines for the treatment of malaria* was prepared in accordance with the updated WHO standard methods for guideline development *[1]*. This involved planning, “scoping” and needs assessment, establishment of a GDG, formulation of key questions (PICO questions: population, participants or patients; intervention or indicator; comparator or control; outcome), commissioning of reviews, Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and making recommendations. This method ensures a transparent link between the evidence and the recommendations. The GRADE system is a uniform, widely adopted approach based on explicit methods for formulating and evaluating the strength of recommendations for specific clinical questions on the basis of the robustness of the evidence.

The GDG, co-chaired by Professor Fred Binka and Professor Nick White (other participants are listed below), organized a technical consultation on preparation of the third edition of the Guidelines. Declarations of conflicts of interest were received from all participants. A WHO Guideline Steering Group facilitated the scoping meeting, which was convened in February 2013, to set priorities and identify which sections of the second edition of the Guidelines were to be reviewed and to define potential new recommendations. Draft PICO questions were formulated for collation and review of the evidence. A review of data on pharmacokinetics and pharmacodynamics was considered necessary to support dose recommendations, and a subgroup was formed for this purpose.

After the scoping meeting, the Cochrane Infectious Diseases Group at the Liverpool School of Tropical Medicine in Liverpool, United Kingdom, was commissioned to undertake systematic reviews and to assess the quality of the evidence for each priority question. The reviews involved extensive searches for published and unpublished reports of trials and highly sensitive searches of the Cochrane Infectious Diseases Group trials register, the Cochrane Central Register of Controlled Trials, MEDLINE®, Embase and LILACS. All the reviews have been published on line in the Cochrane Library. When insufficient evidence was available from randomized trials, published reviews of non-randomized studies were considered.

The subgroup on dose recommendations reviewed published studies from MEDLINE® and Embase on the pharmacokinetics and pharmacodynamics of antimalarial medicines. For analyses

of pharmacokinetics and simulations of dosing, they used raw clinical and laboratory data from the Worldwide Antimalarial Resistance Network on the concentrations of antimalarial agents in plasma or whole blood measured with validated assays in individual patients. The data had either been included in peer-reviewed publications or been submitted to regulatory authorities for drug registration. Population pharmacokinetics models were constructed, and the plasma or whole blood concentration profiles of antimalarial medicines were simulated (typically 1000 times) for different weight categories.

The GDG met in two technical meetings, in November 2013 and June 2014, to develop and finalize recommendations based on the GRADE tables constructed on the basis of answers to the PICO questions. The Guidelines were written by a subcommittee of the group. At various times during preparation of the Guidelines, sections of the document or recommendations were reviewed by external experts and users who were not members of the group; these external peer reviewers are listed below. Treatment recommendations were agreed by consensus, supported by systematic reviews and review of information on pharmacokinetics and pharmacodynamics. Areas of disagreement were discussed extensively to reach consensus; voting was not required.

Members of the GDG

- Professor K.I. Barnes, Division of Clinical Pharmacology, University of Cape Town, South Africa
- Professor F. Binka, (*co-Chair*), University of Health and Allied Sciences, Ho, Volta Region, Ghana
- Professor A. Bjorkman, Division of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
- Professor M.A. Faiz, Dev Care Foundation, Dhaka, Bangladesh
- Professor O. Gaye, Service de Parasitologie, Faculté de Médicine, Université Cheikh Anta Diop, Dakar-Fann, Senegal
- Dr S. Lutalo, King Faisal Hospital, Kigali, Rwanda
- Dr E. Juma, Kenya Medical Research Institute, Centre for Clinical Research, Nairobi, Kenya
- Dr A. McCarthy, Tropical Medicine and International Health Clinic, Division of Infectious Diseases, Ottawa Hospital General Campus, Ottawa, Canada
- Professor O. Mokuolu, Department of Paediatrics, University of Ilorin Teaching Hospital, Ilorin, Nigeria
- Dr D. Sinclair, International Health Group, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr L. Slutsker, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America
- Dr E. Tjitra, National Institute of Health and Development, Ministry of Health, Jakarta, Indonesia
- Dr N. Valecha, National Institute of Malaria Research, New Delhi, India
- Professor N. White (*co-Chair*), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Members of the sub-group on dose recommendations

- Professor K. Barnes, *(co-Chair)*
- Professor F. Binka
- Dr S. Lutalo
- Dr E. Juma
- Professor O. Mokuolu
- Dr S. Parikh, Department of Medicine, Yale University School of Public Health, Connecticut, USA
- Dr D. Sinclair
- Dr J. Tarning, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
- Dr D.J. Terlouw, Malawi-Liverpool Wellcome Trust Clinical Research Programme, Blantyre, Malawi
- Professor N. White *(co-Chair)*

Guideline Steering Group

- Dr A. Bosman, Global Malaria Programme, WHO, Geneva, Switzerland
- Dr K. Carter, Malaria Regional Adviser, WHO Regional Office for the Americas, Washington D.C., United States of America
- Dr N.Dhingra-Kumar, Health Systems Policies and Workforce, WHO, Geneva, Switzerland
- Dr M. Gomes, Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland
- Dr P.E. Olumese (*Secretary*), Global Malaria Programme WHO, Geneva, Switzerland
- Dr F. Pagnoni, Special Programme for Research and Training in Tropical Diseases, WHO, Geneva, Switzerland
- Dr A.E.C. Rietveld, Global Malaria Programme WHO, Geneva, Switzerland
- Dr P. Ringwald, Global Malaria Programme WHO, Geneva, Switzerland
- Dr M. Warsame, Global Malaria Programme WHO, Geneva, Switzerland
- Dr W. Were, Child and Adolescent Health, WHO, Geneva, Switzerland

External reviewers

- Dr F. ter-Kuile, Liverpool School of Tropical Medicine, Liverpool, United Kingdom
- Dr R. McGready, Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
- Professor F. Nosten, Shoklo Malaria Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Guidelines methodologist

Professor P. Garner, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Declaration of interests

Participants in the technical consultation for the review of the *Guidelines for the treatment of malaria* and the external expert reviewers of the Guidelines reported relevant interests, in accordance with WHO procedures. These were discussed extensively by the committee. Although it was considered that none of the declared interests had direct relevance to the

deliberations or recommendations of the meeting, the panel members with declared interests were excluded from the subcommittees on GRADE and recommendations and the drafting group. The declared interests, as per WHO regulations, were reviewed through the Legal Department of WHO.

Dr K. Barnes reported being a grants co-recipient from the Medicines for Malaria Venture to undertake clinical trials to evaluate antimalarial medicines.

Dr F. Binka reported being a member of the INDEPTH network that was a recipient of a research grant from the Bill & Melinda Gates Foundation to conduct Phase IV post licensure studies on "Euratesim".

Dr P. Garner reported receiving a grant from the Department for International Development (UK) to help ensure global guidelines and decisions are based on reliable evidence.

Dr N. Valecha reported serving as an investigator for a clinical trial supported by the Department of Science and Technology India, and Ranbaxy Laboratories Limited. There were no monetary benefits and no conflicts with the subject of this review.

Professor N. White reported being an advisor to all pharmaceutical companies developing new antimalarial medicines. This is done on a pro bono basis; it did not include consultancy fees or any form of remuneration.

Members of the GDG (2022)

- Dr Dorothy Achu, Programme Manager, National Malaria Control Programme, Yaoundé, Cameroon
- Professor Karen Barnes, Clinical Pharmacology, University of Cape Town, South Africa
- Dr Constance Bart-Plange, Independent Malaria Consultant, Accra, Ghana
- Professor Adrianus Dondorp, Deputy Director, Mahidol Oxford Tropical Medicine Research Unit, Mahidol University, Thailand
- Professor Sanjeev Krishna, (Co-chair) Molecular Parasitology and Medicine, St George's University London, United Kingdom of Great Britain and Northern Ireland
- Professor Marcus Lacerda, Infectious Disease Researcher, Tropical Medicine Foundation
- Dr Miriam Laufer, Director, Office of Student Research, University of Maryland School of Medicine, United States of America
- Professor Rose Leke, Professor, Immunology and Parasitology, Faculty of Medicine and Biomedical Sciences, University of Yaoundé, Cameroon
- Professor Olugbenga Mokuolu, (Co-chair) Professor, Paediatrics & Child Health, Department of Paediatrics, College of Health Sciences, University of Ilorin, Nigeria
- Professor Bernhards Ogutu, Senior Principal Clinical Research Scientist, Kenya Medical Research Institute, Kenya
- Professor Stephen Rogerson, Professor, Department of Infectious Diseases, Doherty Institute, University of Melbourne, Australia
- Professor Philip Rosenthal, Professor, Department of Medicine, University of California, United States of America
- Professor Terrie Taylor, Professor, Department of Osteopathic Medical Specialties, College of Osteopathic Medicine, Michigan State University, United States of America

Members of the Guidelines Steering Group (2022)

- Andrea Bosman, Coordinator, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Maurice Bucagu, Family, Women, Children and Adolescents, World Health Organization, Geneva, Switzerland
- Maria Bustos, Technical Officer, Malaria Control, WHO Country Office, Thailand
- Jane Cunningham, Technical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Bayo Fatunmbi, Technical Officer, Malaria, WHO Country Office, Uganda
- Elizabeth Juma, WHO Country Office, Ghana
- Roberto Montoya, Regional Malaria Adviser, WHO Regional Office for the Americas, United States of America
- Deus Mubangizi, Coordinator, Prequalification Regulation and Prequalification, Access to Medicines and Health Products, World Health Organization, Geneva, Switzerland
- Peter Olumese, (Secretary) Medical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Shanthi Pal, Technical Officer, Pharmacovigilance, Regulation and Safety/ Regulation and Prequalification, World Health Organization, Geneva, Switzerland
- Pascal Ringwald, Medical Officer, Global Malaria Programme, World Health Organization, Geneva, Switzerland
- Neena Valecha, Regional Malaria Adviser, WHO Regional Office for South-East Asia, India
- Wilson Were, Medical Officer, Child Health and Development HQ/UHL/MCA/CHD, Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland
- Ghasem Zamani, Regional Malaria Adviser, WHO Regional Office for the Eastern Mediterranean, Egypt

Members of the External Review Group (ERG) (2022)

- Professor Ahmed Adeel, Independent Consultant, United States of America
- Professor Umberto d'Alessandro, Director, Medical Research Council Unit, Gambia

Members of the Systematic Review Team members (2022)

- Stephanie Dellicour, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Martha Chaplin, Liverpool School of Tropical Medicine, Centre for Evidence Synthesis, United Kingdom of Great

Britain and Northern Ireland
- Paul Garner, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, Centre for Evidence Synthesis, United Kingdom of Great Britain and Northern Ireland
- Patricia Graves, College of Public Health Medical & Vet Sciences, Australian Institute of Tropical Health and Medicine, Australia
- Jenny Hill, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Paul Hine, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Feiko ter Kuile, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Makoto Saito, WorldWide Antimalarial Resistance Network, Institute of Medical Science, University of Tokyo, Japan
- Kasia Stepniewska, WorldWide Antimalarial Resistance Network, Infectious Disease Data Observatory, Oxford, United Kingdom of Great Britain and Northern Ireland
- Melissa Taylor, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland
- Rebecca Thomas, Cochrane Infectious Diseases Group, Liverpool School of Tropical Medicine, United Kingdom of Great Britain and Northern Ireland

Guidelines methodologist and co-chair (2022)

Leonila Dans, Independent Methodologist and World Health Organization consultant, Philippines

Declarations of interest (2022)
Members of the GDG, the ERG, the methodologist and members of systematic review teams who were commissioned to undertake reviews by WHO were requested to declare any interests related to the topic of the meeting. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed. Below is a summary of the declared interests of members.

Professor Karen Barnes declared that she is currently serving as staff with Oxford University in the WorldWide Antimalarial Resistance Network, Infectious Disease Data Observatory, receiving around US$ 3000 per month, and her institution University of Cape Town is currently running projects on antimalarial pharmacology translational research with funding from Bill & Melinda Gates Foundation and the South African Ministry of Health of around US$ 450 000. She is not a direct beneficiary of this funding. Although the funding was for studies with antimalarial medicines, , it is not related to the subject of this Guideline. It was judged that none of these research projects or appointments had any direct relationship to the agenda of this meeting. These declarations were assessed as non-personal and non-specific, and of no direct or indirect personal or financial benefit; therefore, they were considered non-significant

Professor Arjen Dondrop declared that, starting in February 2021, he has chaired the Malaria Advisory Council of Novartis, but he does not receive remuneration for this consultancy. In 2014, his research group received a grant from Guilin Pharma (now Fosun) to study intravenous artesunate. His group is currently investigating the efficacy and safety of triple ACTs for uncomplicated falciparum malaria in the context of increasing antimalarial drug resistance. One of the triple ACTs, artemether-lumefantrine-amodiaquine, is provided for free by Fosun Pharma. These declarations were assessed as not directly related to any of the medicines being discussed by this GDG. These declarations were assessed as non-personal and non-specific, and of no direct or indirect personal or financial benefit; therefore, they were considered non-significant.

Professor Lacerda declared institutional grants from Medicines for Malaria Venture and Bill & Melinda Gates Foundation to study the operational feasibility of appropriate P. vivax radical cure with tafenoquine or primaquine. These interests were assessed as being of no direct or indirect personal or financial benefit; therefore, they were considered non-significant.

Professor Terrie Taylor declared serving on two advisory boards of Novartis AG and receiving US$ 3125 in 2019; her University and research group has received several rounds of research funding from the United States National Institutes of Health. None of these were directly related to the considerations of the GDG, and it was determined that she could join the discussions of the group. These interests were assessed as non-personal and non-specific.

10.5 Recommendations for interventions in the final phase of elimination and prevention of re-establishment

The following outlines the constitution of the Guidelines Development Group, Guidelines Steering Group, and External Review Group for the recommendations listed below, published in 2022. Also indicated are members of the systematic review production and management team as well as the guidelines methodologist. Final compositions of these groups are shown as of the date of finalization of the Guidelines.

Recommendations

- Mass drug administration for reduction of transmission of *P. falciparum* in very low to low transmission settings (4.2.6.3)
- Mass drug administration for reduction of transmission of *P. falciparum* in moderate to high transmission settings (4.2.6.4)
- Mass drug administration for reduction of transmission of *P. vivax* (4.2.6.5)
- Mass relapse prevention to reduce transmission of *P. vivax* (4.2.6.6)
- Mass testing and treatment (6.1.1)
- Targeted drug administration (6.2.1)
- Targeted testing and treatment (6.2.2)
- Targeted testing and treatment at points of entry (6.2.3)

- Reactive drug administration (6.3.1)
- Reactive case detection and treatment (6.3.2)
- Reactive indoor residual spraying (6.3.3)

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Preparation of background papers (2022)

- Dr Gillian Stresman, Assistant Professor, London School of Hygiene and Tropical Medicine, London, United Kingdom of Great Britain and Northern Ireland

Guidelines methodologist (2022)

- Professor Elie Akl, Department of Medicine, American University of Beirut, Beirut, Lebanon

Declaration of interests (2022)

Members of the Guideline Development Group were requested to declare any interests related to the topic of the meeting. Additionally, The WHO Secretariat conducted due diligence online searches for other interests or public statements that could constitute a potential conflict of interests. Any potential conflicts identified through the diligence search were referred back to the GDG member to update their DOI. The declared interests, as per WHO regulations, were assessed by the WHO Secretariat with support from the Office of Compliance, Risk Management and Ethics as needed.

The relevant declared interests for the Guideline Development Group and their management are summarized as follows:

Dr Kevin Baird reported research support for a clinical trial of tafenoquine combined with ACT for radical cure of *P. vivax*. It was determined that these interests do not present a conflict with respect to the meeting but would be disclosed to the GDG members.

Professor Teun Bousema reported research funding related to evaluating the impact of MDA and MTaT on malaria transmission. It was determined that these interests do not present a serious conflict with respect to the meeting but would be disclosed to the GDG members.

Professor Donicia Gamboa reported research support from FIND diagnostics to serve as a co-principle investigator on a study to validate a malaria rapid diagnostic test. It was determined that

this interest does not present a serious conflict with respect to the meeting but would be disclosed to the GDG members

Dr Marcus Lacerda reported research interests related to use of tafenoquine, an 8-aminoquinoline, for radical cure of *P. vivax* infections. It was determined that this interest does not present a conflict with respect to the meeting but would be disclosed to GDG members.

Dr Kevin Marsh reported that he is an advisor to several WHO, USAID, Malaria Vaccine Initiative and PATH groups. It was determined that this interest does not present a conflict with respect to the meeting topics but would be disclosed to GDG members.

Dr Kamini Mendis reported that she is the Director of the Board of the Asia Pacific Leaders Malaria Alliance, and that she wrote the following paper published in the Malaria Journal in 2019, on invitation by the journal to participate in a debate series. The specific topics were pre-defined by the journal, and the authors could choose among the topics presented. Mendis K. (2019). Mass drug administration should be implemented as a tool to accelerate elimination: against. Malaria Journal. 18:281. https://doi.org/10.1186/s12936-019-2907-7. As the paper could be perceived as presenting a bias against implementation of MDA, Dr Mendis was recused from making judgments related to any of the MDA recommendations.

Professor Melissa Penny declared financial research support her institute receives related to the overall topic of discussion on malaria elimination, and grants that she holds on the broader subject of malaria. It was determined that this interest does not present a conflict with respect to the meeting but would be disclosed to GDG members.

Dr Allan Schapira reported that he is on the Board of Trustees of the UK-based charity, Malaria Consortium. It was determined that this interest does not present a conflict with respect to the meeting but would be disclosed to GDG members.

Dr Chansuda Wongsrichanalai reported two interests, a paid consultancy to Medicines for Malaria Venture on radical therapy for *P. vivax* and travel and per diem to attend international *P. vivax* meetings. It was determined that these interests do not present a conflict with respect to the meeting topics but would be disclosed to GDG members.

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Annex: All evidence profiles, sorted by sections

1. ABBREVIATIONS

2. EXECUTIVE SUMMARY

2.1. Guideline Translations

3. INTRODUCTION

4. PREVENTION

4.1. Vector control

4.1.1. Interventions recommended for large-scale deployment

Clinical Question/ PICO

Population:	Adults and children living in areas with ongoing malaria transmission
Intervention:	Pyrethroid-only nets or curtains
Comparator:	No nets or curtains

Summary

Of the 23 included studies, 21 were cluster RCTs (six with households as the cluster and 15 with villages as the cluster) and two were individual RCTs; 12 studies compared ITNs with untreated nets, and 11 studies compared ITNs with no nets. Based on WHO regions, 12 studies were conducted in Africa (Burkina Faso, Republic of Côte d'Ivoire, the Republic of Cameroon, Republic of the Gambia [two studies], Republic of the Ghana, the Republic of Kenya [three studies], the Republic of Madagascar, the Republic of Sierra Leone and the United Republic of Tanzania), six in the Americas (the Bolivarian Republic of Venezuela, the Republic of Colombia, the Republic of Ecuador, the Republic of Nicaragua [two studies] and the Republic of Peru), four in South-East Asia (Republic of India, the Republic of Union of Myanmar, The Kingdom of Thailand [two studies]) and one in the Eastern Mediterranean (the Islamic Republic of Pakistan).

Pyrethroid-only nets or curtains versus no ITNs or curtains:
Pyrethroid-only nets or curtains reduce the child mortality from all causes compared to no nets or curtains.
(Rate ratio: 0.83; 95% CI: 0.77–0.89; five studies; high-certainty evidence)
Pyrethroid-only nets or curtains reduce the incidence of uncomplicated episodes of P. falciparum malaria compared to no nets or curtains.
(Rate ratio: 0.54; 95% CI: 0.48–0.60; five studies; high-certainty evidence)
Pyrethroid-only nets or curtains reduce the prevalence of P. falciparum malaria compared to no nets or curtains
(ate ratio: 0.69; 95% CI: 0.54–0.89; five studies; high-certainty evidence)
Pyrethroid-only nets or curtains may have little or no effect on P. vivax prevalence malaria compared to no nets or curtains.
(Risk ratio: 1.00; 95% CI: 0.75–1.34; two studies; low-certainty evidence)
Pyrethroid-only nets or curtains reduce the incidence of severe malaria episodes compared to no nets or curtains.
(Rate ratio: 0.56; 95% CI: 0.38–0.82; two studies; high-certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** No nets or curtains	**Intervention** Pyrethroid-treated nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality	Relative risk 0.83 (CI 95% 0.77 — 0.89) Based on data from 129,714 participants in 5 studies. (Randomized controlled)	33 per 1000 Difference:	27 per 1000 **6 fewer per 1000** (CI 95% 8 fewer — 4 fewer)	High	Pyrethroid-only nets or curtains reduce the child mortality from all causes compared to no nets or curtains.
P. falciparum uncomplicated episodes	Relative risk 0.54 (CI 95% 0.48 — 0.6) Based on data from 32,699 participants in 5 studies. (Randomized controlled)	178 per 1000 Difference:	96 per 1000 **82 fewer per 1000** (CI 95% 93 fewer — 71 fewer)	High	Pyrethroid-only nets or curtains reduce the incidence of uncomplicated episodes of P. falciparum malaria compared to no nets or curtains.
P. falciparum uncomplicated episodes (cumulative incidence)	Relative risk 0.44 (CI 95% 0.31 — 0.62) Based on data from 10,964 participants in 2 studies. (Randomized controlled)	137 per 1000 Difference:	60 per 1000 **77 fewer per 1000** (CI 95% 95 fewer — 52 fewer)	Moderate Due to serious indirectness [1]	Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated episodes of P. falciparum malaria compared to no nets or curtains.
P. falciparum prevalence	Relative risk 0.69 (CI 95% 0.54 — 0.89) Based on data from 17,860 participants in 5 studies. (Randomized controlled)	120 per 1000 Difference:	83 per 1000 **37 fewer per 1000** (CI 95% 55 fewer — 13 fewer)	High	Pyrethroid-only nets or curtains reduce the prevalence of P. falciparum malaria compared to no nets or curtains.
P. vivax uncomplicated episodes (cumulative incidence)	Relative risk 0.61 (CI 95% 0.48 — 0.77) Based on data from 10,972 participants in 2 studies. (Randomized controlled)	149 per 1000 Difference:	91 per 1000 **58 fewer per 1000** (CI 95% 77 fewer — 34 fewer)	Moderate Due to serious indirectness [2]	Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated episodes of P. vivax malaria compared to no nets or curtains.
P. vivax prevalence	Relative risk 1 (CI 95% 0.75 — 1.34) Based on data from 9,900 participants in 2 studies. (Randomized controlled)	130 per 1000 Difference:	130 per 1000 **0 fewer per 1000** (CI 95% 32 fewer — 44 more)	Low Due to serious indirectness and serious imprecision [3]	Pyrethroid-only nets or curtains may have little or no effect on P. vivax prevalence malaria compared to no nets or curtains.

Outcome Timeframe	**Study results and measurements**	**Comparator** No nets or curtains	**Intervention** Pyrethroid-treated nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Any Plasmodium spp. uncomplicated episodes	Relative risk 0.5 (CI 95% 0.28 — 0.9) Based on data from 5,512 participants in 1 studies. (Randomized controlled)	256 per 1000 Difference:	128 per 1000 **128 fewer per 1000** (CI 95% 184 fewer — 26 fewer)	Low Due to very serious indirectness [4]	Pyrethroid-only nets or curtains curtains probably reduce the incidence of uncomplicated episodes of malaria compared to no nets or curtains.
Severe malaria episodes	Relative risk 0.56 (CI 95% 0.38 — 0.82) Based on data from 31,173 participants in 2 studies. (Randomized controlled)	15 per 1000 Difference:	8 per 1000 **7 fewer per 1000** (CI 95% 9 fewer — 3 fewer)	High	Pyrethroid-only nets or curtains reduce the incidence of severe malaria episodes compared to no nets or curtains.

1. **Inconsistency: no serious. Indirectness: serious. Imprecision: no serious. Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: serious. Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: serious. Imprecision: serious. Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: very serious. Imprecision: no serious. Publication bias: no serious.**

Attached Images

References

55. Pryce J, Richardson M, Lengeler C : Insecticide-treated nets for preventing malaria. Cochrane Database of Systematic Reviews 2018;(11): Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Pyrethroid-only nets or curtains
Comparator: Untreated nets or curtains

Summary

Of the 23 included studies, 21 were cluster RCTs (six with households as the cluster and 15 with villages as the cluster) and two were individual RCTs; 12 studies compared ITNs with untreated nets, and 11 studies compared ITNs with no nets. Based on WHO regions, 12 studies were conducted in Africa (Burkina Faso, Republic of Cote d'Ivoire, Cameroon, Gambia (two studies), Ghana, Kenya (three studies), Madagascar, Sierra Leone, United Republic of Tanzania), six in the Americas (Colombia, Ecuador, Nicaragua (two studies), Peru and Venezuela) and four in South-East Asia (India, Myanmar, Thailand (two studies)) and one in the Eastern Mediterranean (Pakistan).

Pyrethroid-only nets or curtains versus untreated nets or curtains:
Pyrethroid-only nets or curtains probably reduce all-cause child mortality compared to untreated nets or curtains.
(Rate ratio: 0.67; 95% CI (0.36–1.23); two studies; moderate certainty evidence)
Pyrethroid-only nets or curtains reduce the incidence of uncomplicated P. falciparum malaria episodes compared to untreated nets or curtains.
(Rate ratio: 0.58; 95% CI (0.43–0.79); five studies; high certainty evidence)

Pyrethroid-only nets or curtains reduce the prevalence of P. falciparum malaria compared to untreated nets or curtains.
(Risk ratio: 0.81; 95% CI (0.68–0.97); four studies; high certainty evidence)
Pyrethroid-only nets or curtains may reduce the incidence of uncomplicated P. vivax malaria episodes compared to untreated nets or curtains.
(Rate ratio: 0.73; 95% CI (0.51–1.05); three studies; low certainty evidence)
he evidence is very uncertain about the effect of pyrethroid-only nets or curtains on P. vivax prevalence compared to untreated nets or curtains.
(Risk ratio: 0.52; 95% CI (0.13–2.04); two studies; very low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** Untreated nets or curtains	**Intervention** Pyrethroid-only nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality	Relative risk 0.67 (CI 95% 0.36 — 1.23) Based on data from 32,721 participants in 2 studies. (Randomized controlled)	19 per 1000 Difference:	13 per 1000 **6 fewer per 1000** (CI 95% 12 fewer — 4 more)	Moderate Due to serious imprecision [1]	Pyrethroid-only nets or curtains probably reduce all-cause child mortality compared to untreated nets or curtains.
P. falciparum uncomplicated episodes	Relative risk 0.58 (CI 95% 0.43 — 0.79) Based on data from 2,084 participants in 5 studies. (Randomized controlled)	180 per 1000 Difference:	104 per 1000 **76 fewer per 1000** (CI 95% 103 fewer — 38 fewer)	High	Pyrethroid-only nets or curtains reduce the incidence of uncomplicated P. falciparum malaria episodes compared to untreated nets or curtains.
P. falciparum prevalence	Relative risk 0.81 (CI 95% 0.68 — 0.97) Based on data from 300 participants in 4 studies. (Randomized controlled)	85 per 1000 Difference:	69 per 1000 **16 fewer per 1000** (CI 95% 27 fewer — 3 fewer)	High	Pyrethroid-only nets or curtains reduce the prevalence of P. falciparum malaria compared to untreated nets or curtains.
P. vivax uncomplicated episodes	Relative risk 0.73 (CI 95% 0.51 — 1.05) Based on data from 1,771 participants in 3 studies. (Randomized controlled)	143 per 1000 Difference:	104 per 1000 **39 fewer per 1000** (CI 95% 70 fewer — 7 more)	Low Due to serious indirectness, Due to serious imprecision [2]	Pyrethroid-only nets or curtains may reduce the incidence of uncomplicated P. vivax malaria episodes compared to untreated nets or curtains.
P. vivax uncomplicated episodes (cumulative incidence)	Relative risk 0.58 (CI 95% 0.3 — 1.14) Based on data from 17,910 participants in 3 studies. (Randomized controlled)	168 per 1000 Difference:	97 per 1000 **71 fewer per 1000** (CI 95% 118 fewer — 23 more)	Low Due to serious imprecision, Due to serious inconsistency [3]	Pyrethroid-only nets or curtains may reduce the incidence of uncomplicated P. vivax malaria episodes compared to untreated nets or curtains.

Outcome Timeframe	**Study results and measurements**	**Comparator** Untreated nets or curtains	**Intervention** Pyrethroid-only nets or curtains	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. vivax prevalence	Relative risk 0.52 (CI 95% 0.13 — 2.04) Based on data from 300 participants in 1 studies. (Randomized controlled)	85 per 1000 Difference:	44 per 1000 **41 fewer per 1000** (CI 95% 74 fewer — 88 more)	Very low Due to very serious imprecision, Due to very serious indirectness [4]	The evidence is very uncertain about the effect of pyrethroid-only nets or curtains on P. vivax prevalence compared to untreated nets or curtains.
Any Plasmodium spp. uncomplicated episodes (cumulative incidence)	Relative risk 0.47 (CI 95% 0.17 — 1.28) Based on data from 7,082 participants in 2 studies. (Randomized controlled)	69 per 1000 Difference:	32 per 1000 **37 fewer per 1000** (CI 95% 57 fewer — 19 more)	Moderate Due to serious imprecision [5]	Pyrethroid-only nets or curtains probably reduce the incidence of uncomplicated malaria episodes compared to untreated nets or curtains.
Any Plasmodium spp. prevalence	Relative risk 0.17 (CI 95% 0.05 — 0.53) Based on data from 691 participants in 1 studies. (Randomized controlled)	104 per 1000 Difference:	18 per 1000 **86 fewer per 1000** (CI 95% 99 fewer — 49 fewer)	Very low Due to serious imprecision, Due to very serious indirectness [6]	The evidence is very uncertain about the effect of pyrethroid-only nets or curtains on Plasmodium prevalence compared to untreated nets or curtains.

1. **Imprecision: serious.**
2. **Indirectness: serious. Imprecision: serious.**
3. **Inconsistency: serious. Imprecision: serious.**
4. **Indirectness: very serious. Imprecision: very serious.**
5. **Imprecision: serious.**
6. **Indirectness: very serious. Imprecision: serious.**

Attached Images

References

55. Pryce J, Richardson M, Lengeler C : Insecticide-treated nets for preventing malaria. Cochrane Database of Systematic Reviews 2018;(11): Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children in areas with ongoing malaria transmission and high insecticide resistance
Intervention: ITNs treated with both piperonyl butoxide (PBO) and pyrethroid
Comparator: ITNs treated with pyrethroid only

Summary

Two cRCTs from the Republic of Uganda and the United Republic of Tanzania were included in the review.

Pyrethroid-PBO ITNs versus pyrethroid-only LLINs:
Pyrethroid-PBO ITNs reduce malaria parasite prevalence at 4- to 6-month follow-up compared to pyrethroid-only LLINs.
(Odds ratio:0.74; 95% CI (0.62 to 0.89); two studies; high certainty evidence)
Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence at 9- to 12-month follow-up compared to pyrethroid-only LLINs.
(Odds ratio: 0.72; 95% CI (0.61–0.86); two studies; moderate certainty evidence)
Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence at 16- to 18-month follow-up compared to pyrethroid-only LLINs
(Odds ratio: 0.88; 95% CI (0.74–1.04); two studies; moderate certainty evidence)
Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence at 21- to 25-month follow-up compared to pyrethroid-only LLINs
(Odds ratio:0.79; 95% CI (0.67 to 0.95); two studies; moderate certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only LLINs	**Intervention** Pyrethroid-PBO ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Parasite prevalence - 4 to 6 months	Odds ratio 0.74 (CI 95% 0.62 — 0.89) Based on data from 11,582 participants in 2 studies. (Randomized controlled)	**254** per 1000 Difference:	**201** per 1000 **53 fewer per 1000** (CI 95% 80 fewer — 21 fewer)	**High**	Pyrethroid-PBO ITNs reduce malaria parasite prevalence in areas of high insecticide resistance at 4- to 6-month follow-up compared to pyrethroid-only LLINs.
Parasite prevalence - 9 to 12 months	Odds ratio 0.72 (CI 95% 0.61 — 0.86) Based on data from 11,370 participants in 2 studies. (Randomized controlled)	**224** per 1000 Difference:	**172** per 1000 **52 fewer per 1000** (CI 95% 74 fewer — 25 fewer)	**Moderate** Due to serious inconsistency [1]	Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence in areas of high insecticide resistance at 9- to 12-month follow-up compared to pyrethroid-only LLINs.
Parasite prevalence - 16 to 18 months	Odds ratio 0.88 (CI 95% 0.74 — 1.04) Based on data from 11,822 participants in 2 studies. (Randomized controlled)	**248** per 1000 Difference:	**225** per 1000 **23 fewer per 1000** (CI 95% 52 fewer — 7 more)	**Moderate** Due to serious inconsistency [2]	Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence in areas of high insecticide resistance at 16- to 18-month follow-up compared to pyrethroid-only LLINs.
Parasite prevalence - 21 to 25 months	Odds ratio 0.79 (CI 95% 0.67 — 0.95) Based on data from 10,603 participants in 2 studies. (Randomized controlled)	**350** per 1000 Difference:	**298** per 1000 **52 fewer per 1000** (CI 95% 85 fewer — 12 fewer	**Moderate** Due to serious inconsistency [3]	Pyrethroid-PBO ITNs probably reduce malaria parasite prevalence in areas of high insecticide resistance at 21- to 25-month follow-up compared to pyrethroid-only LLINs.

Outcome Timeframe	Study results and measurements	Comparator Pyrethroid-only LLINs	Intervention Pyrethroid-PBO ITNs	Certainty of the Evidence (Quality of evidence)	Plain language summary
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1. **Inconsistency: serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
2. **Inconsistency: serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

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References

59. Gleave K, Lissenden N, Richardson M, Choi L, Ranson H : Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. The Cochrane Database of Systematic Reviews 2021;5 CD012776 Pubmed Journal

60. Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. 2021; Pubmed

Clinical Question/ PICO

Population: Adults and children in areas with ongoing malaria transmission and high insecticide resistance
Intervention: ITNs treated with both piperonyl butoxide (PBO) and pyrethroid
Comparator: ITNs treated with pyrethroid only

Summary

Ten experimental hut trials from Republic of Benin, Burkina Faso, Republic of Cameroon, Republic of Côte d'Ivoire and United Republic of Tanzania were included in the review.

Pyrethroid-PBO ITNs vs pyrethroid-only LLINs
In highly pyrethroid-resistant areas:
Mosquito mortality is higher with unwashed pyrethroid-PBO ITNs compared to unwashed pyrethroid-only LLINs (Risk ratio: 1.84; 95% CI: 1.60–2.11; five trials; high-certainty evidence)
It is not known if mosquito mortality is higher with washed pyrethroid-PBO ITNs compared to washed pyrethroid-only LLINs
(Risk ratio: 1.20; 95% CI: 0.88–1.63; four trials, very low-certainty evidence)
Blood-feeding success is decreased with unwashed pyrethroid-PBO ITNs compared to unwashed pyrethroid-only LLINs
(Risk ratio: 0.60; 95% CI: 0.50–0.71; four trials, high-certainty evidence)
Blood-feeding success is decreased with washed pyrethroid-PBO ITNs compared to washed pyrethroid-only LLINs (Risk ratio: 0.81; 95% CI: 0.72–0.92; three trials; high-certainty evidence)

Outcome Timeframe	Study results and measurements	Comparator Pyrethroid-only LLINs	Intervention Pyrethroid-PBO ITNs	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mosquito mortality -	Relative risk 1.84 (CI 95% 1.6 — 2.11)	238	438	High Not downgraded	Unwashed pyrethroid-PBO ITNs

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only LLINs	**Intervention** Pyrethroid-PBO ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Unwashed nets	Based on data from 4,896 participants in studies. [1]	per 1000 Difference:	per 1000 **200 more per 1000** (CI 95% 143 more — 264 more)	for imprecision: both best- and worst-case scenarios in this situation are important effects	results in higher mosquito mortality with unwashed pyrethroid-PBO ITNs compared to unwashed pyrethroid-only LLINs .
Mosquito mortality - Washed nets	Relative risk 1.2 (CI 95% 0.88 — 1.63) Based on data from 3,101 participants in studies. [2]	201 per 1000 Difference:	242 per 1000 **40 more per 1000** (CI 95% 24 fewer — 127 more)	Very low Due to imprecision and inconsistency	The evidence is very uncertain about the effect of washed pyrethroid-PBO ITNs on mosquito mortality compared to washed pyrethroid-only LLINs
Mosquito blood-feeding success - Unwashed nets	Relative risk 0.6 (CI 95% 0.5 — 0.71) Based on data from 4,458 participants in studies. [3]	438 per 1000 Difference:	263 per 1000 **175 fewer per 1000** (CI 95% 219 fewer — 127 fewer)	High	Unwashed pyrethroid-PBO ITNs results in lower mosquito blood-feeding success compared to unwashed pyrethroid-only LLINs.
Mosquito blood-feeding success - Washed nets	Relative risk 0.81 (CI 95% 0.72 — 0.92) Based on data from 2,676 participants in studies. [4]	494 per 1000 Difference:	400 per 1000 **94 fewer per 1000** (CI 95% 138 fewer — 40 fewer)	High	Washed pyrethroid-PBO ITNs results in lower mosquito blood-feeding success compared to washed pyrethroid-only LLINs.

1. Systematic review [60] with included studies: Toé 2018, Toé 2018, Koudou 2011, Toé 2018, Bayili 2017, Pennetier 2013, Corbel 2010, Bayili 2017, Toé 2018. **Baseline/comparator:** Control arm of reference used for intervention.
2. Systematic review [60] with included studies: Koudou 2011, Pennetier 2013, Bayili 2017, Bayili 2017, Corbel 2010. **Baseline/comparator:** Control arm of reference used for intervention.
3. Systematic review [60] with included studies: Bayili 2017, Toé 2018, Toé 2018, Pennetier 2013, Toé 2018, Corbel 2010, Bayili 2017, Toé 2018. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [60] with included studies: Pennetier 2013, Corbel 2010, Bayili 2017, Bayili 2017. **Baseline/comparator:** Control arm of reference used for intervention.

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59. Gleave K, Lissenden N, Richardson M, Choi L, Ranson H : Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. The Cochrane Database of Systematic Reviews 2021;5 CD012776 Pubmed Journal

60. Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. 2021; Pubmed

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Pyrethroid-chlorfenapyr ITNs for prevention of malaria
Comparator: Pyrethroid-only ITNs for prevention of malaria

Summary

The systematic review [Barker *et al unpublished evidence*] included two RCTs, one from Benin *[62]* and one from the United Republic of Tanzania *[61]* that compared the epidemiological impact against malaria of pyrethroid-chlorfenapyr ITNs (alphacypermethrin-chlorfenapyr) against pyrethroid-only LLINs (alphacypermethrin). Both trials were conducted in areas of high malaria transmission and pyrethroid-resistance. The review provided high to moderate certainty evidence that incidence of clinical malaria was lower in areas where pyrethroid-chlorfenapyr ITNs were deployed than in those with pyrethroid-only LLINs, at one and two years after ITN deployment (one-year incidence rate ratio (IRR): 0.44; 95% CI: 0.37–0.52; two-year IRR: 0.57; 95% CI: 0.51–0.63). The review also provided high certainty evidence that prevalence of malaria infection was lower where pyrethroid-chlorfenapyr ITNs were deployed than in those with pyrethroid-only LLINs, at several time points after ITN deployment (six-month relative risk (RR): 0.50; 95% CI: 0.43–0.59; 12-month RR: 0.78; 95% CI: 0.72–0.85; 18-month RR: 075; 95% CI: 0.70–0.80; 24-month RR: 0.56; 95% CI: 0.50–0.63).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only ITNs	**Intervention** Pyrethroid-chlorfenapyr ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria case incidence (overall)	Rate ratio 0.72 (CI 95% 0.67 — 0.78) Based on data from 61,183 participants in 2 studies. (Randomized controlled)	**678** per 1000 Difference:	**487** per 1000 **190 fewer per 1000** (CI 95% 224 fewer — 149 fewer)	**Moderate** Due to serious inconsistency. [1]	2000-person years (2 RCTs) Length of time observed: <1 month to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (1-year post-intervention)	Rate ratio 0.44 (CI 95% 0.37 — 0.52) Based on data from 61,183 participants in 2 studies. (Randomized controlled)	**487** per 1000 Difference:	**213** per 1000 **272 fewer per 1000** (CI 95% 307 fewer — 234 fewer)	**High**	2000-person years (2 RCTs) Length of time observed: <1 month to 12 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence	Rate ratio 0.57 (CI 95% 0.51 — 0.63) Based on data from	**815** per 1000	**465** per 1000	**High**	2000 (2 RCTs) Length of time observed: 12 months to 24 months

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only ITNs	**Intervention** Pyrethroid-chlorfenapyr ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
(2-years post-intervention)	61,183 participants in 2 studies. (Randomized controlled)	Difference:	**351 fewer per 1000** (CI 95% 400 fewer — 302 fewer)		Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Parasite prevalence (6-months follow-up)	Relative risk 0.5 (CI 95% 0.43 — 0.59) Based on data from 2,249 participants in 1 studies. (Randomized controlled)	312 per 1000 Difference:	156 per 1000 **156 fewer per 1000** (CI 95% 178 fewer — 128 fewer)	High	
Parasite prevalence (12-months follow-up)	Relative risk 0.78 (CI 95% 0.72 — 0.85) Based on data from 2,473 participants in 1 studies. (Randomized controlled)	523 per 1000 Difference:	409 per 1000 **115 fewer per 1000** (CI 95% 147 fewer — 78 fewer)	High	
Parasite prevalence (18-months follow-up)	Relative risk 0.75 (CI 95% 0.7 — 0.85) Based on data from 5,445 participants in 2 studies. (Randomized controlled)	448 per 1000 Difference:	338 per 1000 **112 fewer per 1000** (CI 95% 135 fewer — 90 fewer)	High	
Parasite prevalence (24-months follow-up)	Relative risk 0.56 (CI 95% 0.5 — 0.63) Based on data from 2,471 participants in 1 studies. (Randomized controlled)	458 per 1000 Difference:	256 per 1000 **201 fewer per 1000** (CI 95% 229 fewer — 169 fewer)	High	

1. **Inconsistency: serious.** Point estimates vary widely (from 0.49 to 0.87 with no overlap of confidence intervals). This heterogeneity appears to be unexplained but important (chi2, p <0.0001, I2 = 98%). But may not impact on a recommendation for the intervention. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

Attached Images

References

61. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. : Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

62. Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, et al. : Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet (London, England) 2023;401(10375):435-446 Pubmed Journal

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Pyrethroid-chlorfenapyr ITNs for prevention of malaria

Comparator: Pyrethroid-PBO ITNs for prevention of malaria

Summary

The review [Barker *et al unpublished evidence*] compared the epidemiological impact against malaria of pyrethroid-chlorfenapyr ITNs against pyrethroid-PBO ITNs (permethrin-piperonyl butoxide), based on one RCT *[61]* in the United Republic of Tanzania. The review provided high to low certainty evidence that incidence of clinical malaria was lower in areas where pyrethroid-chlorfenapyr ITNs were deployed than in those with pyrethroid-PBO ITNs, at two years after ITN deployment, but possibly not at one year post-deployment (one-year IRR: 0.98; 95% CI: 0.71–1.36; two-year IRR: 0.65; 95% CI: 0.55–0.77). The review also provided high to moderate certainty evidence that prevalence of malaria infection was generally lower where pyrethroid-chlorfenapyr ITNs were deployed, compared to those with pyrethroid-only LLINs, at several time points after ITN deployment (12-month RR: 0.81; 95% CI: 0.68–0.98; 18-month RR: 0.94; 95% CI: 0.86–1.04; 24-month RR: 0.63; 95% CI: 0.56–0.71).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-PBO nets for prevention of malaria	**Intervention** Pyrethroid-chlorfenapyr nets for prevention of malaria	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria case incidence (overall)	Rate ratio 0.68 (CI 95% 0.59 — 0.79) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	**333** per 1000 Difference:	**227** per 1000 **107 fewer per 1000** (CI 95% 137 fewer — 70 fewer)	**High**	2000-person years (1 RCT) Length of time observed: <1 month to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (1-year post-intervention)	Rate ratio 0.98 (CI 95% 0.71 — 1.36) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	**133** per 1000 Difference:	**131** per 1000 **3 fewer per 1000** (CI 95% 39 fewer — 48 more	**Low** Due to very serious imprecision [1]	2000-person years (1 RCT) Length of time observed: <1 month to 12 months Based on data from at least 61,183 participants (1 study) Absolute

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-PBO nets for prevention of malaria	**Intervention** Pyrethroid-chlorfenapyr nets for prevention of malaria	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			)		calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (2-years post-intervention)	Rate ratio 0.65 (CI 95% 0.55 — 0.77) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	**483** per 1000 Difference:	**315** per 1000 **155 fewer per 1000** (CI 95% 198 fewer — 101 fewer)	**High**	2000-person years (1 RCT) Length of time observed: 12 months to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Parasite prevalence (12-months follow-up)	Relative risk 0.81 (CI 95% 0.68 — 0.98) Based on data from 2,197 participants in 1 studies. (Randomized controlled)	**192** per 1000 Difference:	**156** per 1000 **37 fewer per 1000** (CI 95% 62 fewer — 4 fewer)	**Moderate** Due to serious imprecision [2]	
Parasite prevalence (18-months follow up)	Relative risk 0.94 (CI 95% 0.86 — 1.04) Based on data from 2,406 participants in 1 studies. (Randomized controlled)	**433** per 1000 Difference:	**409** per 1000 **26 fewer per 1000** (CI 95% 61 fewer — 17 more)	**Moderate** Due to serious imprecision [3]	
Parasite prevalence (24-months follow-up)	Relative risk 0.63 (CI 95% 0.56 — 0.71) Based on data from 2,531 participants in 1 studies. (Randomized controlled)	**407** per 1000 Difference:	**256** per 1000 **150 fewer per 1000** (CI 95% 179 fewer — 118 fewer)	**High**	

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Confidence intervals are very wide (39 fewer to 48 more) and may have crossed many important decision-making threshold (including line of no effect). **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (62 fewer to 4 fewer) and may have crossed many important decision-making threshold. **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 61 fewer to 17 more) and may have crossed many important decision-making threshold (including line of no effect). **Publication bias: no serious.**

Attached Images

References

61. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. : Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

62. Accrombessi M, Cook J, Dangbenon E, Yovogan B, Akpovi H, Sovi A, et al. : Efficacy of pyriproxyfen-pyrethroid long-lasting insecticidal nets (LLINs) and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs for malaria control in Benin: a cluster-randomised, superiority trial. Lancet (London, England) 2023;401(10375):435-446 Pubmed Journal

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Pyrethroid-pyriproxyfen nets for prevention of malaria
Comparator: Pyrethroid-only nets for prevention of malaria

Summary

The systematic review [Barker *et al unpublished evidence*] included three trials from Benin *[62]*, Burkina Faso *[63]* and the United Republic of Tanzania *[61]* that compared the epidemiological impact against malaria of pyrethroid-pyriproxyfen ITNs (either alphacypermethrin-pyriproxyfen or permethrin-pyriproxyfen) against that of pyrethroid-only LLINs (either permethrin or alphacypermethrin). All three trials were conducted in areas of high malaria transmission and pyrethroid-resistance. The review provided high-certainty evidence that incidence of clinical malaria was lower in areas where pyrethroid-pyriproxyfen ITNs were deployed, compared to where pyrethroid-only LLINs were deployed, at one and two years after ITN deployment (one-year incidence rate ratio (IRR): 0.81; 95% CI: 0.70–0.93; two-year IRR: 0.87; 95% CI: 0.80–0.95). The review also provided moderate to high certainty evidence that prevalence of malaria infection was lower in areas where pyrethroid-pyriproxyfen ITNs were deployed than in those where pyrethroid-only LLINs were deployed, at some, but not all, time points after ITN deployment (six-month relative risk (RR): 0.96; 95% CI: 0.85–1.08; 12-month RR: 0.70; 95% CI: 0.60–0.80; 18-month RR: 0.98; 95% CI: 0.92–1.04; 24-month RR: 0.82; 95% CI: 0.75–0.90).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria case incidence (overall)	Rate ratio 0.86 (CI 95% 0.81 — 0.92) Based on data from 63,163 participants in 2 studies. (Randomized controlled)	1,037 per 1000 Difference:	929 per 1000 **145 fewer per 1000** (CI 95% 197 fewer — 83 fewer)	**High**	2000-person years (3 RCTs); Length of time observed: 5 months to 24 months; Based on data from at least 63,163 participants (2 studies); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria case incidence (1-year post-intervention)	Rate ratio 0.81 (CI 95% 0.7 — 0.93) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	487 per 1000 Difference:	393 per 1000 **92 fewer per 1000** (CI 95% 146 fewer — 34 fewer)	High	2000 person-years; (2 RCTs); Length of time observed: < 1 month to 12 months Based on data from at least 61 183 participants (1 study); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.
Malaria case incidence (2-year post-intervention)	Rate ratio 0.87 (CI 95% 0.8 — 0.95) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	815 per 1000 Difference:	715 per 1000 **106 fewer per 1000** (CI 95% 163 fewer — 41 fewer)	High	2000 (2 RCTs); Length of time observed: 12 months to 24 months; Based on data from at least 61,183 participants (1 study); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.
Parasite prevalence (6-months follow-up)	Relative risk 0.96 (CI 95% 0.85 — 1.08) Based on data from 2,934 participants in 1 studies. (Randomized controlled)	280 per 1000 Difference:	269 per 1000 **11 fewer per 1000** (CI 95% 42 fewer — 22 more)	Moderate Due to serious imprecision [1]	
Parasite prevalence (12-months follow-up)	Relative risk 0.7 (CI 95% 0.6 — 0.8) Based on data from 2,192 participants in 1 studies. (Randomized controlled)	312 per 1000 Difference:	217 per 1000 **93 fewer per 1000** (CI 95% 125 fewer — 62 fewer)	High	
Parasite prevalence (18-months follow-up)	Relative risk 0.98 (CI 95% 0.92 — 1.04) Based on data from 5,337 participants in 2 studies. (Randomized controlled)	448 per 1000 Difference:	438 per 1000 **9 fewer per 1000** (CI 95% 36 fewer — 18 more)	Moderate Due to serious imprecision. [2]	
Parasite prevalence (24-months follow-up)	Relative risk 0.82 (CI 95% 0.75 — 0.9) Based on data from 2,457 participants in 1 studies. (Randomized	458 per 1000 Difference:	375 per 1000 **82 fewer per 1000**	High	

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-only nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	controlled)		(CI 95% 114 fewer — 46 fewer)		

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 42 fewer to 22 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 36 fewer to 18 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**

Attached Images

References

61. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. : Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

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63. Tiono AB, Ouédraogo A, Ouattara D, Bougouma EC, Coulibaly S, Diarra A, et al. : Efficacy of Olyset Duo, a bednet containing pyriproxyfen and permethrin, versus a permethrin-only net against clinical malaria in an area with highly pyrethroid-resistant vectors in rural Burkina Faso: a cluster-randomised controlled trial. Lancet (London, England) 2018;392(10147):569-580 Pubmed Journal

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Pyrethroid-pyriproxyfen nets for prevention of malaria
Comparator: Pyrethroid-PBO nets for prevention of malaria

Summary

The review [Barker *et al unpublished evidence*] compared pyrethroid-pyriproxyfen ITNs (alphacypermethrin-pyriproxyfen) to pyrethroid-PBO ITNs (permethrin-piperonyl butoxide) in terms of their epidemiological impact against malaria, based on only one trial *[61]* conducted in the United Republic of Tanzania. The review provided high to moderate certainty evidence that incidence of clinical malaria was higher at one year after ITN deployment (IRR: 2.04; 95% CI: 1.55–2.68) in areas where pyrethroid-pyriproxyfen ITNs were deployed that in those where pyrethroid-PBO ITNs were deployed; there was little or no effect on malaria incidence two years post-deployment (IRR: 1.10; 95% CI: 0.95–1.27). The review also provided high- to moderate-certainty evidence that pyrethroid-pyriproxyfen only performed as well as, or worse than, pyrethroid-PBO ITNs in reducing prevalence of malaria infection at all time points after ITN deployment (12-month RR: 1.13; 95% CI: 0.95–1.33; 18-month RR: 1.17; 95% CI: 1.07–1.27; 24-month RR: 0.88; 95% CI: 0.75–1.03).

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-PBO nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria case incidence (overall)	Rate ratio 1.25 (CI 95% 1.1 — 1.41) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	333 per 1000 Difference:	416 per 1000 **83 more per 1000** (CI 95% 33 more — 137 more)	**High**	2000-person years (1 RCT); Length of time observed: <1 month to 24 months; Based on data from at least 61,183 participants (1 study); Absolute calculation performed manually as GRADEPro cannot calculate using IRR.
Malaria case incidence (1-year post-intervention)	Rate ratio 2.04 (CI 95% 1.55 — 2.68) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	131 per 1000 Difference:	266 per 1000 **136 more per 1000** (CI 95% 72 more — 220 more)	**High**	2000-person years (1 RCT) Length of time observed: <1 month to 12 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Malaria case incidence (2-years post-intervention)	Rate ratio 1.1 (CI 95% 0.95 — 1.27) Based on data from 61,183 participants in 1 studies. (Randomized controlled)	483 per 1000 Difference:	531 per 1000 **48 more per 1000** (CI 95% 24 fewer — 130 more)	**Moderate** Due to serious imprecision [1]	2000-person years (1 RCT) Length of time observed: 12 months to 24 months Based on data from at least 61,183 participants (1 study) Absolute calculation performed manually as GRADEPro cannot calculate using IRR
Parasite prevalence (12-months follow-up)	Relative risk 1.13 (CI 95% 0.95 — 1.33) Based on data from 2,140 participants in 1 studies. (Randomized controlled)	192 per 1000 Difference:	217 per 1000 **25 more per 1000** (CI 95% 10 fewer — 63 more)	**Moderate** Due to serious imprecision [2]	
Parasite prevalence (18-months follow-up)	Relative risk 1.17 (CI 95% 1.07 — 1.27) Based on data from 2,313 participants in 1 studies. (Randomized controlled)	433 per 1000 Difference:	506 per 1000 **74 more per 1000** (CI 95% 30 more — 117 more)	**High**	
Parasite	Odds ratio 0.88	407	375	**Moderate**	

Outcome Timeframe	**Study results and measurements**	**Comparator** Pyrethroid-PBO nets for prevention of malaria	**Intervention** Pyrethroid-pyriproxyfen nets for prevention of malaria	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
prevalence (24-months follow-up)	(CI 95% 0.75 — 1.03) Based on data from 2,517 participants in studies. (Randomized controlled)	per 1000 Difference:	per 1000 **30 fewer per 1000** (CI 95% 67 fewer — 7 more)	Due to serious imprecision [3]	

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are very wide (from 24 fewer 130 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 10 fewer to 63 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence intervals are wide (from 67 fewer to 7 more) and may have crossed many important decision-making thresholds (including line of no effect). **Publication bias: no serious.**

Attached Images

References

61. Mosha JF, Kulkarni MA, Lukole E, Matowo NS, Pitt C, Messenger LA, et al. : Effectiveness and cost-effectiveness against malaria of three types of dual-active-ingredient long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs in Tanzania: a four-arm, cluster-randomised trial. Lancet (London, England) 2022;399(10331):1227-1241 Pubmed Journal

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63. Tiono AB, Ouédraogo A, Ouattara D, Bougouma EC, Coulibaly S, Diarra A, et al. : Efficacy of Olyset Duo, a bednet containing pyriproxyfen and permethrin, versus a permethrin-only net against clinical malaria in an area with highly pyrethroid-resistant vectors in rural Burkina Faso: a cluster-randomised controlled trial. Lancet (London, England) 2018;392(10147):569-580 Pubmed Journal

Clinical Question/ PICO

Population: Refugees and IDP adults and children affected by humanitarian emergencies living in areas with ongoing malaria transmission

Intervention: Insecticide-treated nets

Comparator: No insecticide-treated nets

Summary

Of the four included ITN studies, two were cluster RCTs (one with households as the cluster and one with villages as the cluster) and two were individual-level RCTs. The two individual-level RCTs were conducted on the Myanmar–Thailand border, the village-level RCT was conducted in the Republic of Union of the Myanmar and the

household-level RCT was performed in the Islamic Republic of Pakistan.

ITNs versus no ITNs:
ITNs reduce P. falciparum case incidence compared to no nets
(Rate ratio: 0.55; 95% CI: 0.37–0.79; four studies; high-certainty evidence)
ITNs reduce P. falciparum prevalence compared to no nets
(Rate ratio: 0.60; 95% CI: 0.40–0.88; two studies; high-certainty evidence)
ITNs likely reduce P. vivax case incidence compared to no nets
(Rate ratio: 0.69; 95% CI: 0.51–0.94; three studies; moderate-certainty evidence)
ITNs may have little or no effect on the prevalence of P. vivax compared to no nets
(Risk ratio: 1.00; 95% CI: 0.75–1.34; two studies; low-certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** no ITNs	**Intervention** ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. falciparum case incidence	Relative risk 0.55 (CI 95% 0.37 — 0.79) Based on data from 3,200 participants in 4 studies.	70 per 1000 Difference:	39 per 1000 **31 fewer per 1000** (CI 95% 44 fewer — 15 fewer)	High	ITNs reduce P. falciparum case incidence compared to no ITNs.
P. falciparum prevalence	Relative risk 0.6 (CI 95% 0.4 — 0.88) Based on data from 2,079 participants in 2 studies.	37 per 1000 Difference:	22 per 1000 **15 fewer per 1000** (CI 95% 22 fewer — 4 fewer)	High	ITNs reduce P. falciparum prevalence compared to no ITNs.
P. vivax case incidence	Relative risk 0.69 (CI 95% 0.51 — 0.94) Based on data from 2,997 participants in 3 studies.	116 per 1000 Difference:	80 per 1000 **36 fewer per 1000** (CI 95% 57 fewer — 7 fewer)	Moderate Due to serious imprecision	ITNs probably reduce P. vivax case incidence compared to no ITNs.
P. vivax prevalence	Relative risk 1 (CI 95% 0.75 — 1.34) Based on data from 2,079 participants in 2 studies.	99 per 1000 Difference:	99 per 1000 **0 fewer per 1000** (CI 95% 25 fewer — 34 more)	Low Due to very serious imprecision	ITNs may result in little to no difference in P. vivax prevalence compared to no ITNs.

Attached Images

References

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Clinical Question/ PICO

Population: Adults and children in areas with ongoing malaria transmission
Intervention: IRS
Comparator: No IRS

Summary

The systematic review included 1 RCT from the United Republic of Tanzania that reported the effect of IRS on malaria in an area of intense malaria transmission and another RCT from Islamic Republic of Pakistan that investigated the epidemiological impact of IRS in an area with unstable malaria.

IRS versus no IRS in areas with intense malaria transmission:
IRS may reduce malaria incidence compared to no IRS
(Risk ratio: 0.86; 95% CI: 0.77–0.95; one study; low-certainty evidence)
IRS may have reduce parasite prevalence compared to no IRS
(Risk ratio: 0.94; 95% CI: 0.82–1.08; one study; low-certainty evidence)

IRS versus no IRS in areas with unstable malaria transmission:
IRS may reduce malaria incidence compared to no IRS
(Risk Ratio: 0.12; 95% CI (0.04–0.31); one study; low certainty evidence)
IRS may reduce parasite prevalence compared to no IRS
(Risk Ratio: 0.24; 95% CI (0.17–0.34); one study; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** No IRS	**Intervention** IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Incidence of malaria in children under 5 years in areas of intense malaria transmission	Relative risk 0.86 (CI 95% 0.77 — 0.95) Based on data from 884 participants in 1 studies. (Randomized controlled)	650 per 1000 Difference:	560 per 1000 **90 fewer per 1000** (CI 95% 150 fewer — 40 fewer)	**Low** Due to serious indirectness, Due to serious imprecision [1]	IRS may reduce P. falciparum incidence compared to no IRS in areas of intense malaria transmission.
Parasite prevalence in children under 5 years in areas of intense malaria transmission	Relative risk 0.94 (CI 95% 0.82 — 1.08) Based on data from 452 participants in 1 studies. (Randomized controlled)	680 per 1000 Difference:	630 per 1000 **50 fewer per 1000** (CI 95% 130 fewer — 50 more)	**Low** Due to serious indirectness, Due to serious imprecision [2]	IRS may reduce P. falciparum prevalence compared to no IRS in areas of intense malaria transmission.

Outcome Timeframe	**Study results and measurements**	**Comparator** No IRS	**Intervention** IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Incidence of malaria in all ages in areas of unstable malaria	Relative risk 0.12 (CI 95% 0.04 — 0.31) Based on data from 18,261 participants in 1 studies. (Randomized controlled)	50 per 1000 Difference:	10 per 1000 **40 fewer per 1000** (CI 95% 50 fewer — 40 fewer)	**Low** Due to serious indirectness, Due to serious imprecision [3]	IRS may reduce P. falciparum incidence compared to no IRS in areas of unstable malaria
Parasite prevalence in children aged 5–15 years in areas of unstable malaria	Relative risk 0.24 (CI 95% 0.17 — 0.34) Based on data from 2,359 participants in 1 studies. (Randomized controlled)	110 per 1000 Difference:	30 per 1000 **80 fewer per 1000** (CI 95% 90 fewer — 70 fewer)	**Low** Due to serious indirectness, Due to serious imprecision [4]	IRS may reduce P. falciparum prevalence compared to no IRS in areas of unstable malaria

1. **Indirectness: serious. Imprecision: serious.**
2. **Indirectness: serious. Imprecision: serious.**
3. **Indirectness: serious. Imprecision: serious.**
4. **Indirectness: serious. Imprecision: serious.**

Attached Images

References

70. Pluess B, Tanser FC, Lengeler C, Sharp BL : Indoor residual spraying for preventing malaria. The Cochrane database of systematic reviews 2010;(4):CD006657 Pubmed Journal

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: IRS
Comparator: ITNs

Summary

The systematic review included 1 RCT from the United Republic of Tanzania that reported the effect of IRS compared to ITNs on malaria in an area of intense malaria transmission and another study from the Republic of India that investigated the epidemiological impact of IRS in an area with unstable malaria.

IRS versus ITNs in areas with intense transmission:

IRS may reduce malaria incidence compared to ITNs
(Rate ratio: 0.88; 95% CI (0.78–0.98); one study; low certainty evidence)
There may be little or no difference between IRS and ITNs in terms of parasite prevalence
(Risk ratio: 1.06; 95% CI (0.91–1.22); one study; very low certainty evidence)

IRS versus ITNs in areas with unstable transmission:
IRS may increase malaria incidence compared to ITNs
(Rate ratio: 1.48; 95% CI (1.37–1.60); one study; low certainty evidence)
IRS may increase parasite prevalence compared to ITNs
(Risk ratio: 1.70; 95% CI (1.18–2.44); one study; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** ITNs	**Intervention** IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Incidence of malaria in children under 5 years in areas of intense malaria transmission	Relative risk 0.88 (CI 95% 0.78 — 0.98) Based on data from 818 participants in 1 studies. (Randomized controlled)	630 per 1000 Difference:	550 per 1000 **80 fewer per 1000** (CI 95% 140 fewer — 10 fewer)	**Low** Due to serious indirectness, Due to serious imprecision [1]	IRS may reduce P. falciparum incidence compared to no ITNs in areas of intense malaria transmission.
Parasite prevalence in children under 5 years in areas of intense malaria transmission	Relative risk 1.06 (CI 95% 0.91 — 1.22) Based on data from 449 participants in 1 studies. (Randomized controlled)	600 per 1000 Difference:	640 per 1000 **40 more per 1000** (CI 95% 50 fewer — 140 more)	**Low** Due to serious indirectness, Due to serious imprecision [2]	IRS may result in little to no difference in parasite prevalence compared to ITNs in areas of intense malaria transmission.
Incidence of malaria in all ages in areas of unstable malaria	Relative risk 1.48 (CI 95% 1.37 — 1.6) Based on data from 88,100 participants in 1 studies. (Randomized controlled)	20 per 1000 Difference:	30 per 1000 **10 more per 1000** (CI 95% 10 more — 20 more)	**Low** Due to serious imprecision, Due to serious indirectness [3]	IRS may increase incidence of malaria compared to ITNs in areas of unstable malaria.
Parasite prevalence in all ages in areas of unstable malaria	Relative risk 1.7 (CI 95% 1.18 — 2.44) Based on data from 52,934 participants in 1 studies. (Randomized controlled)	2 per 1000 Difference:	3 per 1000 **1 more per 1000** (CI 95% 0 fewer — 3 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	IRS may result in little to no difference in parasite prevalence compared to ITNs in areas of unstable malaria.

1. **Indirectness: serious. Imprecision: serious.**

2. **Indirectness: serious. Imprecision: serious.**
3. **Indirectness: serious. Imprecision: serious.**
4. **Indirectness: serious. Imprecision: serious.**

Attached Images

References

70. Pluess B, Tanser FC, Lengeler C, Sharp BL : Indoor residual spraying for preventing malaria. The Cochrane database of systematic reviews 2010;(4):CD006657 Pubmed Journal

Clinical Question/ PICO

Population: Refugees and IDP adults and children affected by humanitarian emergencies living in areas with ongoing malaria transmission

Intervention: Indoor residual spraying

Comparator: No indoor residual spraying

Summary

Of the four included IRS studies, one was a cluster RCT at the village-level and three were observational studies (one controlled before-after, one before-after and one cross-sectional). The cRCT was conducted in The Republic of the Sudan and the three observational studies were undertaken in the Islamic Republic of Pakistan.

IRS versus no IRS:
The evidence is very uncertain about the effect of IRS on P. falciparum incidence compared to no IRS (Incidence rate ratio: 0.57; 95% CI: 0.53–0.61; one before-after study; very low-certainty evidence)
IRS may result in little to no difference in P. falciparum prevalence compared to no IRS (Rate ratio: 1.31; 95% CI: 0.91–1.88; one cRCT; low-certainty evidence)
The evidence is very uncertain about the effect of IRS on P. vivax incidence compared to no IRS (Incidence rate ratio: 0.51; 95% CI: 0.49–0.52; one before-after study; very low-certainty evidence)
The evidence is very uncertain about the effect of IRS on P. vivax prevalence compared to no IRS (Odds ratio: 0.74; 95% CI: 0.25–2.14; one controlled before-after study and one cross-sectional study; very low-certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** no IRS	**Intervention** IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. falciparum incidence	Relative risk 0.57 (CI 95% 0.53 — 0.61) Based on data from 480,377 participants in 1 studies.	7 per 1000 Difference:	4 per 1000 **3 fewer per 1000** (CI 95% 3 fewer — 3 fewer)	Very low	The evidence is very uncertain about the effect of IRS on P. falciparum incidence compared to no IRS.
P. falciparum prevalence	Relative risk 1.31 (CI 95% 0.91 — 1.88) Based on data from 278 participants in 1 studies.	257 per 1000 Difference:	337 per 1000 **80 more per 1000**	Low Due to very serious imprecision.	IRS may result in little to no difference in P. falciparum prevalence compared to no IRS.

Outcome Timeframe	**Study results and measurements**	**Comparator** no IRS	**Intervention** IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 23 fewer — 226 more)		
P. vivax incidence	Relative risk 0.51 (CI 95% 0.49 — 0.52) Based on data from 480,372 participants in 1 studies.	57 per 1000 Difference:	29 per 1000 **28 fewer per 1000** (CI 95% 29 fewer — 27 fewer)	Very low Due to serious risk of bias; due to serious indirectness. Upgraded because all plausible confounding would reduce the demonstrated effect.	The evidence is very uncertain about the effect of IRS on P. vivax incidence compared to no IRS.
P. vivax prevalence	Odds ratio 0.74 (CI 95% 0.25 — 2.14) Based on data from 4,708 participants in 2 studies.	78 per 1000 Difference:	59 per 1000 **19 fewer per 1000** (CI 95% 57 fewer — 75 more)	Very low Due to serious inconsistency; due to serious indirectness; due to serious imprecision. Upgraded because all plausible confounding would reduce demonstrated effect.	The evidence is very uncertain about the effect of IRS on P. vivax prevalence compared to no IRS.

Attached Images

References

54. Messenger LA, Furnival-Adams J, Pelloquin B, Rowland M : Vector control for malaria prevention during humanitarian emergencies: protocol for a systematic review and meta-analysis. BMJ Open 2021/07/27;11(7):e046325-e046325 Pubmed Journal Website

4.1.2. Co-deploying ITNs and IRS

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Pyrethroid-like indoor residual spraying (IRS) plus insecticide-treated nets (ITNs)
Comparator: ITNs

Summary

Four RCTs were included in the systematic review. Studies were conducted in the Republic of Benin, the State of Eritrea, the Republic of the Gambia and the United Republic of Tanzania.

IRS and ITNs vs ITNs
IRS in addition to ITNs probably has little or no effect on malaria incidence compared to ITNs alone (Rate ratio: 1.17; 95% CI (0.92–1.46); two studies; moderate certainty evidence)
IRS in addition to ITNs may have little or no effect on parasite prevalence compared to ITNs alone (Odds ratio: 1.04; 95% CI (0.73–1.48); four studies; low certainty evidence)
It is unknown whether IRS in addition to ITNs reduces the EIR compared to ITNs alone (Rate ratio: 0.57; 95% CI (0.26–1.25); two studies; very low certainty evidence)
IRS in addition to ITNs probably has little or no effect on anaemia prevalence compared to ITNs alone (Odds ratio: 1.04; 95% CI (0.83–1.30); two studies; moderate certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** ITNs	**Intervention** Pyrethroid-like IRS plus ITNs	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria incidence	Relative risk 1.17 (CI 95% 0.92 — 1.46) Based on data from 5,249 participants in 2 studies. (Randomized controlled)	600 per 1000 Difference:	700 per 1000 **100 more per 1000** (CI 95% 50 fewer — 280 more)	**Moderate** Due to serious imprecision [1]	IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs probably has little or no effect on malaria incidence compared to pyrethroid ITNs alone.
Malaria prevalence	Odds ratio 1.04 (CI 95% 0.73 — 1.48) Based on data from 34,530 participants in 4 studies. (Randomized controlled)	180 per 1000 Difference:	190 per 1000 **10 more per 1000** (CI 95% 40 fewer — 70 more)	**Low** Due to serious inconsistency, Due to serious imprecision [2]	IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs may have little or no effect on parasite prevalence compared to pyrethroid ITNs alone
Entomological inoculation rate	Relative risk 0.57 (CI 95% 0.26 — 1.25) Based on data from participants in 2 studies. (Randomized controlled)	1,170 per 1000 Difference:	670 per 1000 **500 fewer per 1000** (CI 95% 870 fewer — 290 fewer)	**Very low** Due to serious inconsistency, Due to very serious imprecision [3]	The evidence is very uncertain about the effect of IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs on EIR compared to pyrethroid ITNs alone.
Anaemia prevalence (haemoglobin <8g/dl)	Odds ratio 1.04 (CI 95% 0.83 — 1.3) Based on data from 12,940 participants in 2 studies. (Randomized controlled)	50 per 1000 Difference:	50 per 1000 **0 fewer per 1000** (CI 95% 10 fewer — 10 more)	**Moderate** Due to serious imprecision [4]	IRS using pyrethroid-like insecticides in addition to pyrethroid ITNs probably has little or no effect on anaemia prevalence compared to pyrethroid ITNs alone

1. **Imprecision: serious.**

2. **Inconsistency: serious. Imprecision: serious.**
3. **Inconsistency: serious. Imprecision: very serious.**
4. **Imprecision: serious.**

Attached Images

References

74. Choi L, Pryce J, Garner P : Indoor residual spraying for preventing malaria in communities using insecticide-treated nets. The Cochrane database of systematic reviews 2019;(5):CD012688 Pubmed Journal Website

4.1.3. Supplementary interventions

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Larviciding
Comparator: No larviciding

Summary

Four studies were included in the systematic review, of which only one was an RCT; the remaining three studies were non-randomized. Studies were undertaken in Gambia, Kenya, Sri Lanka and United Republic of Tanzania.

Larviciding applied to mosquito aquatic habitats exceeding 1km^2 in area:
It is unknown whether larviciding has an effect on malaria incidence compared to no larviciding
(Odds ratio: 1.97; 95% CI (1.39–2.81); one study; very low certainty evidence)
It is unknown whether larviciding has an effect on parasite prevalence compared to no larviciding
(Odds ratio: 1.49; 95% CI (0.45–4.93); one study; very low certainty evidence)

Larviciding applied to mosquito aquatic habitats less than 1km^2 in area:
Larviciding probably reduces malaria incidence compared to no larviciding
(Rate ratio: 0.20; 95% CI (0.16–0.25); one study; moderate certainty evidence)
Larviciding may reduce parasite prevalence compared to no larviciding
(Odds ratio: 0.72; 95% CI (0.58–0.89); two studies; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** No larviciding	**Intervention** Larviciding	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria incidence of habitats >1km2	Odds ratio 1.97 (CI 95% 1.39 — 2.81) Based on data from 1,793 participants in 1 studies. (Observational (non-randomized))	230 per 1000 Difference:	370 per 1000 **140 more per 1000** (CI 95% 70 more — 230 more)	**Very low** Due to serious inconsistency, Due to serious imprecision [1]	The evidence is very uncertain about the effect of larviciding on malaria incidence in areas where mosquito aquatic habitats are more than 1 km² compared to no larviciding.

Outcome Timeframe	**Study results and measurements**	**Comparator** No larviciding	**Intervention** Larviciding	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Parasite prevalence of habitats >1km2	Odds ratio 1.49 (CI 95% 0.45 — 4.93) Based on data from 3,574 participants in 1 studies. (Observational (non-randomized))	140 per 1000 Difference:	190 per 1000 **50 more per 1000** (CI 95% 70 fewer — 300 more)	**Very low** Due to serious inconsistency, Due to very serious imprecision [2]	The evidence is very uncertain about the effect of larviciding on parasite prevalence in areas where mosquito aquatic habitats are more than 1 km² compared to no larviciding.
Malaria incidence of habitats <1km2	Relative risk 0.2 (CI 95% 0.16 — 0.25) Based on data from 4,649 participants in 1 studies. (Randomized controlled)	230 per 1000 Difference:	50 per 1000 **180 fewer per 1000** (CI 95% 190 fewer — 170 fewer)	**Moderate** Due to serious imprecision [3]	Larviciding probably decreases malaria incidence in areas where mosquito aquatic habitats are less than 1 km² compared to no larviciding.
Parasite prevalence of habitats <1km2	Odds ratio 0.72 (CI 95% 0.58 — 0.89) (Observational (non-randomized))	120 per 1000 Difference:	90 per 1000 **30 fewer per 1000** (CI 95% 50 fewer — 10 fewer)	**Low**	Larviciding may reduce parasite prevalence in areas where mosquito aquatic habitats are less than 1 km² compared to no larviciding

1. **Inconsistency: serious. Imprecision: serious.**
2. **Inconsistency: serious. Imprecision: very serious.**
3. **Imprecision: serious.**

Attached Images

References

82. Choi L, Majambere S, Wilson AL : Larviciding to prevent malaria transmission. The Cochrane database of systematic reviews 2019;(8):CD012736 Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Larval habitat manipulation (water management using spillways across streams)
Comparator: No larval habitat manipulation

Summary

The systematic review identified one study from the Republic of the Philippines that investigated the impact of habitat manipulation by controlling the release of water from spillways (overflow channels) across streams to flush

downstream areas with water against malaria. It is unknown whether larval habitat manipulation has an effect on malaria parasite prevalence compared to no larval habitat manipulation (relative risk: 0.01; 95% CI: 0.0–0.16; one study; very low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** No larval habitat manipulation	**Intervention** Larval habitat manipulation	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria parasite prevalence in children aged 2 -10 years	Relative risk 0.01 (CI 95% 0 — 0.16) Based on data from 866 participants in 1 studies. (Observational (non-randomized))	86 per 1000 Difference:	0 per 1000 **86 fewer per 1000** (CI 95% 86 fewer — 72 fewer)	**Very low** Due to very serious risk of bias, due to very serious imprecision [1]	The evidence is very uncertain about the effect of using spillways across streams to manipulate larval habitats on malaria parasite prevalence compared to no larval habitat manipulation.

1. **Risk of Bias: very serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

Attached Images

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission

Intervention: Larval habitat manipulation (water management using floodgates on a dam across a stream) and annual IRS

Comparator: Annual IRS

Summary

The systematic review identified one study from the Republic of India that investigated the impact of habitat manipulation by controlling the release of water using floodgates on dams in areas with IRS. It is unknown whether larval habitat manipulation combined with IRS has an effect on malaria clinical incidence compared to IRS alone (odds ratios or relative risks could not be calculated because the numbers of participants in each arm or at follow-up were not reported; one study; very low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** IRS	**Intervention** Larval habitat manipulation and IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria incidence	Based on data from participants in 1 studies. (Observational (non-randomized))	The study did not report the number of participants in either arm. At baseline, the mean annual incidence rates were 1304 cases per 1000 children in control villages versus 786 per 1000 children in intervention villages. Following dam construction,		**Very low** Due to serious risk of bias, due to very serious imprecision [1]	The evidence is very uncertain about the effect of using floodgates on a dam to manipulate larval habitats on clinical malaria incidence compared to no larval

Outcome Timeframe	**Study results and measurements**	**Comparator** IRS	**Intervention** Larval habitat manipulation and IRS	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		a decline in malaria incidence was seen each year in the intervention villages (1000, 636.4, 181.8 and 181.8 per 1000 children), compared to increases in malaria incidence during the corresponding periods in the control villages.			habitat manipulation in areas with IRS.
Malaria parasite prevalence (all ages)	Based on data from participants in 1 studies. (Observational (non-randomized))	At baseline there were 271 participants in the intervention group and 299 in the comparator group. The parasite prevalence in intervention villages and control villages during the pre-construction year were 17.6% and 18.9%, respectively. However, in subsequent years after construction of the dam, there was gradual and significant decline in parasite rate (P < 0.01) in intervention villages. (Data on numbers of participants at follow-up not provided)		Very low Due to serious risk of bias, due to very serious imprecision [2]	The evidence is very uncertain about the effect of using flushing through floodgates on a dam to manipulate larval habitats on malaria parasite prevalence compared to no flushing in areas with IRS.

1. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**
2. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious. Publication bias: no serious.**

Attached Images

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Larvivorous fish
Comparator: no larvivorous fish

Summary

Fifteen studies were included in the systematic review. Studies were undertaken in Comoros, Ethiopia, India (three studies), Indonesia, Kenya, Republic of Korea (two studies), Sri Lanka (two studies), Sudan, and Tajikistan (two studies).
Treated aquatic habitats included wells, domestic water containers, fishponds and pools (seven studies); river bed pools below dams (two studies); rice field plots (four studies); and canals (two studies).
No studies reported on clinical malaria, EIR or adult vector densities; 12 studies reported on density of immature stages; and five studies reported on the number of aquatic habitats positive for immature stages of the vector species.

The studies were not suitable for a pooled analysis.
It is unknown whether larvivorous fish reduce the density of immature vector stages compared to no larvivorous fish (unpooled data; 12 studies; very low certainty evidence)
Larvivorous fish may reduce the number of larval sites positive for immature vector stages compared to no larvivorous fish
(unpooled data; five studies; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** no larvivorous fish	**Intervention** Larvivorous fish	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria (incidence)					No studies
Entomological inoculation rate					No studies
Density of adult malaria vectors					No studies
Density of immature stages of vectors in aquatic habitats (Quasi-experimental studies)	Based on data from participants in 12 studies. (Observational (non-randomized))	Not pooled. Variable effects reported.		**Very low** Due to serious inconsistency [1]	The evidence is very uncertain about the effect of larvivorous fish on the density of immature anopheline mosquitoes in water bodies compared to no fish.
Larval sites positive for immature stages of the vectors (Quasi-experimental studies)	Based on data from participants in 5 studies. (Observational (non-randomized))	Not pooled. Positive effects reported		**Low** Downgraded by two: the included studies were non-randomized controlled trials	Larvivorous fish may reduce the number of larval sites positive for immature anopheline mosquitoes compared to no fish.

1. **Inconsistency: serious.**

Attached Images

References

83. Walshe DP, Garner P, Adeel AA, Pyke GH, Burkot TR : Larvivorous fish for preventing malaria transmission. The Cochrane database of systematic reviews 2017;(12):CD008090 Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Topical repellent
Comparator: placebo or no topical repellent

Summary

A total of six RCTs were included in the review. Studies were conducted among residents in Plurinational State of Bolivia, Cambodia, Lao People's Democratic Republic and United Republic of Tanzania, and in specific populations in Pakistan (refugees) and Thailand (pregnant women).

It is unknown whether topical repellents have an effect on clinical malaria caused by *P. falciparum*
(Risk ratio: 0.65; 95% CI (0.40–1.07); three studies; very low certainty evidence)
Topical repellents may or may not have a protective effect against *P. falciparum* parasitaemia
(Risk ratio: 0.84; 95% CI (0.64–1.12); four studies; low certainty evidence)
Topical repellents may increase the number of clinical cases caused by *P. vivax*
(Risk ratio: 1.32; 95% CI (0.99–1.76); two studies; low certainty evidence)
Topical repellents may or may not have a protective effect against *P. vivax* parasitaemia
(Risk ratio: 1.07; 95% CI (0.80–1.41); three studies; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** placebo or no topical repellent	**Intervention** Topical repellent	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria (P. falciparum)	Relative risk 0.65 (CI 95% 0.4 — 1.07) Based on data from 4,450 participants in 3 studies.	39 per 1000 Difference:	25 per 1000 **14 fewer per 1000** (CI 95% 24 fewer — 2 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [1]	The evidence is very uncertain about the effect of topical repellents on P. falciparum clinical malaria compared to no topical repellents.
Parasitaemia (P. falciparum)	Relative risk 0.84 (CI 95% 0.64 — 1.12) Based on data from 13,310 participants in 4 studies.	15 per 1000 Difference:	12 per 1000 **3 fewer per 1000** (CI 95% 6 fewer — 2 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Topical repellents may result in little to no difference in P. falciparum parasitaemia compared to no topical repellents.
Clinical malaria (P. vivax)	Relative risk 1.32 (CI 95% 0.99 — 1.76) Based on data from 3,996 participants in 2 studies.	36 per 1000 Difference:	48 per 1000 **12 more per 1000** (CI 95% 0 more — 28 more)	**Low** Due to serious risk of bias, Due to serious imprecision [3]	Topical repellents may increase the number of P. vivax clinical cases compared to no topical repellents.
Parasitaemia (P. vivax)	Relative risk 1.07 (CI 95% 0.8 — 1.41) Based on data from 9,434 participants in 3 studies.	18 per 1000 Difference:	19 per 1000 **1 more per 1000** (CI 95% 4 fewer — 7 more)	**Low** Due to serious risk of bias, Due to serious imprecision [4]	Topical repellents may result in little to no difference in P. vivax parasitaemia compared to no topical repellents.

1. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**
3. **Risk of Bias: serious. Imprecision: serious.**
4. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

References

77. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ : Mosquito repellents for malaria prevention. The Cochrane database of systematic reviews 2018;(2):CD011595 Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Insecticide-treated clothing
Comparator: placebo or untreated clothing

Summary

Two RCTs were included in the systematic review. Studies were conducted in specific populations in the Republic of Colombia (military personnel) and the Islamic Republic of Pakistan (Afghan refugees).
Insecticide-treated clothing may have a protective effect against clinical malaria caused by *P. falciparum*
(Risk ratio: 0.49; 95% CI (0.29–0.83); two studies; low certainty evidence)
Insecticide-treated clothing may have a protective effect against clinical malaria caused by *P. vivax*
(Risk ratio: 0.64; 95% CI (0.40–1.01); two studies; low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** placebo or untreated clothing	**Intervention** Insecticide-treated clothing	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria (P. falciparum)	Relative risk 0.49 (CI 95% 0.29 — 0.83) Based on data from 997 participants in 2 studies.	**35** per 1000 Difference:	**17** per 1000 **18 fewer per 1000** (CI 95% 25 fewer — 6 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Insecticide-treating clothing may reduce P. falciparum clinical malaria compared to no insecticide-treated clothing.
Clinical malaria (P. vivax)	Relative risk 0.64 (CI 95% 0.4 — 1.01) Based on data from 997 participants in 2 studies.	**116** per 1000 Difference:	**74** per 1000 **42 fewer per 1000** (CI 95% 69 fewer — 1 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	Insecticide-treating clothing may reduce P. vivax clinical malaria compared to no insecticide-treated clothing.

1. **Risk of Bias: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Imprecision: serious.**

Attached Images

References

77. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ : Mosquito repellents for malaria prevention. The Cochrane database of systematic reviews 2018;(2):CD011595 Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Spatial/airborne repellents
Comparator: placebo or no malaria prevention intervention

Summary

Two RCTs were included in the systematic review. Studies were conducted in the People's Republic of China and the Republic of Indonesia.

It is unknown whether spatial repellents protect against malaria parasitaemia
(Risk ratio: 0.24; 95% CI (0.03–1.72); two studies; very low certainty evidence)

Outcome Timeframe	**Study results and measurements**	**Comparator** placebo or no malaria prevention intervention	**Intervention** Spatial/ airborne repellents	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Parasitaemia (all species)	Relative risk 0.24 (CI 95% 0.03 — 1.72) Based on data from 6,683 participants in 2 studies.	10 per 1000 Difference:	2 per 1000 **8 fewer per 1000** (CI 95% 10 fewer — 8 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [1]	The evidence is very uncertain about the effect of spatial repellents on malaria parasitaemia compared to no spatial repellents.

1. **Risk of Bias: serious. Inconsistency: serious. Imprecision: serious.**

Attached Images

References

77. Maia MF, Kliner M, Richardson M, Lengeler C, Moore SJ : Mosquito repellents for malaria prevention. The Cochrane database of systematic reviews 2018;(2):CD011595 Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Space spraying
Comparator: no space spraying

Summary

The review included a single interrupted time series study from the Republic of India that reported the monthly incidence of malaria over a four-year period, with at least one year prior and at least two years post-intervention.

It is not known if space spraying causes a step change in malaria incidence (1.00, 95% CI 0.51 to 1.92, 1 study, very low-certainty evidence).

It is not known if if space spraying causes a change in the slope of malaria incidence over time (risk ratio 0.85, 95% CI 0.79 to 0.91, 1 study, very low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** no space spraying	**Intervention** Space spraying	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria cases per month (Instant effect)	Relative risk 1 (CI 95% 0.51 — 1.92) Based on data from participants in 1 studies. (Observational (non-randomized))	6 per 1000 Difference:	6 per 1000 **0 more per 1000** (CI 95% 3 fewer — 6 more)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [1]	The evidence is very uncertain about the effect of space spraying on monthly malaria cases compared to no space spraying.
Malaria cases per month (Effect after 12 months follow-up)	Relative risk 0.85 (CI 95% 0.79 — 0.91) Based on data from participants in 1 studies. (Observational (non-randomized))	6 per 1000 Difference:	1 per 1000 **5 fewer per 1000** (CI 95% 6 fewer — 4 fewer)	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [2]	The evidence is very uncertain about the effect of space spraying on monthly malaria cases after 12 months compared to no space spraying.

1. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**
2. **Risk of Bias: serious. Indirectness: serious. Imprecision: serious.**

Attached Images

References

84. Pryce J, Choi L, Richardson M, Malone D : Insecticide space spraying for preventing malaria transmission. The Cochrane database of systematic reviews 2018;(11):CD012689 Pubmed Journal Website

Clinical Question/ PICO

Population: Adults and children living in areas with ongoing malaria transmission
Intervention: Screening of windows, ceilings, doors and eaves with untreated material
Comparator: No house screening

Summary

Two cRCTs met the inclusion criteria and were included in the meta-analysis. One trial in the Federal Democratic Republic of Ethiopia assessed screening of windows and doors. Another trial in the Republic of the Gambia assessed full screening (screening of eaves, doors and windows), as well as screening of ceilings only.

Screening may reduce clinical malaria incidence caused by *Plasmodium falciparum* (rate ratio 0.38, 95% CI 0.18 to 0.82; 1 trial, low-certainty evidence; Ethiopian study).

Screening may have a small effect on malaria parasite prevalence, (RR 0.84, 95% CI 0.60 to 1.17; 1 trial; low-certainty evidence).

Screening probably reduces anaemia (RR 0.61, 95% CI 0.42, 0.89; 705 participants; 1 trial, moderate-certainty evidence).

Screening may reduce the entomological inoculation rate (EIR). In the Gambian trial, there was a mean difference in EIR between the control houses and treatment houses ranging from 0.45 to 1.50 (CIs ranged from -0.46 to 2.41;

low-certainty evidence), The Ethiopian trial reported a mean difference in EIR of 4.57, favouring screening (95% CI 3.81 to 5.33; low-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** No screening	**Intervention** Screening	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria incidence caused by P. falciparum	Relative risk 0.38 (CI 95% 0.18 — 0.82) Based on data from participants in 1 studies. (Randomized controlled) Follow up: 6 months.	91 per 1000 Difference:	35 per 1000 **56 fewer per 1000** (CI 95% 75 fewer — 21 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision [1]	Screening of houses may reduce clinical P. falciparum malaria incidence compared to no screening.
Malaria parasite prevalence	Relative risk 0.84 (CI 95% 0.6 — 1.17) Based on data from 713 participants in 1 studies. [2] (Randomized controlled) Follow up: 1 year.	234 per 1000 Difference:	197 per 1000 **37 fewer per 1000** (CI 95% 94 fewer — 40 more)	**Low** Due to serious imprecision [3]	Screening of houses may result in little to no effect on malaria parasite prevalence compared to no screening.
Anaemia (haemoglobin conc <80g/L) prevalence	Relative risk 0.61 (CI 95% 0.42 — 0.89) Based on data from 705 participants in 1 studies. [4] (Randomized controlled) Follow up: 1 year.	211 per 1000 Difference:	128 per 1000 **82 fewer per 1000** (CI 95% 122 fewer — 23 fewer)	**Moderate** Due to serious imprecision [5]	Screening of houses probably reduces anaemia prevalence compared to no house screening.
Entomological Inoculation Rate (EIR)	Based on data from participants in 2 studies. (Randomized controlled) Follow up: range 6 months to 2 years.	In one study, the mean difference in EIR between the control houses and treatment houses ranged from 0.45 to 1.50 (CIs ranged from -0.46 to 2.41), depending on the study year and treatment arm; in a second study, there was a mean difference in EIR of 4.57 (95% CI 3.81 to 5.33).		**Low** Due to very serious imprecision [6]	Screening of houses may reduce EIR compared to no house screening.

1. **Risk of Bias: serious. Imprecision: serious.**
2. Systematic reviewwith included studies: Kirby 2009. **Baseline/comparator:** Control arm of reference used for intervention.
3. **Imprecision: serious.**
4. Systematic reviewwith included studies: Kirby 2009. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Imprecision: serious.**
6. **Imprecision: very serious.** the CIs around the mean estimates are very wide..

Attached Images

References

85. Furnival-Adams JA, Olanga EA, Napier M, Garner M : House modifications for preventing malaria. The Cochrane database of systematic reviews 2021;(1):CD013398 Pubmed Journal Website

4.1.4. Research needs

4.2. Preventive chemotherapies

4.2.1. Intermittent preventive treatment of malaria in pregnancy (IPTp)

Clinical Question/ PICO

Population: Pregnant women
Intervention: Therapeutic course of SP
Comparator: No medicine

Outcome Timeframe	**Study results and measurements**	**Comparator** No medicine	**Intervention** Therapeutic course of SP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Low birthweight, per dose of SP (low prevalence – 2.5%) 9 Critical	Relative risk 0.75 (CI 95% 0.71 — 0.78) Based on data from 80,519 participants in 98 studies. (Observational (non-randomized))	25 per 1000 Difference:	19 per 1000 **6 fewer per 1000** (CI 95% 7 fewer — 5 fewer)	Low Upgraded due to clear dose-response gradient, Due to serious publication bias [1]	Therapeutic courses of SP may improve low birthweight in low-burden areas.
Low birthweight, per dose of SP (high prevalence – 56.7%) 9 Critical	Relative risk 0.75 (CI 95% 0.71 — 0.78) Based on data from 80,519 participants in 98 studies. (Observational (non-randomized))	567 per 1000 Difference:	425 per 1000 **142 fewer per 1000** (CI 95% 164 fewer — 125 fewer)	Low Upgraded due to clear dose-response gradient, Due to serious publication bias [2]	Therapeutic courses of SP may result in a large improvement in low birthweight in high-burden areas.
Maternal anaemia, per dose of SP 8 Critical	Relative risk 0.9 (CI 95% 0.87 — 0.93) Based on data from participants in 53 studies. (Observational (non-randomized))	108 per 1000 Difference:	97 per 1000 **11 fewer per 1000** (CI 95% 14 fewer — 8 fewer)	Low Upgraded due to clear dose-response gradient, Due to serious publication bias [3]	Therapeutic courses of SP may decrease maternal anaemia.

Outcome Timeframe	**Study results and measurements**	**Comparator** No medicine	**Intervention** Therapeutic course of SP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Maternal malaria infection at delivery, per dose of SP 7 Critical	Relative risk 0.8 (CI 95% 0.75 — 0.85) Based on data from participants in 72 studies. (Observational (non-randomized))	20 per 1000 Difference:	16 per 1000 **4 fewer per 1000** (CI 95% 5 fewer — 3 fewer)	**Moderate** Upgraded due to clear dose-response gradient [4]	Therapeutic courses of SP probably decrease maternal malaria infection at delivery.
Placental malaria infection 6 Important	Relative risk 0.78 (CI 95% 0.74 — 0.84) Based on data from participants in 76 studies. (Observational (non-randomized))	9 per 1000 Difference:	7 per 1000 **2 fewer per 1000** (CI 95% 2 fewer — 1 fewer)	**Moderate** Upgraded due to clear dose-response gradient [5]	Therapeutic courses of SP probably decrease placental malaria infection.
Preterm delivery, per dose of SP 6 Important	Relative risk 0.76 (CI 95% 0.71 — 0.81) Based on data from participants in 59 studies. (Observational (non-randomized))	16 per 1000 Difference:	12 per 1000 **4 fewer per 1000** (CI 95% 5 fewer — 3 fewer)	**Very low** Due to serious publication bias, Due to serious inconsistency [6]	We are uncertain whether therapeutic courses of SP improve or worsen preterm delivery.
Stillbirths and/ or abortions 6 Important	Relative risk 0.68 (CI 95% 0.59 — 0.78) Based on data from 0 participants in 46 studies. (Observational (non-randomized))	10 per 1000 Difference:	7 per 1000 **3 fewer per 1000** (CI 95% 4 fewer — 2 fewer)	**Very low** Due to serious inconsistency, Due to serious indirectness [7]	We are uncertain whether therapeutic courses of SP improve or worsen stillbirths and/or abortions.
Maternal deaths 5 Important	Relative risk 1.17 (CI 95% 0.49 — 2.8) Based on data from 8,755 participants in 6 studies. (Randomized controlled)	3 per 1000 Difference:	4 per 1000 **1 more per 1000** (CI 95% 2 fewer — 5 more)	**Low** Very few events, Wide CIs include both no effect and appreciable risk [8]	Therapeutic courses of SP may result in little to no difference in maternal deaths.
Mean birthweight, per dose of SP 5 Important	Based on data from participants in 82 studies. (Observational (non-randomized))	Difference:	**MD 57 higher** (CI 95% 44 higher — 69 higher)	**Moderate** Upgraded due to clear dose-response gradient [9]	Therapeutic courses of SP probably improve mean birthweight.
Maternal haemoglobin, per dose of SP 4 Important	Based on data from participants in 46 studies. (Observational (non-randomized))	Difference:	**MD 0.19 higher** (CI 95% 0.15 higher — 0.22 higher)	**Low** Upgraded due to clear dose-response gradient [10]	Therapeutic courses of SP may improve maternal haemoglobin.

Outcome Timeframe	**Study results and measurements**	**Comparator** No medicine	**Intervention** Therapeutic course of SP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Maternal serious adverse events 6 Important	Based on data from participants in 8 studies. (Randomized controlled)	The pooled prevalence of serious adverse events among IPTp-SP recipients was 3.84% (95% CI 2.20-5.88).		Low Due to very serious risk of bias (no events reported in comparison arm) [11]	Therapeutic courses of SP may increase maternal serious adverse events.
Maternal adverse events, IPTp-SP vs placebo or case management	Based on data from 8,122 participants in 16 studies. (Randomized controlled)	The pooled prevalence of adverse events was 14.3% (95% CI 4.9-27.5%)		Moderate Due to serious imprecision [12]	Therapeutic courses of SP probably increase maternal adverse events compared to placebo or case management.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: serious.** Due to participation bias (women who did not attend ANC are likely to be different from those receiving three doses of IPTp). **Upgrade: clear dose-response gradient.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: serious.** Due to participation bias (women who did not attend ANC are likely to be different from those receiving three doses of IPTp). **Upgrade: clear dose-response gradient.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: serious.** Due to participation bias (women who did not attend ANC are likely to be different from those receiving three doses of IPTp). **Upgrade: clear dose-response gradient.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious. Upgrade: clear dose-response gradient.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious. Upgrade: clear dose-response gradient.**
6. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared 77.0%.. **Indirectness: no serious. Imprecision: no serious. Publication bias: serious.** Due to participation bias (women who did not attend ANC are likely to be different from those receiving three doses of IPTp).
7. **Inconsistency: serious.** Small numbers. The magnitude of statistical heterogeneity was high, with I-squared 79%. **Indirectness: serious.** Low numbers contributing to outcome. Distinction is not always made between these outcomes in participating studies. **Imprecision: no serious. Publication bias: no serious.**
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events, Wide CIs include both no effect and appreciable risk. **Publication bias: no serious.**
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious. Upgrade: clear dose-response gradient.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious. Upgrade: clear dose-response gradient.**
11. **Risk of Bias: very serious.** No events reported in comparison arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Very few events. **Publication bias: no serious.**
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CI crosses the null. **Publication bias: no serious.**

Attached Images

4.2.2. Perennial malaria chemoprevention (PMC) - formerly intermittent preventive treatment of malaria in infants (IPTi)

Clinical Question/ PICO

Population: Children up to 24 months living in malaria-endemic areas
Intervention: PMC
Comparator: No intervention, or alternative medicines

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention, or alternative medicines	**Intervention** PMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria: all antimalarials, various regimens 9 Critical	Rate ratio 0.7 (CI 95% 0.62 — 0.8) Based on data from 10,602 participants in 10 studies. (Randomized controlled) Follow up: 9-36 months of age.	Difference:	**220 fewer per 1000** (CI 95% 280 fewer — 150 fewer)	Moderate Due to serious imprecision [1]	PMC probably reduces incidence of clinical malaria.
Clinical malaria: SP (various dosing regimens) [2] 9 Critical	Rate ratio 0.78 (CI 95% 0.69 — 0.88) Based on data from 8,774 participants in 8 studies. (Randomized controlled) Follow up: 9-36 months of age.	Difference:	**160 fewer per 1000** 230 fewer — 90 fewer	Moderate Due to serious imprecision [3]	PMC with SP probably reduces incidence of clinical malaria.
Clinical malaria: AS-AQ (at 10, 14 weeks and 9 months) 9 Critical	Rate ratio 0.75 (CI 95% 0.61 — 0.94) Based on data from 547 participants in 1 studies. (Randomized controlled) Follow up: 24 months of age.	Difference:	**330 fewer per 1000** (CI 95% 520 fewer — 120 fewer)	Moderate Due to serious imprecision [4]	PMC with AS-AQ probably reduces incidence of clinical malaria.
Clinical malaria: DHAP (monthly doses from 6–24 months of age) 9 Critical	Rate ratio 0.42 (CI 95% 0.33 — 0.54) Based on data from 147 participants in 1 studies. (Randomized controlled) Follow up: 36 months of age.	Difference:	**3,720 fewer per 1000** (CI 95% 430 fewer — 325 fewer)	Moderate Due to serious imprecision [5]	PMC with DHAP probably reduces incidence of clinical malaria.
Clinical malaria: SP+AS (at 10, 14 weeks and 9 months) 9 Critical	Rate ratio 0.78 (CI 95% 0.62 — 0.97) Based on data from 508 participants in 1 studies. (Randomized controlled) Follow up: up to 24 months of age.	Difference:	**290 fewer per 1000** (CI 95% 510 fewer — 40 fewer)	High	PMC with SP+AS reduces incidence of clinical malaria.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention, or alternative medicines	**Intervention** PMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Severe malaria incidence: SP (various dosing regimens) 8 Critical	Rate ratio 0.92 (CI 95% 0.47 — 1.81) Based on data from 1,347 participants in 2 studies. (Randomized controlled)	Difference:	**1 fewer per 1000** (CI 95% 9 fewer — 11 more)	**Low** Due to serious inconsistency, Due to serious imprecision [6]	PMC with SP may reduce severe malaria incidence.
Severe malaria incidence: DHAP (monthly doses from 6–24 months of age) [7] 8 Critical	Rate ratio 1.29 (CI 95% 0.28 — 5.98) Based on data from 147 participants in 1 studies. (Randomized controlled)	Difference:	**8 more per 1000** (CI 95% 21 fewer — 144 more)	**Low** Due to very serious imprecision [8]	PMC with DHAP may increase severe malaria incidence.
Anaemia incidence: AS-AQ (at 10, 14 weeks and 9 months) 7 Critical	Rate ratio 0.77 (CI 95% 0.53 — 1.12) Based on data from 684 participants in 1 studies. (Randomized controlled)	Difference:	**70 fewer per 1000** 140 fewer — 40 more	**Moderate** Due to serious imprecision [9]	PMC with AS-AQ probably reduces anaemia incidence.
Anaemia incidence: SP+AS (at 10, 14 weeks and 9 months) 7 Critical	Rate ratio 0.72 (CI 95% 0.49 — 1.07) Based on data from 676 participants in 1 studies. (Randomized controlled)	Difference:	**80 fewer per 1000** (CI 95% 150 fewer — 20 more)	**Moderate** Due to serious imprecision [10]	PMC with SP+AS probably reduces anaemia incidence.
Anaemia incidence: SP (various dosing regimens) 7 Critical	Rate ratio 0.82 (CI 95% 0.68 — 0.98) Based on data from 7,438 participants in 6 studies. (Randomized controlled)	Difference:	**6 fewer per 1000** (CI 95% 100 fewer — 10 fewer)	**Moderate** Due to serious inconsistency [11]	PMC with SP probably reduces anaemia incidence.
Anaemia incidence: MQ (at 10, 14 weeks and 9 months) 7 Critical	Rate ratio 1.06 (CI 95% 0.78 — 1.44) Based on data from 480 participants in 1 studies. (Randomized controlled)	Difference:	**20 fewer per 1000** (CI 95% 60 fewer — 130 more)	**Moderate** Due to serious imprecision [12]	PMC with MQ probably increases anaemia incidence.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention, or alternative medicines	**Intervention** PMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality: SP (various dosing regimens) 5 Important	Relative risk 0.93 (CI 95% 0.74 — 1.15) Based on data from 14,588 participants in 9 studies. (Randomized controlled)	23 per 1000 Difference:	21 per 1000 **2 fewer per 1000** (CI 95% 6 fewer — 3 more)	Moderate Due to serious inconsistency [13]	PMC with SP probably reduces all-cause mortality slightly.
All-cause mortality: AS-AQ (at 10, 14 weeks and 9 months) 5 Important	Relative risk 1.21 (CI 95% 0.58 — 2.55) Based on data from 684 participants in 1 studies. (Randomized controlled)	36 per 1000 Difference:	44 per 1000 **8 more per 1000** (CI 95% 15 fewer — 56 more)	Moderate Due to serious imprecision [14]	PMC with AS-AQ probably increases all-cause mortality slightly.
All-cause mortality: DHAP (monthly doses from 6–24 months of age) 5 Important	Relative risk 0.33 (CI 95% 0.01 — 8.08) Based on data from 196 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	3 per 1000 **7 fewer per 1000** (CI 95% 10 fewer — 71 more)	Low Due to very serious imprecision [15]	PMC with DHAP may reduce all-cause mortality slightly.
All-cause mortality: SP+AS (at 10, 14 weeks and 9 months) 5 Important	Relative risk 0.83 (CI 95% 0.36 — 1.89) Based on data from 676 participants in 1 studies. (Randomized controlled)	36 per 1000 Difference:	30 per 1000 **6 fewer per 1000** (CI 95% 23 fewer — 32 more)	Moderate Due to serious imprecision [16]	PMC with SP+AS probably reduces all-cause mortality slightly.
Adverse events: DHAP (monthly doses from 6–24 months of age) 4 Important	Relative risk 0.58 (CI 95% 0.46 — 0.73) Based on data from 980 participants in 1 studies. (Randomized controlled)	227 per 1000 Difference:	132 per 1000 **95 fewer per 1000** (CI 95% 122 fewer — 61 fewer)	Moderate Due to serious imprecision [17]	PMC with DHAP probably reduces adverse events slightly.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The overall meta-analysis was underpowered to detect a difference or to prove equivalence. **Publication bias: no serious.**
2. Per 1000 person years
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The overall meta-analysis was underpowered to detect a difference or to prove equivalence. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small population, wide CIs around effect estimate. **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Very few infants contributed to this

analysis. Only data from one study. **Publication bias: no serious.**
6. **Inconsistency: serious.** There was considerable variation in the size of effect. The direction of the effect was not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** The trials were underpowered to detect a difference or to prove equivalence. Wide CIs including a null effect.. **Publication bias: no serious.**
7. DHAP given monthly for 18 months
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few infants contributed to this analysis. Only data from one study. Wide CIs. **Publication bias: no serious.**
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Only data from one study. **Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. Only data from one study. **Publication bias: no serious.**
11. **Inconsistency: serious.** Unexplained statistical heterogeneity observed in this meta-analysis (I-squared: 67%.). **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
13. **Inconsistency: serious.** Wide variance of point estimates observed among the nine trials in this meta-analysis. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs include potential for important harm and benefit. **Publication bias: no serious.**
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Wide CIs. Only data from one study. **Publication bias: no serious.**
16. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** CIs include potential for important harm and benefit. **Publication bias: no serious.**
17. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Very few infants contributed to this analysis. **Publication bias: no serious.**

Attached Images

4.2.3. Seasonal malaria chemoprevention (SMC)

Clinical Question/ PICO

Population: Children aged ≤10 years in areas of seasonal transmission
Intervention: Full treatment doses of antimalarial medicines monthly during the malaria transmission season
Comparator: No intervention, or alternative medicines

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria: children <5 years (various regimens) Per 100 person-years 7 Critical	Rate ratio 0.27 (CI 95% 0.25 — 0.29) Based on data from participants in 8 studies. (Randomized controlled)	Difference:	**315 fewer per 1000** (CI 95% 335 fewer — 212 fewer)	**Moderate** Due to serious inconsistency [1]	SMC probably reduces clinical malaria incidence in children <5 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria: children <5 years, 3–4 cycles, SP+AQ 7 Critical	Rate ratio 0.28 (CI 95% 0.26 — 0.31) Based on data from participants in 4 studies. (Randomized controlled)	Difference:	**338 fewer per 1000** (CI 95% 374 fewer — 314 fewer)	**Moderate** Due to serious inconsistency [2]	3–4 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <5 years.
Clinical malaria: children <5 years, 5–6 cycles, SP+AQ 7 Critical	Rate ratio 0.22 (CI 95% 0.18 — 0.25) Based on data from participants in 2 studies. (Randomized controlled)	Difference:	**205 fewer per 1000** (CI 95% 233 fewer — 168 fewer)	**Moderate** Due to serious inconsistency [3]	5–6 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <5 years.
Clinical malaria: children <5 years, 5–6 cycles, AS-AQ 7 Critical	Rate ratio 0.31 (CI 95% 0.26 — 0.37) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**122 fewer per 1000** (CI 95% 146 fewer — 103 fewer)	**High**	5–6 cycles of SMC with AS-AQ reduces clinical malaria incidence in children <5 years.
Clinical malaria: children <5 years, 3–4 cycles, SP+AS 7 Critical	Rate ratio 0.14 (CI 95% 0.1 — 0.2) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**315 fewer per 1000** (CI 95% 450 fewer — 225 fewer)	**High**	3–4 cycles of SMC with SP+AS reduces clinical malaria incidence in children <5 years.
Clinical malaria incidence: children ≥5 years (various regimens) 7 Critical	Rate ratio 0.27 (CI 95% 0.25 — 0.3) Based on data from participants in 3 studies. (Randomized controlled)	Difference:	**170 fewer per 1000** (CI 95% 189 fewer — 158 fewer)	**Low** Due to serious risk of bias, Due to serious inconsistency [4]	SMC may reduce clinical malaria incidence in children ≥ 5 years.
Clinical malaria: children 5–9 years, 3–4 cycles, SP+AQ 7 Critical	Rate ratio 0.39 (CI 95% 0.35 — 0.44) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**2 fewer per 1000** (CI 95% 3 fewer — 2 fewer)	**Moderate** Due to serious risk of bias [5]	3–4 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children 5–9 years.
Clinical malaria: children 5–9 years, 5–6 cycles, SP+AQ	Rate ratio 0.17 (CI 95% 0.15 — 0.2) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**248 fewer per 1000** (CI 95% 292 fewer — 219	**High**	5–6 cycles of SMC with SP+AQ reduces clinical malaria incidence in children 5–9 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
7 Critical			fewer)		
Clinical malaria: children <10 years, 3–4 cycles, SP+AQ 7 Critical	Rate ratio 0.4 (CI 95% 0.35 — 0.45) Based on data from participants in 2 studies. (Randomized controlled)	Difference:	**53 fewer per 1000** (CI 95% 60 fewer — 46 fewer)	**Moderate** Due to serious risk of bias [6]	3–4 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <10 years.
Clinical malaria: children <10 years, 5–6 cycles, SP+AQ 7 Critical	Rate ratio 0.17 (CI 95% 0.15 — 0.2) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**262 fewer per 1000** (CI 95% 308 fewer — 231 fewer)	**Moderate** Due to serious risk of bias [7]	5–6 cycles of SMC with SP+AQ probably reduces clinical malaria incidence in children <10 years.
Clinical malaria: children 6–15 years, 3–4 cycles, AS-AQ 7 Critical	Rate ratio 0.15 (CI 95% 0.11 — 0.21) Based on data from participants in 1 studies. (Randomized controlled)	Difference:	**64 fewer per 1000** (CI 95% 89 fewer — 47 fewer)	**Low** Due to very serious risk of bias [8]	3–4 cycles of SMC with AS-AQ may reduce clinical malaria incidence in children 6–15 years.
Incidence of severe malaria, children <5 years, SP+AQ, 3–4 cycles 9 Critical	Rate ratio 0.57 (CI 95% 0.37 — 0.89) Based on data from 2,000 participants in 3 studies. (Randomized controlled)	Difference:	**14 fewer per 1000** (CI 95% 22 fewer — 9 fewer)	**High**	3–4 cycles of SMC with SP+AQ decreases incidence of severe malaria in children <5 years.
Incidence of severe malaria, children 5–9 years, SP+AQ, 3–4 cycles 9 Critical	Rate ratio 0.44 (CI 95% 0.23 — 0.84) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**4 fewer per 1000** (CI 95% 8 fewer — 2 fewer)	**Moderate** Due to serious risk of bias [9]	3–4 cycles of SMC with SP+AQ probably decreases incidence of severe malaria in children 5–9 years.
Incidence of severe malaria, children <10 years 9 Critical	Rate ratio 0.53 (CI 95% 0.37 — 0.76) Based on data from 2,000 participants in 4 studies. (Randomized controlled)	Difference:	**11 fewer per 1000** (CI 95% 16 fewer — 8 fewer)	**High**	SMC decreases incidence of severe malaria in children <10 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Incidence of all-cause hospitalization, children <5 years, SP+AQ moderate transmission, 3–4 cycles 8 Critical	Rate ratio 1.38 (CI 95% 0.71 — 2.67) Based on data from 2,000 participants in 2 studies. (Randomized controlled)	Difference:	**8 more per 1000** (CI 95% 4 fewer — 86 more)	Moderate Due to serious imprecision [10]	3-4 cycles of SMC with SP+AQ probably increases incidence of all-cause hospitalization in children <5 years in moderate transmission settings.
Incidence of all-cause hospitalization, children <5 years, SP+AQ, high transmission, 3–4 cycles 8 Critical	Rate ratio 0.54 (CI 95% 0.31 — 0.94) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**50 fewer per 1000** (CI 95% 87 fewer — 29 fewer)	High	3-4 cycles of SMC with SP+AQ reduces incidence of all-cause hospitalization in children <5 years in high transmission settings.
Incidence of all-cause hospitalization, children <5 years, AS-AQ, 5–6 cycles 8 Critical	Rate ratio 0.42 (CI 95% 0.2 — 0.87) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**23 fewer per 1000** (CI 95% 48 fewer — 11 fewer)	High	5–6 cycles of SMC with AS-AQ reduces incidence of all-cause hospitalization in children <5 years.
All-cause mortality, children <5 years (various regimens) 6 Important	Rate ratio 0.89 (CI 95% 0.68 — 1.17) Based on data from 2,000 participants in 6 studies. (Randomized controlled)	Difference:	**8 fewer per 1000** (CI 95% 10 fewer — 6 fewer)	Low Due to serious inconsistency, Due to serious imprecision [11]	SMC may reduce all-cause mortality in children <5 years.
All-cause mortality, children <5 years, SP+AQ, 3–4 cycles 6 Important	Rate ratio 0.86 (CI 95% 0.64 — 1.16) Based on data from 2,000 participants in 4 studies. (Randomized controlled)	Difference:	**7 fewer per 1000** (CI 95% 10 fewer — 5 fewer)	Low Due to serious inconsistency, Due to serious imprecision [12]	3–4 cycles of SMC with SP+AQ may reduce all-cause mortality in children <5 years.
All-cause mortality,	Rate ratio 1.06 (CI 95% 0.47 — 2.4) Based on data from	Difference:	**2 fewer per 1000**	Very low Due to serious	We are uncertain about the effect of 5–6 cycles of SMC with SP+AQ on

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
children <5 years, SP+AQ, 5–6 cycles 6 Important	2,000 participants in 1 studies. (Randomized controlled)		(CI 95% 1 fewer — 5 more)	imprecision, Due to very serious risk of bias [13]	all-cause mortality in children <5 years.
All-cause mortality, children <5 years, AS-AQ, 5–6 cycles 6 Important	Rate ratio 1.04 (CI 95% 0.39 — 2.77) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**18 fewer per 1000** (CI 95% 7 fewer — 9 more)	Moderate Due to serious imprecision [14]	5–6 cycles of SMC with AS-AQ probably has little or no difference on all-cause mortality in children <5 years.
All-cause mortality, children 5–9 years, SP+AQ, 3–4 cycles 6 Important	Rate ratio 0.97 (CI 95% 0.6 — 1.57) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**5 fewer per 1000** (CI 95% 4 fewer — 2 more)	Low Due to serious risk of bias, Due to serious imprecision [15]	3–4 cycles of SMC with SP+AQ may have little or no difference on all-cause mortality in children 5–9 years.
All-cause mortality, children 5–9 years, SP+AQ, 5–6 cycles 6 Important	Rate ratio 1.82 (CI 95% 0.16 — 20.24) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	Difference:	**0 fewer per 1000** (CI 95% 0 fewer — 4 more)	Very low Due to serious imprecision, Due to very serious risk of bias [16]	We are uncertain whether 5–6 cycles of SMC with SP+AQ increases or decreases all-cause mortality in children 5–9 years.
Parasite prevalence, children <5 years (various regimens) 4 Important	Relative risk 0.38 (CI 95% 0.34 — 0.43) Based on data from 200 participants in 9 studies. (Randomized controlled)	221 per 1000 Difference:	84 per 1000 **137 fewer per 1000** (CI 95% 146 fewer — 126 fewer)	Moderate Due to serious inconsistency [17]	SMC probably reduces parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, SP+AQ, 3–4 cycles 4 Important	Relative risk 0.28 (CI 95% 0.24 — 0.32) Based on data from 200 participants in 4 studies. (Randomized controlled)	159 per 1000 Difference:	45 per 1000 **114 fewer per 1000** (CI 95% 121 fewer — 108 fewer)	High	3–4 cycles of SMC with SP+AQ reduces parasite prevalence in children <5 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Parasite prevalence, children <5 years, SP+AQ, 5–6 cycles 4 Important	Relative risk 0.55 (CI 95% 0.43 — 0.7) Based on data from 200 participants in 2 studies. (Randomized controlled)	192 per 1000 Difference:	106 per 1000 **86 fewer per 1000** (CI 95% 109 fewer — 58 fewer)	**Moderate** Due to serious inconsistency [18]	5–6 cycles of SMC with SP+AQ probably reduces parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, AS-AQ, 3–4 cycles 4 Important	Relative risk 0.67 (CI 95% 0.53 — 0.85) Based on data from 200 participants in 1 studies. (Randomized controlled)	412 per 1000 Difference:	276 per 1000 **136 fewer per 1000** (CI 95% 194 fewer — 62 fewer)	**Moderate** Due to serious risk of bias [19]	3–4 cycles of SMC with AS-AQ probably reduces parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, SP+AS, 3–4 cycles 4 Important	Relative risk 0.32 (CI 95% 0.15 — 0.67) Based on data from 200 participants in 1 studies. (Randomized controlled)	370 per 1000 Difference:	118 per 1000 **252 fewer per 1000** (CI 95% 314 fewer — 122 fewer)	**Low** Due to very serious imprecision [20]	3–4 cycles of SMC with SP+AS may reduce parasite prevalence in children <5 years.
Parasite prevalence, children <5 years, AS-AQ, 5–6 cycles 4 Important	Relative risk 0.24 (CI 95% 0.16 — 0.36) Based on data from 200 participants in 1 studies. (Randomized controlled)	196 per 1000 Difference:	47 per 1000 **149 fewer per 1000** (CI 95% 165 fewer — 125 fewer)	**High**	5–6 cycles of SMC with AS-AQ reduces parasite prevalence in children <5 years.
Parasite prevalence, children 5–9 years, SP+AQ, 5–6 cycles 4 Important	Relative risk 0.23 (CI 95% 0.11 — 0.48) Based on data from 200 participants in 1 studies. (Randomized controlled)	250 per 1000 Difference:	57 per 1000 **193 fewer per 1000** (CI 95% 223 fewer — 130 fewer)	**High**	5–6 cycles of SMC with SP+AQ reduces parasite prevalence in children 5–9 years.
Parasite prevalence, children <10 years, SP+AQ, 3–6 cycles 4 Important	Relative risk 0.28 (CI 95% 0.17 — 0.44) Based on data from 200 participants in 2 studies. (Randomized controlled)	84 per 1000 Difference:	24 per 1000 **60 fewer per 1000** 70 fewer — 47 fewer	**High**	SMC with SP+AQ reduces parasite prevalence of malaria in children <10 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Parasite prevalence, children <10 years, SP+AQ, 3–4 cycles 4 Important	Relative risk 0.29 (CI 95% 0.14 — 0.61) Based on data from 200 participants in 1 studies. (Randomized controlled)	**19** per 1000 Difference:	**6** per 1000 **13 fewer per 1000** (CI 95% 16 fewer — 7 fewer)	**High**	3–4 cycles of SMC with SP+AQ reduces parasite prevalence in children <10 years.
Parasite prevalence, children <10 years, SP+AQ, 5–6 cycles 4 Important	Relative risk 0.27 (CI 95% 0.15 — 0.48) Based on data from 200 participants in 1 studies. (Randomized controlled)	**215** per 1000 Difference:	**58** per 1000 **157 fewer per 1000** (CI 95% 183 fewer — 112 fewer)	**High**	5–6 cycles of SMC with SP+AQ reduces parasite prevalence in children <10 years.
Any anaemia, children <5 years 2 Not Important	Relative risk 0.84 (CI 95% 0.8 — 0.88) Based on data from 200 participants in 6 studies. (Randomized controlled)	**524** per 1000 Difference:	**440** per 1000 **84 fewer per 1000** (CI 95% 105 fewer — 63 fewer)	**Moderate** Due to serious inconsistency [21]	SMC probably reduces any anaemia in children <5 years.
Anaemia prevalence: SP+AQ 2 Not Important	Relative risk 0.47 (CI 95% 0.35 — 0.63) (Randomized controlled)	Difference:	**26 fewer per 1000** (CI 95% 32 fewer — 18 fewer)	**High**	SMC with SP+AQ reduces anaemia prevalence.
Any anaemia, children <5 years, SP+AQ, 3–4 cycles 2 Not Important	Relative risk 0.77 (CI 95% 0.72 — 0.83) Based on data from 200 participants in 3 studies. (Randomized controlled)	**494** per 1000 Difference:	**380** per 1000 **114 fewer per 1000** (CI 95% 138 fewer — 84 fewer)	**Moderate** Due to serious inconsistency [22]	3–4 cycles of SMC with SP+AQ probably decreases any anaemia in children <5 years.
Any anaemia, children <5 years, SP+AQ, 5–6 cycles 2 Not Important	Relative risk 0.88 (CI 95% 0.82 — 0.95) Based on data from 200 participants in 2 studies. (Randomized controlled)	**598** per 1000 Difference:	**526** per 1000 **72 fewer per 1000** (CI 95% 108 fewer — 30 fewer)	**High**	5–6 cycles of SMC with SP+AQ reduces any anaemia in children <5 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Any anaemia, children <5 years, AS-AQ, 3–4 cycles 2 Not Important	Relative risk 0.98 (CI 95% 0.85 — 1.13) Based on data from 200 participants in 1 studies. (Randomized controlled)	463 per 1000 Difference:	454 per 1000 **9 fewer per 1000** (CI 95% 69 fewer — 60 more)	Very low Due to serious imprecision [23]	We are uncertain whether 3–4 cycles of SMC with AS-AQ increases or decreases any anaemia in children <5 years.
Any anaemia, children 5–9 years, SP+AQ, 5–6 cycles 2 Not Important	Relative risk 0.7 (CI 95% 0.52 — 0.95) Based on data from 200 participants in 1 studies. (Randomized controlled)	475 per 1000 Difference:	332 per 1000 **143 fewer per 1000** (CI 95% 228 fewer — 24 fewer)	High	5–6 cycles of SMC with SP+AQ reduces any anaemia in children 5–9 years.
Moderate anaemia in children <5 years (various regimens) 2 Not Important	Relative risk 0.82 (CI 95% 0.73 — 0.93) Based on data from 200 participants in 6 studies. (Randomized controlled)	100 per 1000 Difference:	82 per 1000 **18 fewer per 1000** (CI 95% 27 fewer — 7 fewer)	Moderate Due to serious inconsistency [24]	SMC probably reduces moderate anaemia in children <5 years slightly.
Moderate anaemia in children <5 years, SP+AQ, 3–4 cycles, moderate to high transmission 2 Not Important	Relative risk 0.47 (CI 95% 0.35 — 0.63) Based on data from 200 participants in 2 studies. (Randomized controlled)	48 per 1000 Difference:	22 per 1000 **26 fewer per 1000** (CI 95% 32 fewer — 18 fewer)	High	3–4 cycles of SMC with SP+AQ decreases moderate anaemia in children <5 years, in moderate to high transmission areas.
Moderate anaemia in children <5 years, SP+AQ, 3–4 cycles, low transmission 2 Not Important	Relative risk 0.93 (CI 95% 0.81 — 1.07) Based on data from 200 participants in 2 studies. (Randomized controlled)	184 per 1000 Difference:	171 per 1000 **13 fewer per 1000** (CI 95% 35 fewer — 13 more)	High	3–4 cycles of SMC with SP+AQ reduces moderate anaemia in children <5 years, in low transmission areas.
Moderate anaemia in children <5 years, AS-AQ, 5–6 cycles	Relative risk 0.91 (CI 95% 0.64 — 1.3) Based on data from 200 participants in 1 studies. (Randomized controlled)	102 per 1000 Difference:	93 per 1000 **9 fewer per 1000** (CI 95% 37	High	5–6 cycles of SMC with AS-AQ reduces moderate anaemia in children <5 years.

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention or alternative medicines	**Intervention** SMC	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
2 Not Important			fewer — 31 more)		
Adverse events, children up to 15 years, various regimens, 3–4 cycles, active surveillance 5 Important	Relative risk 1.4 (CI 95% 1.31 — 1.51) Based on data from 18,042 participants in 4 studies. (Randomized controlled)	**114** per 1000 Difference:	**160** per 1000 **46 more per 1000** (CI 95% 35 more — 58 more)	**High**	SMC increases adverse events in children up to 15 years.

1. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared > 50%.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
2. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared > 50%.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** Randomization was imbalanced. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared: > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Imbalanced randomization. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: very serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9. **Risk of Bias: serious.** Outcome evaluated by health system staff aware of study arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
11. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: serious.** Wide range of effect sizes. **Publication bias: no serious.**
12. **Inconsistency: serious.** Wide range of effect sizes. **Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
13. **Risk of Bias: very serious.** Extra method of finding deaths in intervention arm. Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. Only data from one study. **Publication bias: no serious.**
15. **Risk of Bias: serious.** Outcome evaluated by health system staff aware of study arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
16. **Risk of Bias: very serious.** Extra method of finding deaths in intervention arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
17. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
18. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
19. **Risk of Bias: serious.** High loss to follow-up, much higher in control arm. **Inconsistency: no serious. Indirectness: no**

serious. Imprecision: no serious. Publication bias: no serious.
20. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs. Only data from one study. **Publication bias: no serious.**
21. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
22. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
23. **Risk of Bias: very serious.** High loss to follow-up, much higher in control arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
24. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

Attached Images

4.2.4. Intermittent preventive treatment of malaria in school-aged children (IPTsc)

Clinical Question/ PICO

Population: School-aged children
Intervention: Therapeutic course of an antimalarial medicine
Comparator: No intervention

Outcome Timeframe	**Study results and measurements**	**Comparator** No intervention	**Intervention** Therapeutic course of an antimalarial medicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria during follow-up (6 to 103 weeks) 8 Critical	Relative risk 0.5 (CI 95% 0.36 — 0.6) Based on data from 1,815 participants in 4 studies. (Randomized controlled)	226 per 1000 Difference:	113 per 1000 **113 fewer per 1000** (CI 95% 145 fewer — 90 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [1]	Therapeutic courses of an antimalarial medicine may decrease clinical malaria during follow-up.
Anaemia 8 Critical	Relative risk 0.85 (CI 95% 0.77 — 0.92) Based on data from 14,940 participants in 11 studies. (Randomized controlled)	279 per 1000 Difference:	237 per 1000 **42 fewer per 1000** (CI 95% 64 fewer — 22 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [2]	Therapeutic courses of an antimalarial medicine may decrease anaemia.
Parasite prevalence	Relative risk 0.46 (CI 95% 0.4 — 0.53) Based on data from 15,658 participants in 11 studies. (Randomized controlled)	349 per 1000 Difference:	160 per 1000 **189 fewer per 1000**	Low Due to serious risk of bias, Due to serious inconsistency [3]	Therapeutic courses of an antimalarial medicine may decrease parasite prevalence.

Outcome Timeframe	Study results and measurements	Comparator No intervention	Intervention Therapeutic course of an antimalarial medicine	Certainty of the Evidence (Quality of evidence)	Plain language summary
			(CI 95% 209 fewer — 164 fewer)		

1. **Risk of Bias: serious.** Participants and personnel giving the treatments were not blinded. **Inconsistency: serious.** Unexplained between-study heterogeneity . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
2. **Risk of Bias: serious.** Participants and personnel giving the treatments were not blinded. **Inconsistency: serious.** Unexplained between-study heterogeneity . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: serious.** Participants and personnel giving the treatments were not blinded. **Inconsistency: serious.** Unexplained between-study heterogeneity . **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

Attached Images

4.2.5. Post-discharge malaria chemoprevention (PDMC)

Clinical Question/ PICO

Population: Post-discharge children hospitalized with severe anaemia
Intervention: Therapeutic courses of an antimalarial medicine
Comparator: Placebo or no intervention

Outcome Timeframe	Study results and measurements	Comparator Placebo or no intervention	Intervention Therapeutic courses of an antimalarial medicine	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (intervention period) 9 Critical	Relative risk 0.23 (CI 95% 0.08 — 0.7) Based on data from 3,356 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	12 per 1000 Difference:	3 per 1000 **9 fewer per 1000** (CI 95% 11 fewer — 4 fewer)	High	Therapeutic courses of an antimalarial medicine decrease all-cause mortality in the intervention period.
All-cause mortality (post-intervention period) 9 Critical	Relative risk 1.61 (CI 95% 0.81 — 3.19) Based on data from 3,352 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	8 per 1000 Difference:	13 per 1000 **5 more per 1000** (CI 95% 2 fewer — 18 more)	Moderate Due to serious imprecision [1]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in all-cause mortality in the post-intervention period.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no intervention	**Intervention** Therapeutic courses of an antimalarial medicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality (intervention plus post-intervention period) 8 Critical	Relative risk 0.77 (CI 95% 0.47 — 1.28) Based on data from 3,387 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 26 weeks.	21 per 1000 Difference:	16 per 1000 **5 fewer per 1000** (CI 95% 11 fewer — 6 more)	**Moderate** Due to serious imprecision [2]	Therapeutic courses of an antimalarial medicine probably reduce all-cause mortality. However, the effect varies and it is possible that it makes little to no difference for all-cause mortality.
All-cause re-admission (intervention period) 9 Critical	Relative risk 0.42 (CI 95% 0.34 — 0.52) Based on data from 682 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	833 per 1000 Difference:	350 per 1000 **483 fewer per 1000** (CI 95% 550 fewer — 400 fewer)	**Moderate** Due to serious inconsistency [3]	Therapeutic courses of an antimalarial medicine probably decrease all-cause re-admission in the intervention period.
All-cause re-admission (post-intervention period) 9 Critical	Hazard ratio 1.04 (CI 95% 0.83 — 1.3) Based on data from 558 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	632 per 1000 Difference:	646 per 1000 **14 more per 1000** (CI 95% 68 fewer — 95 more)	**Moderate** Due to serious imprecision [4]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in all-cause re-admission in the post-intervention period.
Severe anaemia re-admission (intervention period) 8 Critical	Hazard ratio 0.38 (CI 95% 0.26 — 0.56) Based on data from 5,481 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	44 per 1000 Difference:	17 per 1000 **27 fewer per 1000** (CI 95% 32 fewer — 19 fewer)	**Moderate** Due to serious inconsistency [5]	Therapeutic courses of an antimalarial medicine probably decrease severe anaemia re-admission in the intervention period.
Severe anaemia re-admission (post-intervention period) 8 Critical	Hazard ratio 0.74 (CI 95% 0.52 — 1.05) Based on data from 558 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	289 per 1000 Difference:	223 per 1000 **66 fewer per 1000** (CI 95% 126 fewer — 12 more)	**Moderate** Due to serious imprecision [6]	Therapeutic courses of an antimalarial medicine probably decrease severe anaemia re-admission in the post-intervention period.
Severe malaria re-admission (intervention period) 8 Critical	Hazard ratio 0.32 (CI 95% 0.22 — 0.48) Based on data from 470 participants in 2 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	851 per 1000 Difference:	456 per 1000 **395 fewer per 1000** (CI 95% 509 fewer — 252	**Moderate** Due to serious inconsistency [7]	Therapeutic courses of an antimalarial medicine probably decrease severe malaria re-admission in the intervention period

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no intervention	**Intervention** Therapeutic courses of an antimalarial medicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			fewer)		
Severe malaria re-admission (post-intervention period) 8 Critical	Hazard ratio 1.06 (CI 95% 0.81 — 1.39) Based on data from 558 participants in 2 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	368 per 1000 Difference:	385 per 1000 **17 more per 1000** (CI 95% 58 fewer — 104 more)	**Moderate** Due to serious imprecision [8]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in severe malaria re-admission in the post-intervention period.
Clinical malaria (intervention period) 6 Important	Hazard ratio 0.43 (CI 95% 0.36 — 0.5) Based on data from 3,356 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 14 weeks.	372 per 1000 Difference:	181 per 1000 **191 fewer per 1000** (CI 95% 218 fewer — 164 fewer)	**Moderate** Due to serious inconsistency [9]	Therapeutic courses of an antimalarial medicine probably decrease clinical malaria (intervention period).
Clinical malaria (post-intervention period) 6 Important	Hazard ratio 0.96 (CI 95% 0.83 — 1.11) Based on data from 3,325 participants in 3 studies. (Randomized controlled) Follow up: 15 weeks to 26 weeks.	241 per 1000 Difference:	233 per 1000 **8 fewer per 1000** (CI 95% 36 fewer — 23 more)	**Moderate** Due to serious imprecision [10]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in clinical malaria (post-intervention period).
Clinical malaria (intervention plus post-intervention period) 6 Important	Hazard ratio 0.64 (CI 95% 0.58 — 0.72) Based on data from 3,387 participants in 3 studies. (Randomized controlled) Follow up: 2 weeks to 26 weeks.	607 per 1000 Difference:	450 per 1000 **157 fewer per 1000** (CI 95% 189 fewer — 117 fewer)	**Moderate** Due to serious inconsistency [11]	Therapeutic courses of an antimalarial medicine probably decrease clinical malaria (intervention plus post-intervention period).
Drug-related adverse events (safety) 8 Critical	Based on data from 0 participants in 3 studies. (Randomized controlled)	Monthly SP was well tolerated. Minor symptoms recorded during the 30 days after the administration of each treatment were similar in the SP and placebo groups. The proportion of participants who vomited DHAP at least once within 60 minutes after drug intake was higher (12.4%) compared to placebo (3.8%), but no participant stopped the study medicine. DHAP was associated with an 18.6ms (95% CI: 15.6–21.8) increase in the QTc interval (Fridericia correction) after the third dose of each course (n = 33, all asymptomatic). All events of QTc (Fridericia's method for rate		**Moderate** Due to serious indirectness [12]	Therapeutic courses of an antimalarial medicine probably result in little to no difference in the risk of drug-related adverse events (safety). Most adverse events are minor.

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no intervention	**Intervention** Therapeutic courses of an antimalarial medicine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		correction) prolongation were asymptomatic. None of the children in the DHAP group had QTc values of more than 500 ms.			

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The range of effect includes the null. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The range of effect includes the null. **Publication bias: no serious.**
3. **Inconsistency: serious.** Considerable heterogeneity with I-squared = 87%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The range of effect includes the null. **Publication bias: no serious.**
5. **Inconsistency: serious.** Substantial heterogeneity with I-squared = 69%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The range of effect includes the null. **Publication bias: no serious.**
7. **Inconsistency: serious.** Considerable heterogeneity with I-squared = 93%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The range of effect includes the null. **Publication bias: no serious.**
9. **Inconsistency: serious.** Substantial heterogeneity with I-squared = 71%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The range of effect includes the null. **Publication bias: no serious.**
11. **Inconsistency: serious.** Substantial heterogeneity with I-squared = 71%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. **Inconsistency: no serious. Indirectness: serious.** ECG monitoring was conducted in a nested cardiac monitoring study involving 33 children receiving DHAP (one study). **Imprecision: no serious. Publication bias: no serious.**

Attached Images

4.2.6. Mass drug administration (MDA)

4.2.6.1. MDA for burden reduction

Clinical Question/ PICO

Population: Adults and children residing in a delimited geographical area
Intervention: MDA
Comparator: No MDA, routine service

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria incidence: RCT, Pf, mod/high transmission 1–3 months post-MDA 9 Critical	Rate ratio 0.41 (CI 95% 0.04 — 4.42) Based on data from 144,422 participants in 1 studies. (Randomized controlled)	Difference:	**1 fewer per 1000** (CI 95% 2 fewer — 8 more)	**Low** Due to very serious imprecision [1]	MDA may decrease clinical malaria incidence in delimited moderate to high malaria transmission areas 1–3 months post-MDA.
Clinical malaria incidence: RCT, Pf, low/very low transmission 1–3 months post-MDA 9 Critical	Rate ratio 0.58 (CI 95% 0.12 — 2.73) Based on data from 130,651 participants in 2 studies. (Randomized controlled)	Difference:	**20 fewer per 1000** (CI 95% 50 fewer — 90 more)	**Low** Due to very serious imprecision [2]	MDA may decrease clinical malaria incidence in delimited low to very low malaria transmission areas 1–3 months post-MDA.
Clinical malaria incidence: RCT, Pf, low/very low transmission 4–12 months post-MDA 9 Critical	Rate ratio 0.47 (CI 95% 0.21 — 1.03) Based on data from 26,576 participants in 3 studies. (Randomized controlled)	Difference:	**5 fewer per 1000** (CI 95% 7 fewer — 0 fewer)	**Very low** Due to serious risk of bias, Due to serious imprecision [3]	We are uncertain whether MDA increases or decreases clinical malaria incidence in delimited low to very low transmission areas 4–12 months post-MDA.
Clinical malaria incidence: RCT, Pf, low/very low transmission 12–24 months post-MDA 9 Critical	Rate ratio 0.77 (CI 95% 0.2 — 3.03) Based on data from 23,251 participants in 1 studies. (Randomized controlled)	Difference:	**4 fewer per 1000** (CI 95% 14 fewer — 34 more)	**Low** Due to very serious imprecision [4]	MDA may decrease clinical malaria incidence in delimited low to very low malaria transmission areas 12–24 months post-MDA.
Clinical malaria incidence: RCT, Pv 4–12 months post-MDA 9 Critical	Rate ratio 1.38 (CI 95% 0.97 — 1.95) Based on data from 3,325 participants in 2 studies. (Randomized controlled)	Difference:	**16 fewer per 1000** (CI 95% 39 fewer — 1 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [5]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence 4–12 months post-MDA.
Clinical malaria incidence: non-RCT, Pv	Rate ratio 0.23 (CI 95% 0.21 — 0.25) Based on data from	Difference:	**36 fewer per 1000**	**Very low** Due to very serious risk of	We are uncertain whether MDA increases or decreases

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
<1 month post-MDA 9 Critical	62,744 participants in 2 studies. (Observational (non-randomized))		(CI 95% 39 fewer — 33 fewer)	bias [6]	P. vivax clinical malaria incidence <1 month post-MDA.
Clinical malaria incidence: non-RCT, Pv 1–3 months post-MDA 9 Critical	Rate ratio 0.29 (CI 95% 0.26 — 0.31) Based on data from 62,744 participants in 2 studies. (Observational (non-randomized))	Difference:	**45 fewer per 1000** (CI 95% 48 fewer — 41 fewer)	**Very low** Due to serious inconsistency [7]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence 1–3 months post-MDA.
Clinical malaria incidence: non-RCT, Pv 4–12 months post-MDA 9 Critical	Rate ratio 0.72 (CI 95% 0.68 — 0.76) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	Difference:	**44 fewer per 1000** (CI 95% 50 fewer — 37 fewer)	**Very low** Due to very serious risk of bias [8]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence 4–12 months post-MDA.
Clinical malaria incidence: non-RCT, Pv 12–24 months post-MDA 9 Critical	Rate ratio 0.04 (CI 95% 0.02 — 0.07) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	Difference:	**150 fewer per 1000** (CI 95% 153 fewer — 145 fewer)	**Very low** Due to very serious risk of bias [9]	We are uncertain whether MDA increases or decreases P. vivax clinical malaria incidence 12–24 months post-MDA.
All-cause mortality: all ages, non-RCT, Pf, mod/high transmission <1 month post-MDA 7 Critical	Relative risk 0.68 (CI 95% 0.57 — 0.81) Based on data from 7,541,000 participants in 1 studies. (Observational (non-randomized))	81 per 1 million Difference:	55 per 1 million **26 fewer per 1 million** (CI 95% 35 fewer — 15 fewer)	**Very low** Due to serious risk of bias [10]	We are uncertain whether MDA increases or decreases all-cause mortality in all ages <1 month post-MDA.
All-cause mortality: <5 years, non-RCT, Pf, mod/high transmission <1 month post-MDA 7 Critical	Relative risk 0.34 (CI 95% 0.25 — 0.47) Based on data from 1,353,070 participants in 1 studies. (Observational (non-randomized))	250 per 1 million Difference:	85 per 1 million **165 fewer per 1 million** (CI 95% 187 fewer — 132 fewer)	**Very low** Due to serious risk of bias [11]	We are uncertain whether MDA increases or decreases all-cause mortality in children <5 years <1 month post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality: all ages, non-RCT, Pf, mod/high transmission 1–3 months post-MDA 7 Critical	Odds ratio 1.77 (CI 95% 1.54 — 2.04) Based on data from 11,419,200 participants in 1 studies. (Observational (non-randomized))	51 per 1 million Difference:	87 per 1 million **36 more per 1 million** (CI 95% 25 more — 48 more)	**Very low** Due to serious risk of bias [12]	We are uncertain whether MDA increases or decreases all-cause mortality in all ages 1–3 months post-MDA.
All-cause mortality: <5 years, non-RCT, Pf, mod/high transmission 1–3 months post-MDA 7 Critical	Odds ratio 1.13 (CI 95% 0.87 — 1.46) Based on data from 2,008,720 participants in 1 studies. (Observational (non-randomized))	106 per 1 million Difference:	118 per 1 million **12 more per 1 million** (CI 95% 12 fewer — 42 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [13]	We are uncertain whether MDA increases or decreases all-cause mortality in children <5 years 1–3 months post-MDA.
Parasite prevalence: non-RCT, Pf, mod/high transmission 4–12 months post-MDA 6 Important	Relative risk 0.6 (CI 95% 0.55 — 0.67) Based on data from 3,154 participants in 1 studies. (Observational (non-randomized))	418 per 1000 Difference:	251 per 1000 **167 fewer per 1000** (CI 95% 188 fewer — 138 fewer)	**Very low** Due to serious risk of bias [14]	We are uncertain whether MDA increases or decreases P. falciparum parasite prevalence in moderate to high transmission areas 4–12 months post-MDA.
Parasite incidence: RCT, Pf, mod/high transmission 1–3 months post-MDA 3 Not Important	Rate ratio 0.61 (CI 95% 0.4 — 0.92) Based on data from 820 participants in 1 studies. (Randomized controlled)	57 per 1000 Difference:	35 per 1000 **22 fewer per 1000** (CI 95% 20 fewer — 205 more)	**Moderate** Due to serious risk of bias [15]	MDA probably reduces the incidence of P. falciparum in moderate to high transmission areas 1–3 months post-MDA.
Parasite incidence: RCT, Pf, mod/high transmission 4–12 months post-MDA 3 Not Important	Rate ratio 0.91 (CI 95% 0.55 — 1.5) Based on data from 518 participants in 1 studies. (Randomized controlled)	108 per 1000 Difference:	98 per 1000 **10 fewer per 1000** (CI 95% 53 fewer — 270 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [16]	We are uncertain whether MDA increases or decreases the incidence of P. falciparum in moderate to high transmission areas 4–12 months post-MDA.
Parasite incidence: RCT,	Rate ratio 0.37 (CI 95% 0.21 — 0.66)	12	5	**Moderate** Due to serious	MDA probably reduces the incidence of P.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Pf, low/very low transmission 1–3 months post-MDA 3 Not Important	Based on data from 812 participants in 1 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **7 fewer per 1000** (CI 95% 20 fewer — 205 more)	risk of bias [17]	falciparum in low to very low transmission areas 1– 3 months post-MDA.
Parasite prevalence: RCT, Pf, mod/ high transmission 1–3 months post-MDA 6 Important	Relative risk 1.76 (CI 95% 0.58 — 5.36) Based on data from 786 participants in 1 studies. (Randomized controlled)	47 per 1000 Difference:	83 per 1000 **36 more per 1000** (CI 95% 20 fewer — 205 more)	**Low** Due to very serious imprecision [18]	MDA may increase P. falciparum parasite prevalence slightly in moderate to high transmission areas 1–3 months post-MDA.
Parasite prevalence: RCT, Pf, mod/ high transmission 4–12 months post-MDA 6 Important	Relative risk 1.18 (CI 95% 0.89 — 1.56) Based on data from 1,497 participants in 1 studies. (Randomized controlled)	483 per 1000 Difference:	570 per 1000 **87 more per 1000** (CI 95% 53 fewer — 270 more)	**Low** Due to very serious imprecision [19]	MDA may increase P. falciparum parasite prevalence slightly in moderate to high transmission areas 4–12 months post-MDA.
Parasite prevalence: non-RCT, Pf, mod/high transmission 1–3 months post-MDA 6 Important	Relative risk 0.85 (CI 95% 0.78 — 0.93) Based on data from 1,000 participants in 1 studies. (Observational (non-randomized))	723 per 1000 Difference:	615 per 1000 **108 fewer per 1000** (CI 95% 159 fewer — 51 fewer)	**Very low** Due to serious risk of bias [20]	We are uncertain whether MDA increases or decreases P. falciparum parasite prevalence in moderate to high transmission areas 1–3 months post-MDA.
Parasite prevalence: non-RCT, Pf, mod/high transmission 12–24 months post-MDA 6 Important	Relative risk 0.77 (CI 95% 0.7 — 0.84) Based on data from 3,261 participants in 1 studies. (Observational (non-randomized))	431 per 1000 Difference:	332 per 1000 **99 fewer per 1000** (CI 95% 129 fewer — 69 fewer)	**Low**	MDA may decrease P. falciparum parasite prevalence in moderate to high transmission areas 12–24 months post-MDA.
Parasite prevalence: RCT, Pf, low/	Relative risk 0.34 (CI 95% 0.06 — 1.97) Based on data from	32 per 1000	11 per 1000	**Very low** Due to serious risk of bias, Due	We are uncertain whether MDA increases or decreases

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
very low transmission 12–24 months post-MDA 6 Important	1,390 participants in 1 studies. (Randomized controlled)	Difference:	**21 fewer per 1000** (CI 95% 30 fewer — 31 more)	to serious indirectness [21]	P. falciparum parasite prevalence in low to very low transmission areas 12–24 months post-MDA.
Parasite prevalence: RCT, Pf, low/ very low transmission <1 month post-MDA 6 Important	Relative risk 0.12 (CI 95% 0.03 — 0.52) Based on data from 718 participants in 2 studies. (Randomized controlled)	35 per 1000 Difference:	4 per 1000 **31 fewer per 1000** (CI 95% 34 fewer — 17 fewer)	**Moderate** Due to serious risk of bias [22]	MDA probably decreases P. falciparum parasite prevalence in low to very low transmission areas <1 month post-MDA.
Parasite prevalence: RCT, Pf, low/ very low transmission 1–3 months post-MDA 6 Important	Relative risk 0.25 (CI 95% 0.15 — 0.41) Based on data from 6,511 participants in 8 studies. (Randomized controlled)	24 per 1000 Difference:	6 per 1000 **18 fewer per 1000** (CI 95% 20 fewer — 14 fewer)	**Moderate** Due to serious risk of bias [23]	MDA probably decreases P. falciparum parasite prevalence in low to very low transmission areas 1–3 months post-MDA.
Parasite prevalence: RCT, Pv <1 month post-MDA 6 Important	Relative risk 0.18 (CI 95% 0.08 — 0.4) Based on data from 234 participants in 1 studies. (Randomized controlled)	272 per 1000 Difference:	49 per 1000 **223 fewer per 1000** (CI 95% 250 fewer — 163 fewer)	**Moderate** Due to serious risk of bias [24]	MDA probably decreases P. vivax parasite prevalence <1 month post-MDA.
Parasite prevalence: RCT, Pf, low/ very low transmission 4–12 months post-MDA 6 Important	Relative risk 0.82 (CI 95% 0.56 — 1.22) Based on data from 5,102 participants in 6 studies. (Randomized controlled)	19 per 1000 Difference:	16 per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 4 more)	**Low** Due to serious risk of bias, Due to serious inconsistency [25]	MDA may decrease P. falciparum parasite prevalence in low to very low transmission areas 4–12 months post-MDA.
Parasite prevalence: RCT, Pv 1–3 months post-MDA	Relative risk 0.15 (CI 95% 0.1 — 0.24) Based on data from 2,672 participants in 5 studies. (Randomized controlled)	133 per 1000 Difference:	20 per 1000 **113 fewer per 1000**	**Low** Due to serious risk of bias, Due to serious inconsistency [26]	MDA may decrease P. vivax parasite prevalence 1–3 months post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 119 fewer — 101 fewer)		
Parasite prevalence: RCT, Pv 4-12 months post-MDA 6 Important	Relative risk 1.01 (CI 95% 0.87 — 1.18) Based on data from 6,255 participants in 5 studies. (Randomized controlled)	96 per 1000 Difference:	97 per 1000 **1 more per 1000** (CI 95% 12 fewer — 17 more)	**Low** Due to serious risk of bias, Due to serious inconsistency [27]	MDA may have little or no effect on P. vivax parasite prevalence 4–12 months post-MDA.
Parasite prevalence: RCT, Pv 12–24 months post-MDA 6 Important	Relative risk 0.81 (CI 95% 0.44 — 1.48) Based on data from 243 participants in 1 studies. (Randomized controlled)	175 per 1000 Difference:	142 per 1000 **33 fewer per 1000** (CI 95% 98 fewer — 84 more)	**Low** Due to serious risk of bias, Due to serious imprecision [28]	MDA may have little or no effect on P. vivax parasite prevalence 12–24 months post-MDA.
Parasite prevalence: non-RCT, Pv <1 month post-MDA 6 Important	Relative risk 0.32 (CI 95% 0.12 — 0.87) Based on data from 449 participants in 1 studies. (Observational (non-randomized))	71 per 1000 Difference:	23 per 1000 **48 fewer per 1000** (CI 95% 62 fewer — 9 fewer)	**Very low** Due to serious risk of bias [29]	We are uncertain whether MDA increases or decreases P. vivax parasite prevalence <1 month post-MDA.
Parasite prevalence: non-RCT, Pv 1–3 months post-MDA 6 Important	Relative risk 0.18 (CI 95% 0.1 — 0.33) Based on data from 1,024 participants in 2 studies. (Observational (non-randomized))	231 per 1000 Difference:	42 per 1000 **189 fewer per 1000** (CI 95% 208 fewer — 155 fewer)	**Very low** Due to very serious risk of bias [30]	We are uncertain whether MDA increases or decreases P. vivax parasite prevalence 1–3 months post-MDA.
Parasite prevalence: non-RCT, Pv 4–12 months post-MDA 6 Important	Relative risk 0.34 (CI 95% 0.15 — 0.78) Based on data from 939 participants in 1 studies. (Observational (non-randomized))	71 per 1000 Difference:	24 per 1000 **47 fewer per 1000** (CI 95% 60 fewer — 16 fewer)	**Very low** Due to very serious risk of bias [31]	We are uncertain whether MDA increases or decreases P. vivax parasite prevalence 4–12 months post-MDA.
Serious adverse events: Pf, low/very low	Odds ratio 3.61 (CI 95% 0.43 — 30.03) Based on data from 6,911 participants in 1	385 per 1 million Difference:	693 per 1 million **308 more per 1**	**Moderate** Due to serious imprecision [32]	MDA probably increases serious adverse events 0–3 months post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
transmission 0–3 months post-MDA 5 Important	studies. (Randomized controlled)		**million** (CI 95% 173 fewer — 564 more)		
Serious adverse events: RCT, Pf, low/ very low transmission 4–12 months post-MDA 5 Important	Odds ratio 1.47 (CI 95% 0.68 — 3.2) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	3,466 per 1 million Difference:	1,938 per 1 million **1,528 fewer per 1 million** (CI 95% 25,065 fewer — 2,180 fewer)	**Moderate** Due to serious imprecision [33]	MDA probably increases serious adverse events 4–12 months post-MDA.
Adverse events: RCT, Pf, mod/high transmission 1–3 months post-MDA 5 Important	Odds ratio 3.25 (CI 95% 0.68 — 15.53) Based on data from 90 participants in 1 studies. (Randomized controlled)	133 per 1000 Difference:	333 per 1000 **200 more per 1000** (CI 95% 39 fewer — 571 more)	**Very low** [34]	We are uncertain whether MDA increases or decreases adverse events 1–3 months post-MDA.
Adverse event (vomiting): SP+AS +/-PQ, RCT, Pf, low/ very low transmission 4 Important	Odds ratio 0.54 (CI 95% 0.19 — 1.54) Based on data from 703 participants in 1 studies. (Randomized controlled)	43 per 1000 Difference:	24 per 1000 **19 fewer per 1000** (CI 95% 35 fewer — 22 more)	**Moderate** Due to serious imprecision [35]	MDA with SP+AS +/-PQ probably increases vomiting.
Difference in haemoglobin between day 1 and day 7, Pf, low/very low transmission 4 Important	High better Based on data from 680 participants in 1 studies. (Randomized controlled)	Difference:	**MD 0.53 higher** (CI 95% 0.27 higher — 0.79 higher)	**High**	MDA improves difference in haemoglobin levels between day 1 and day 7 post-MDA treatment.
Pf: Adverse events in low/ very low transmission settings, cRCTs	Based on data from participants in 5 studies. (Randomized controlled)	SAE: Morris_2018 reported no SAEs, Shekalaghe_2011 reported two SAEs: a serious skin reaction and severe anaemia, Eisele_2020 reported four SAEs, of which three were deemed unrelated to drug ingestion, and McLean_2021 reported six SAEs (three deaths [all		**Low** [36]	

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		deemed unrelated to the drug], one stillbirth, one miscarriage, and one episode of severe dehydration secondary to vomiting and diarrhoea). AE: Morris_2018 used both active and passive detection of AEs; 298 individuals reported a total of 414 events out of 2411 doses of DHAP + single low dose primaquine; the most commonly reported AEs were nausea and vomiting (33.1% of all reports), dizziness, headache, and fatigue (23.5%), and stomach pain and diarrhoea (18.9%). von Seidlein_2019 reported that "1535 of 8112 (19%) MDA participants recalled 2577 AEs, of which 911 (35%) were considered related to the antimalarials; 592 (23%) of the 2577 AEs were dizziness, 199 (8%) nausea, 96 (4%) vomiting, and 39 (2%) itching, and 1653 (64%) participants reported a range of other minor complaints. There were no cases of severe haemolysis." Among 336821 courses of DHAP, Eisele_2020 reported 687 AEs. The most common AE reported was gastrointestinal disturbances (diarrhoea, vomiting, abdominal pain, and nausea) at 48.6%; dizziness 19.8%; headache 16.0%, and general body weakness at 11.4%. McLean_2021 reported 151 AEs out of a total of 10677 doses. The majority of these (120) were mild, and dizziness and rash or itching were most commonly reported. Only 18 AEs were assessed as probably related to the medicine.		
Drug resistance: PfKelch13 mutations among those who received MDA	Based on data from participants in 1 studies. (Randomized controlled)	269 patients with P. falciparum were identified at baseline, of which 221 completed at least one round of MDA and had parasites sequenced for PfKelch13 at baseline and one month post-MDA. At baseline, 10/221 were positive for PfKelch13 (4.5%) and one month post-MDA, there was one infection out of 14 (7%) remaining P. falciparum infections that showed the PfKelch13 genotype.		**Very low** Due to serious risk of bias [37]	

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
3. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: very serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial

effect . **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
5. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I-squared >50%.. **Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
6. **Risk of Bias: very serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: very serious.** High or unclear risk of bias in included studies. **Inconsistency: serious.** The CIs of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: very serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9. **Risk of Bias: very serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. **Risk of Bias: serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
11. **Risk of Bias: serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. **Risk of Bias: serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
13. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
14. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
15. **Risk of Bias: serious.**
16. **Risk of Bias: serious. Imprecision: serious.**
17. **Risk of Bias: serious.**
18. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
19. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
20. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
21. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: serious.** McLean had contact-tracing for neighbours in the 50 km surrounding positive cases in the intervention, but not for the control arm; this effect measures the combined intervention.. **Imprecision: very serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
22. **Risk of Bias: serious.** High or unclear risk of bias in included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
23. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
24. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
25. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** Completely non-overlapping CIs. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
26. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** I-squared > 50%. Completely non-overlapping CIs. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
27. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: serious.** I-squared > 50%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
28. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
29. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious.**

Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.
30. **Risk of Bias: very serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
31. **Risk of Bias: very serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
32. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect. **Publication bias: no serious.**
33. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect. **Publication bias: no serious.**
34. **Inconsistency: very serious.** Rates of events in both arms are much higher than in other studies; unclear how questions were asked.. **Indirectness: no serious. Imprecision: very serious.** Wide CIs that include both no effect and substantial effect. **Publication bias: no serious.**
35. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect. **Publication bias: no serious.**
36. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Although an RCT, outcome was collected in the MDA arm only, not in the control group. **Publication bias: no serious.**
37. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Although an RCT, data on adverse events, severe adverse events and drug resistance markers were only collected in the MDA arm, thus there is no control. **Publication bias: no serious.**

Attached Images

4.2.6.2. MDA for burden reduction in emergency settings

Clinical Question/ PICO

Population: All ages during emergencies or periods of health service disruption
Intervention: MDA
Comparator: No MDA, routine service

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
All-cause mortality: 3 rounds, <1 month post-MDA, all ages [1] 7 Critical	Relative risk 0.68 (CI 95% 0.57 — 0.81) Based on data from 7,541,000 participants in 1 studies. (Observational (non-randomized))	81 per 1 million Difference:	55 per 1 million **26 fewer per 1 million** (CI 95% 35 fewer — 15 fewer)	Very low Due to serious risk of bias [2]	We are uncertain about the effect of MDA on all-cause mortality in all ages <1 month post-MDA.
All-cause mortality: 3 rounds, <1 month post-MDA, <5 years	Relative risk 0.34 (CI 95% 0.25 — 0.47) Based on data from 1,353,070 participants in 1 studies. (Observational (non-	250 per 1 million Difference:	85 per 1 million **165 fewer per 1 million**	Very low Due to serious risk of bias [4]	We are uncertain about the effect of MDA on all-cause mortality in children <5 years <1 month post-MDA.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
[3] 7 Critical	randomized))		(CI 95% 187 fewer — 132 fewer)		
All-cause mortality: 3 rounds, 1–3 months post-MDA, all ages [5] 7 Critical	Odds ratio 1.77 (CI 95% 1.54 — 2.04) Based on data from 11,419,200 participants in 1 studies. (Observational (non-randomized))	**51** per 1 million Difference:	**87** per 1 million **36 more per 1 million** (CI 95% 25 more — 48 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [6]	We are uncertain about the effect of MDA on all-cause mortality in all ages 1–3 months post-MDA.
All-cause mortality: 3 rounds, 1–3 months post-MDA, <5 years [7] 7 Critical	Odds ratio 1.13 (CI 95% 0.87 — 1.46) Based on data from 2,008,720 participants in 1 studies. (Observational (non-randomized))	**106** per 1 million Difference:	**118** per 1 million **12 more per 1 million** (CI 95% 12 fewer — 42 more)	**Very low** Due to serious risk of bias and serious imprecision [8]	We are uncertain about the effect of MDA on all-cause mortality in children <5 years 1–3 months post-MDA.
All cause hospitalization 0–1 months post-MDA 7 Critical	Based on data from participants in 1 studies. (Observational (non-randomized))	The number of all-cause hospital admissions decreased by between 5% and 21% during the four weeks after the first round of MDA, and by between 8% and 19% during the four weeks after the second round of MDA. Observed statistically significant changes at only one of eight time-points. Data on sample population sizes and from non-MDA control areas were not available, so absolute effects could not be calculated.		**Very low** Due to serious risk of bias and serious imprecision [9]	We are uncertain whether MDA increases or decreases all-cause hospitalization 0–1 months post-MDA.
Severe malaria hospitalization 0–1 months post-MDA 7 Critical	Based on data from participants in 1 studies. (Observational (non-randomized))	Change in the number of hospital admissions secondary to severe malaria ranged from a decrease of 31% to an increase of 8% during the four weeks after the first round of MDA, and by a 19% decrease to an 8% increase during the four weeks after the second round of MDA. Observed statistically significant changes at three of eight time-points. Data on sample population sizes and from non-MDA control areas were not available, so absolute effects could not be calculated.		**Very low** Due to serious risk of bias and serious imprecision [10]	We are uncertain whether MDA increases or decreases severe malaria hospitalization 0–1 months post-MDA.
Parasitologicall y confirmed malaria 0–1	Based on data from participants in 1 studies. (Observational	Point estimates of changes in parasitologically-confirmed malaria cases at health facilities decreased		**Very low** Due to serious risk of bias [11]	We are uncertain about the effect of MDA on parasitologically

Outcome Timeframe	**Study results and measurements**	**Comparator** No MDA	**Intervention** MDA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
months post-MDA 7 Critical	(non-randomized))	by between 35% and 62% during the four weeks after the first round of MDA, and by between 26% and 58% during the four weeks after the second round of MDA. All change estimates represented a statistically significant change from baseline. However, reductions in the number of parasitologically confirmed cases were also observed at all time points in no-MDA control areas during this time. 95% confidence intervals of the estimated changes in both MDA and non-MDA groups overlapped at all but two time points immediately after the first round of MDA. Data on sample population sizes were not available, so calculation of absolute effect was not possible.			confirmed malaria 0–1 months post-MDA.

1. Rounds 1-2 with AS-AQ, round 3 with AS-PYR
2. **Risk of Bias: very serious.** Unclear risk of bias in exposure measurement and control for confounding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. Rounds 1-2 with AS-AQ, round 3 with AS-PYR
4. **Risk of Bias: serious.** Unclear risk of bias in exposure measurement and control for confounding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. Rounds 1-2 with AS-AQ, round 3 with AS-PYR
6. **Risk of Bias: serious.** Unclear risk of bias in exposure measurement and control for confounding. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs. **Publication bias: no serious.**
7. Rounds 1-2 with AS-AQ, round 3 with AS-PYR
8. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
9. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
10. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs that include both no effect and substantial effect . **Publication bias: no serious.**
11. **Risk of Bias: serious.** High or unclear risk of bias in some/ all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

Attached Images

4.2.6.3. MDA to reduce transmission of *P. falciparum* in very low to low transmission settings

Clinical Question/ PICO

Population: Adults and children in delimited geographical area with very low to low transmission of P.

falciparum

Intervention: Mass drug administration (MDA)

Comparator: no MDA

Summary

The systematic review identified eight cRCTs in very low to low transmission settings of six countries (Cambodia, Lao People's Democratic Republic, Myanmar, United Republic of Tanzania, Viet Nam and Zambia) assessing the impact of MDA on *P. falciparum* prevalence or incidence compared to no MDA (Schneider *et al* *unpublished evidence*). Two studies used DP alone; five studies used DP plus single low-dose primaquine; and one study used sulfadoxine-pyrimethamine/artesunate (SP+AS) plus a single dose of primaquine at 0.75 mg/kg. Most (5) studies conducted three rounds of MDA within one year; one study conducted four rounds of MDA over 15 months; one study conducted two rounds and one study conducted one round of MDA over a one-year period.

Meta-analyses of the results showed reductions in prevalence and incidence of *P. falciparum* infection, but not clinical disease, 1–3 months after the last round of MDA. Multiple studies evaluated these outcomes at longer time periods but either no impact was found or the evidence was of very low certainty. Adverse events were often not measured in both arms, which complicated interpretation of the findings, but reported rates of adverse events or serious adverse events were low. Markers of artemisinin resistance were measured in only one study, which found no evidence of increases in drug-resistant parasites.

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
1-3 months - Incidence of clinical malaria	Rate ratio 0.58 (CI 95% 0.12 — 2.73) Based on data from 130,651 participants in 2 studies. (Randomized controlled)	6 per 1000	4 per 1000	**Low** Due to very serious imprecision [1]	MDA may result in little to no difference in the incidence of P. falciparum clinical malaria between 1-3 months
1-3 months - Prevalence	Relative risk 0.25 (CI 95% 0.15 — 0.41) Based on data from 6,511 participants in 8 studies. (Randomized controlled)	24 per 1000 Difference:	6 per 1000 **18 fewer per 1000** (CI 95% 20 fewer — 14 fewer)	**Moderate** Due to serious risk of bias [2]	MDA probably reduces P. falciparum prevalence between 1-3 months
4-12 months - Prevalence	Relative risk 0.82 (CI 95% 0.56 — 1.22) Based on data from 5,102 participants in 6 studies. (Randomized controlled)	19 per 1000 Difference:	16 per 1000 **3 fewer per 1000** (CI 95% 8 fewer — 4 more)	**Low** Due to serious risk of bias, and serious inconsistency [3]	MDA may result in little to no difference in P. falciparum prevalence between 4-12 months
1-3 months - Incidence of parasitaemia	Rate ratio 0.37 (CI 95% 0.21 — 0.66) Based on data from 811 participants in 1 studies. (Randomized controlled)	12 per 1000	5 per 1000	**Moderate** Due to serious risk of bias [4]	MDA probably reduces the incidence of P. falciparum parasitaemia between 1-3 months

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
4-12 months - Incidence of clinical malaria	Rate ratio 0.47 (CI 95% 0.21 — 1.03) Based on data from 26,576 participants in 4 studies. (Randomized controlled)	11 per 1000	5 per 1000	Very low Due to serious risk of bias, and serious imprecision [5]	The evidence is very uncertain about the effect of MDA on the incidence of P. falciparum clinical malaria between 4-12 months
1-3 months - Adverse events	Relative risk 3.25 (CI 95% 0.68 — 15.53) Based on data from 90 participants in 1 studies. (Randomized controlled)	133 per 1000 Difference:	433 per 1000 **300 more per 1000** (CI 95% 43 fewer — 1,000 more)	Very low Due to serious indirectness [6]	The evidence is very uncertain about the effect of MDA on adverse events between 1-3 months
12-24 months - Prevalence	Relative risk 0.34 (CI 95% 0.06 — 1.97) Based on data from 1,390 participants in 1 studies. (Randomized controlled)	32 per 1000 Difference:	11 per 1000 **21 fewer per 1000** (CI 95% 30 fewer — 31 more)	Very low Due to serious risk of bias, and serious indirectness [7]	The evidence is very uncertain about the effect of MDA on the prevalence of P. falciparum clinical malaria between 12-24 months
12-24 months - Incidence of clinical malaria	Rate ratio 0.77 (CI 95% 0.2 — 3.03) Based on data from 23,251 participants in 1 studies. (Randomized controlled)	17 per 1000	13 per 1000	Low Due to very serious imprecision [8]	MDA may reduce the incidence of P. falciparum clinical malaria between 12-24 months
4-12 months - Serious adverse events	Odds ratio 1.47 (CI 95% 0.68 — 3.2) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	3 per 1000 Difference:	5 per 1000 **2 more per 1000** (CI 95% 1 fewer — 8 more)	Low Due to very serious imprecision [9]	MDA may have little to no effect on serious adverse events between 4-12 months
0-3 months - Serious Adverse Events	Odds ratio 3.61 (CI 95% 0.43 — 30.03) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	1 per 1000 **1 more per 1000** (CI 95% 0 more — 11 more)	Moderate Due to serious imprecision [10]	MDA probably results in little to no difference in serious adverse events between 0-3 months
Pf - Vomiting among people receiving SP+AS with or without PQ vs Placebo - Low/	Odds ratio 0.54 (CI 95% 0.19 — 1.54) Based on data from 703 participants in 1 studies. (Randomized controlled)	43 per 1000 Difference:	24 per 1000 **19 fewer per 1000**	Moderate Due to serious imprecision [11]	MDA probably does not increase vomiting among people receiving SP+AS with or without PQ vs Placebo

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Very Low - cRCTs			(CI 95% 35 fewer — 22 more)		
SAEs among people who received MDA	Based on data from 353,143 participants in 4 studies. (Randomized controlled)		0.03 per 1000	[12]	
1-3 months - Drug resistance markers (PfKelch13) among people who were Pf positive	Relative risk 0.82 (CI 95% 0.45 — 1.51) Based on data from 63 participants in 1 studies. (Randomized controlled)	608 per 1000 Difference:	498 per 1000 **109 fewer per 1000** (CI 95% 334 fewer — 310 more)	Very low Due to serious risk of bias [13]	The evidence is very uncertain about the effect of MDA on artemisinin resistance markers (PfKelch13) among P. falciparum infections between 1-3 months
1-3 months - Drug resistance markers (PfKelch13) among all samples	Relative risk 0.13 (CI 95% 0.05 — 0.3) Based on data from 1,232 participants in 1 studies. (Randomized controlled)	64 per 1000 Difference:	8 per 1000 **56 fewer per 1000** (CI 95% 61 fewer — 45 fewer)	Low Due to serious risk of bias, and serious imprecision [14]	MDA may reduce the proportion of drug resistance markers (PfKelch13) among all samples between 1-3 months
4-12 months - Drug resistance markers (PfKelch13) among people who were Pf positive	Relative risk 1.16 (CI 95% 0.83 — 1.61) Based on data from 75 participants in 1 studies. (Randomized controlled)	610 per 1000 Difference:	707 per 1000 **98 more per 1000** (CI 95% 104 fewer — 372 more)	Very low Due to serious risk of bias [15]	The evidence is very uncertain about the effect of MDA on artemisinin resistance markers (PfKelch13) among P. falciparum infections between 4-12 months
4-12 months - Drug resistance markers (PfKelch13) among all samples	Relative risk 0.49 (CI 95% 0.28 — 0.85) Based on data from 2,595 participants in 1 studies. (Randomized controlled)	29 per 1000 Difference:	14 per 1000 **15 fewer per 1000** (CI 95% 21 fewer — 4 fewer)	Low Due to serious risk of bias, and serious imprecision [16]	MDA may reduce the proportion of drug resistance markers (PfKelch13) among all samples between 4-12 months

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
12-24 months - Drug resistance markers (PfKelch13) among people who were Pf positive	Relative risk 1.07 (CI 95% 0.82 — 1.4) Based on data from 78 participants in 1 studies. (Randomized controlled)	714 per 1000 Difference:	764 per 1000 **50 more per 1000** (CI 95% 129 fewer — 286 more)	Very low Due to serious risk of bias [17]	The evidence is very uncertain about the effect of MDA on artemisinin resistance markers (PfKelch13) among P. falciparum infections between 12-24 months
12-24 months - Drug resistance markers (PfKelch13) among all samples	Relative risk 0.66 (CI 95% 0.4 — 1.11) Based on data from 2,990 participants in 1 studies. (Randomized controlled)	25 per 1000 Difference:	17 per 1000 **8 fewer per 1000** (CI 95% 15 fewer — 3 more)	Low Due to serious risk of bias, and serious imprecision [18]	MDA may result in little to no reduction in drug resistance markers (PfKelch13) among all samples between 12-24 months

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Substantial variability in point estimates including both appreciable risk and appreciable benefit.. **Publication bias: no serious.**
2. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
4. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: very serious.** I-squared 72%. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
6. **Inconsistency: no serious. Indirectness: serious.** Self-reported symptoms, serious indirectness. **Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
7. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: serious.** McLean had contact tracing for neighbors in 50 km surrounding positive cases in the intervention but not control arm; this effect measures the combined intervention.. **Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
11. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
12. **Risk of Bias: very serious.** Although an RCT, data on AEs, SAEs and drug resistance markers was only collected in the MDA arm, thus there is no control. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Unable to calculate effect measure as there is no comparison group. **Publication bias: no serious.**
13. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk; Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**

14. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**
15. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk; Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**
16. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**
17. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk; Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**
18. **Risk of Bias: serious.** Some risk of bias in most/all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Small event numbers, does not meet Optimal Information Size. **Publication bias: no serious.**

Attached Images

4.2.6.4. MDA to reduce transmission of *P. falciparum* in moderate to high transmission settings

Clinical Question/ PICO

Population:	Adults and children in a delimited geographic area with moderate to high transmission of P. falciparum
Intervention:	Mass drug administration (MDA)
Comparator:	no MDA

Summary

The systematic review identified two cRCTs and two NRSs in moderate to high transmission settings in four countries (Burkina Faso, Gambia, Nigeria and Zambia) assessing the impact of MDA on *P. falciparum* compared to no MDA (Schneider *et al* unpublished evidence). The cRCTs and NRSs were analysed and GRADEd separately.

Among the cRCTs, one study conducted four rounds of MDA with DP alone over 15 months and the other conducted one round with SP+AS. Among the NRSs, one study provided nine rounds of sulfadoxine-pyrimethamine every 10 weeks over 18 months and the other provided either chloroquine or amodiaquine in combination with single low dose primaquine every 14 days for either eight or 15 rounds.

Meta-analyses of the results from the cRCTs showed little to no effect of MDA on *P. falciparum* prevalence or incidence or the incidence of clinical malaria across all time points with low- to moderate-certainty. The results from the NRSs were more likely to show a slight impact of MDA on *P. falciparum* prevalence at 4 – 12 and 12 – 24 months, with low-certainty evidence. Only one cRCT measured adverse events in a subset of both study arms and found a small increase in adverse events in the MDA arm but the certainty of the evidence was very low. None of the studies measured markers of drug resistance.

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
1-3 months - Prevalence	Relative risk 1.76 (CI 95% 0.58 — 5.36) Based on data from 786 participants in 1 studies. (Randomized controlled)	50 per 1000 Difference:	88 per 1000 **38 more per 1000** (CI 95% 21 fewer — 219 more)	**Low** Due to very serious imprecision [1]	MDA may result in little to no difference in P. falciparum prevalence between 1-3 months
1-3 months - Prevalence (NRS)	Relative risk 0.85 (CI 95% 0.78 — 0.93) Based on data from 1,000 participants in 1 studies. (Observational (non-randomized))	723 per 1000 Difference:	614 per 1000 **108 fewer per 1000** (CI 95% 159 fewer — 51 fewer)	**Very low** Due to serious risk of bias [2]	The evidence is very uncertain about the effect of MDA on P. falciparum prevalence between 1-3 months
1-3 months - Incidence of parasitaemia	Rate ratio 0.61 (CI 95% 0.4 — 0.92) Based on data from 820 participants in 1 studies. (Randomized controlled)	57 per 1000	35 per 1000	**Moderate** Due to serious imprecision [3]	MDA probably reduces the incidence of P. falciparum parasitaemia between 1-3 months
1-3 months - Incidence of clinical malaria	Rate ratio 0.41 (CI 95% 0.04 — 4.42) Based on data from 144,422 participants in 1 studies. (Randomized controlled)	2 per 1000	1 per 1000	**Low** Due to very serious imprecision [4]	MDA may result in little to no difference in the incidence of P. falciparum clinical malaria between 1-3 months
4-12 months - Prevalence	Relative risk 1.18 (CI 95% 0.89 — 1.56) Based on data from 1,497 participants in 1 studies. (Randomized controlled)	483 per 1000 Difference:	570 per 1000 **87 more per 1000** (CI 95% 53 fewer — 271 more)	**Low** Due to very serious imprecision [5]	MDA may result in little to no difference in P. falciparum prevalence between 4-12 months
4- 12 months - Prevalence (NRS)	Relative risk 0.6 (CI 95% 0.55 — 0.67) Based on data from 3,154 participants in 1 studies. (Observational (non-randomized))	418 per 1000 Difference:	251 per 1000 **167 fewer per 1000** (CI 95% 188 fewer — 138 fewer)	**Low**	MDA may reduce the prevalence of P. falciparum between 4-12 months
4-12 months - Incidence of	Rate ratio 0.91 (CI 95% 0.55 — 1.5)	108	98	**Very low** Due to serious	The evidence is very uncertain about the

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
parasitaemia	Based on data from 517 participants in 1 studies. (Randomized controlled)	per 1000	per 1000	risk of bias [6]	effect of MDA on the incidence of P. falciparum parasitaemia between 4-12 months
12-24 months - Prevalence (NRS)	Relative risk 0.77 (CI 95% 0.7 — 0.84) Based on data from 3,261 participants in 1 studies. (Observational (non-randomized))	431 per 1000 Difference:	332 per 1000 **99 fewer per 1000** (CI 95% 129 fewer — 69 fewer)	Low	MDA may reduce P. falciparum prevalence between 12-24 months
Adverse events	Odds ratio 3.25 (CI 95% 0.68 — 15.53) Based on data from 90 participants in 1 studies. (Randomized controlled)	133 per 1000 Difference:	333 per 1000 **200 more per 1000** (CI 95% 39 fewer — 572 more)	Very low Due to very serious inconsistency [7]	The evidence is very uncertain about the effect of MDA on adverse events
AEs among people who received MDA	Based on data from 336,821 participants in 1 studies. (Randomized controlled)		2 per 1000	[8]	The evidence is very uncertain about the effect of MDA on adverse events
SAEs among people who received MDA	Based on data from 336,821 participants in 1 studies. (Randomized controlled)		0.01 per 1000	[9]	The evidence is very uncertain about the effect of MDA on adverse events

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
2. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** GDG determined that the lower confidence bound (5 fewer per 1000) was not an important reduction and concluded that the finding was imprecise.. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
6. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
7. **Inconsistency: very serious.** Rates of events in both arms are much higher than in other studies; unclear how

questions were asked.. **Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals including both no effect and appreciable benefit/ risk. **Publication bias: no serious.**
8. **Risk of Bias: very serious.** Although an RCT, outcome was collected in MDA arm only, not in control group. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**
9. **Risk of Bias: very serious.** Although an RCT, outcome was collected in MDA arm only, not in control group. **Inconsistency: no serious. Indirectness: no serious. Publication bias: no serious.**

Attached Images

4.2.6.5. MDA to reduce transmission of *P. vivax*

Clinical Question/ PICO

Population: Adults and children in a delimited geographical area with transmission of P. vivax
Intervention: Mass drug administration (MDA)
Comparator: no MDA

Summary

The systematic review identified five cRCTs and seven NRSs in eight countries (Cambodia, India, Kenya, Lao People's Democratic Republic, Myanmar, Panama, Solomon Islands, Venezuela [Bolivarian Republic of] and Viet Nam) assessing the impact of MDA on *P. vivax* transmission to no MDA (Schneider *et al* unpublished evidence). All of the cRCTs used DP and four of the studies also administered single low-dose primaquine, but none of the cRCTs used sufficient dosage of an 8-aminoquinoline to achieve radical cure of *P. vivax* hypnozoites[1]. One study provided a single round of MDA while the other four conducted three rounds of MDA. Among the NRSs, only one study reported radical cure of *P. vivax*. There was more variability in the design of MDA among the NRSs with respect to drug regimens and number of rounds, ranging from a single round to 24 weekly rounds.

The meta-analysis of the data from cRCTs showed MDA may reduce *P. vivax* prevalence 1–3 months after the last round of MDA but there was no impact of MDA on prevalence of *P. vivax* at later time periods. The certainty of evidence obtained from the NRSs was very low across all time periods and outcomes. Data from a cRCT that did not provide an 8-aminoquinoline medicine found that MDA probably did not increase the rate of severe adverse events within 0 – 3 months.

[1] The systematic review considered the following as the minimum adult dosage of 8-aminoquinoline medicines to achieve radical cure: 210 mg of primaquine over eight weeks; 1.25 g of plasmochin over 14 days. One study that contributed to the adverse events outcome (Comer 1971) considered its primaquine adult dosage regimen (40 mg of primaquine every two weeks for two years) to be radical cure, but as the total dose for an eight-week period (i.e. 160 mg) was less than 210 mg, the systematic review did not consider this to be radical cure.

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
1-3 months - Prevalence - NRS	Relative risk 0.18 (CI 95% 0.1 — 0.33) Based on data from 1,024 participants in 2 studies. (Observational (non-randomized))	**231** per 1000 Difference:	**42** per 1000 **189 fewer per 1000** (CI 95% 208 fewer — 155 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency [1]	The evidence is very uncertain about the effect of MDA on P. vivax prevalence between 1-3 months

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
1-3 months - Prevalence	Relative risk 0.15 (CI 95% 0.1 — 0.24) Based on data from 2,672 participants in 5 studies. (Randomized controlled)	133 per 1000 Difference:	20 per 1000 **113 fewer per 1000** (CI 95% 119 fewer — 101 fewer)	Low Due to serious risk of bias, Due to serious inconsistency [2]	MDA may reduce P. vivax prevalence between 1-3 months
1-3 months - Incidence of parasitaemia - NRS (low risk)	Rate ratio 0.37 (CI 95% 0.32 — 0.43) Based on data from 226,390 participants in 2 studies. (Observational (non-randomized))	5 per 1000 Difference:	2 per 1000 **3 fewer per 1000** (CI 95% 3 fewer — 3 fewer)	Very low Due to very serious risk of bias [3]	
1-3 months - Incidence of parasitaemia - NRS (high risk)	Rate ratio 0.37 (CI 95% 0.32 — 0.43) Based on data from 226,390 participants in 2 studies. (Observational (non-randomized))	180 per 1000 Difference:	67 per 1000 **113 fewer per 1000** (CI 95% 103 fewer — 122 fewer)	Very low Due to very serious risk of bias [4]	
1-3 months - Incidence of clinical malaria - NRS (low risk)	Rate ratio 0.29 (CI 95% 0.26 — 0.31) Based on data from 62,744 participants in 2 studies. (Observational (non-randomized))	22 per 1000	6 per 1000	Very low Due to serious inconsistency [5]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 1-3 months
1-3 months - Incidence of clinical malaria - NRS (high risk)	Rate ratio 0.29 (CI 95% 0.26 — 0.31) Based on data from 62,744 participants in 2 studies. (Observational (non-randomized))	156 per 1000 Difference:	45 per 1000 **111 fewer per 1000** 108 fewer — 115 fewer	Very low Due to serious inconsistency [6]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 1-3 months
4-12 months - Prevalence	Relative risk 1.01 (CI 95% 0.87 — 1.18) Based on data from 6,255 participants in 5 studies. (Randomized controlled)	96 per 1000 Difference:	97 per 1000 **1 more per 1000** (CI 95% 12 fewer — 17 more)	Low Due to serious risk of bias, Due to serious inconsistency [7]	MDA may result in little to no difference in P. vivax prevalence between 4-12 months

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
4-12 months - Prevalence - NRS	Relative risk 0.34 (CI 95% 0.15 — 0.78) Based on data from 939 participants in 1 studies. (Observational (non-randomized))	71 per 1000 Difference:	24 per 1000 **47 fewer per 1000** (CI 95% 60 fewer — 16 fewer)	Very low Due to very serious risk of bias [8]	The evidence is very uncertain about the effect of MDA on the prevalence of P. vivax between 4-12 months
4-12 months - Incidence of parasitaemia- NRS	Rate ratio 0.15 (CI 95% 0.07 — 0.34) Based on data from 223,990 participants in 1 studies. (Observational (non-randomized))	5 per 1000	1 per 1000	Very low Due to very serious risk of bias [9]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax parasitaemia between 4-12 months
4-12 months - Incidence of clinical malaria	Rate ratio 1.38 (CI 95% 0.97 — 1.95) Based on data from 3,325 participants in 1 studies. (Randomized controlled)	41 per 1000	57 per 1000	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [10]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 4-12 months
4-12 months - Incidence of clinical malaria - NRS	Rate ratio 0.72 (CI 95% 0.68 — 0.76) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	156 per 1000	112 per 1000	Very low Due to very serious risk of bias [11]	The evidence is very uncertain about the effect of MDA on P. vivax clinical malaria between 4-12 months
12-24 months - Prevalence	Relative risk 0.81 (CI 95% 0.44 — 1.48) Based on data from 243 participants in 1 studies. (Randomized controlled)	175 per 1000 Difference:	142 per 1000 **33 fewer per 1000** (CI 95% 98 fewer — 84 more)	Low Due to serious risk of bias, Due to serious imprecision [12]	MDA may result in little to no difference in P. vivax prevalence between 12-24 months
12-24 months - Incidence of clinical malaria - NRS	Rate ratio 0.04 (CI 95% 0.02 — 0.07) Based on data from 11,300 participants in 1 studies. (Observational (non-randomized))	156 per 1000	6 per 1000	Very low Due to very serious risk of bias [13]	The evidence is very uncertain about the effect of MDA on the incidence of P. vivax clinical malaria between 12-24 months
0-3 Months - serious adverse events	Odds ratio 3.61 (CI 95% 0.43 — 30.03) Based on data from 6,911 participants in 1	0.38 per 1000	1.39 per 1000	Moderate Due to serious imprecision [14]	MDA probably results in little to no difference in serious adverse events within 0-3

Outcome Timeframe	**Study results and measurements**	**Comparator** no MDA	**Intervention** Mass drug administration (MDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	studies. (Randomized controlled)				months
4-12 months - serious adverse events	Odds ratio 1.47 (CI 95% 0.68 — 3.2) Based on data from 6,911 participants in 1 studies. (Randomized controlled)	3 per 1000 Difference:	5 per 1000 **2 more per 1000** (CI 95% 1 fewer — 8 more)	**Moderate** Due to serious imprecision [15]	MDA probably results in little to no difference in serious adverse events between 4-12 months

1. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
2. **Risk of Bias: serious.** High or unclear risk of bias in some/ all studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals; I-squared 84%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: very serious.** High risk of bias in all included studies.
4. **Risk of Bias: very serious.** High risk of bias in all included studies.
5. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: serious.** Completely non-overlapping confidence intervals. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** High or unclear risk of bias in some/ all studies. **Inconsistency: serious.** I-squared 74%. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
9. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. **Risk of Bias: serious.** High or unclear risk of bias in some/ all studies. **Inconsistency: serious.** I-squared 52%. **Indirectness: no serious. Imprecision: serious.** Wide confidence interval; include both null effect and appreciable risk/ benefit. **Publication bias: no serious.**
11. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
12. **Risk of Bias: serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval; include both null effect and appreciable risk/ benefit. **Publication bias: no serious.**
13. **Risk of Bias: very serious.** High risk of bias in all included studies. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
14. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval; include both null effect and appreciable risk/ benefit. **Publication bias: no serious.**
15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence interval; include both null effect and appreciable risk/ benefit. **Publication bias: no serious.**

Attached Images

4.2.6.6. Mass relapse prevention (MRP) to reduce transmission of *P. vivax*

Clinical Question/ PICO

Population: Adults and children in a delimited geographical area with transmission of P. vivax
Intervention: Mass relapse prevention
Comparator: No MRP

Summary

The systematic review identified two NRSs that provided data on MRP for *P. vivax* (Shah *et al* *unpublished evidence*). Studies were conducted in the Democratic People's Republic of Korea in 2002 and in the Republic of Azerbaijan in 1970–1971. Both studies provided primaquine for 14 days at 0.25 mg/kg per day, administered in a single round prior to the peak transmission season. Both studies reported decreases in the incidence of *P. vivax* 1–3 months after the start of the intervention but the risk of bias in the studies was considered very serious. Both studies found a decrease in the incidence of *P. vivax* 4–12 months after the intervention and one study reported a decrease in the prevalence of *P. vivax* during that time period but the risk of bias in the studies was considered very serious. Information on adverse events was obtained from the intervention group in one study: no cases of severe haemolysis were reported, and side-effects were reported from less than 4% of 400 000 people. However, the overall certainty of the evidence was GRADEd as very low due to potential biases resulting from the study designs.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MRP	**Intervention** Mass relapse prevention	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
1-3 months - Incidence of P. vivax infection - NRS	Rate ratio 0.08 (CI 95% 0.07 — 0.08) Based on data from 218,308 participants in 2 studies. (Observational (non-randomized))	111 per 1000	9 per 1000	**Very low** Due to very serious risk of bias [1]	The evidence is very uncertain about the effect of MRP on the incidence of P. vivax infection between 1-3 months
4-12 months - Prevalence - NRS	Relative risk 0.07 (CI 95% 0.01 — 0.57) Based on data from 6,710 participants in 1 studies. (Observational (non-randomized))	4 per 1000	0 per 1000	**Very low** Due to risk of bias. [2]	The evidence is very uncertain about the effect of MRP on the prevalence of P. vivax infection between 4-12 months
4-12 months - Incidence of P. vivax infection - NRS	Rate ratio 0.2 (CI 95% 0.18 — 0.22) Based on data from 416,617 participants in 2 studies. (Observational (non-randomized))	13 per 1000 Difference:	3 per 1000 **10 fewer per 1000** (CI 95% 11 fewer — 10 fewer)	**Very low** Due to very serious risk of bias [3]	The evidence is very uncertain about the effect of MRP on the incidence of P. vivax infection between 4-12 months
Adverse events	Based on data from 333,946 participants in 1 studies. (Observational (non-randomized))		40 per 1000	**Very low** Due to serious risk of bias, and very serious indirectness [4]	The evidence is very uncertain about the effect of MRP on adverse events

1. **Risk of Bias: very serious.** Downgraded by 2 due to risk of bias. Many risk of bias domains judged as high risk or not enough information to determine. High risk of bias due to confounding in both studies included for this outcome. **Inconsistency: no serious.** Not downgraded for inconsistency. Both studies provided the same direction and a similar magnitude (qualitatively) of effect. **Indirectness: no serious.** Not downgraded for indirectness since evidence was judged to be sufficiently direct for the domains of population, intervention, comparator, direct comparison, and outcome. **Imprecision: no serious.** Not downgraded for imprecision since lower and upper confidence limits indicate the same direction of effect.
2. **Risk of Bias: serious.** Downgraded by 1 due to risk of bias. Quasi-experimental study design with a control group, but allocation was not done at random and no baseline data were provided to assess potential confounders. **Inconsistency: no serious.** Not downgraded for inconsistency due to single study result. **Indirectness: no serious.** Not downgraded for indirectness since evidence was judged to be sufficiently direct for the domains of population, intervention, comparator, direct comparison, and outcome. **Imprecision: no serious.** Not downgraded for imprecision since lower and upper confidence limits indicate the same direction of effect.
3. **Risk of Bias: very serious.** Downgraded by 2 due to risk of bias. Many risk of bias domains judged as high risk or not enough information to determine. High risk of bias due to confounding in both studies included for this outcome. **Inconsistency: no serious.** Not downgraded for inconsistency. Both studies provided the same direction and a similar magnitude (qualitatively) of effect. **Indirectness: no serious.** Not downgraded for indirectness since evidence was judged to be sufficiently direct for the domains of population, intervention, comparator, direct comparison, and outcome. **Imprecision: no serious.** Not downgraded for imprecision since lower and upper confidence limits indicate the same direction of effect.

4. **Risk of Bias: serious.** Downgraded by 1 due to risk of bias. Quasi-experimental study design with a control group, but allocation was not done at random and no baseline data were provided to assess potential confounders. **Inconsistency: no serious.** Not downgraded for inconsistency due to single study result. **Indirectness: very serious.** Downgraded by 2 due to indirectness. Side effects were not measured or reported in the control group, so evidence is only provided in the intervention population. **Imprecision: no serious.** Not downgraded for imprecision since this criteria is not applicable for this outcome (no effect measure presented). **Upgrade: large magnitude of effect.**

Attached Images

4.3. Vaccine

Clinical Question/ PICO

Population: Children ≥5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission

Intervention: A minimum of four doses of RTS,S/AS01 (given as a three-dose initial series; first dose should be provided between 5 and 17 months of age) with a minimal interval between doses of four weeks

Comparator: Malaria interventions currently in place without malaria vaccination

Summary

Systematic review summary

Three studies form the basis of these recommendations: two were individual randomized controlled trials (RCTs) and one was an open-label extension study of an included RCT. One was a multicentre study comparing three or four doses of the RTS,S/AS01 malaria vaccine to no malaria vaccination. The other RCT compared the RTS,S/AS01 malaria vaccine alone to SMC alone, and also compared a combination of malaria vaccine and SMC to the malaria vaccine alone or SMC alone. Based on WHO regions, all three studies were conducted in Africa, specifically: Burkina Faso (three studies), Gabon, Ghana, Kenya (two studies), Malawi, Mali, Mozambique, and the United Republic of Tanzania (two studies).

In addition, data from the observational evaluation of the first 24 months of pilot implementation in Ghana, Malawi, and Kenya were considered by MPAG/SAGE and included in the evidence summary.

The RCTs showed that RTS,S/AS01 reduces clinical malaria, hospital admissions with a positive malaria test, hospitalization with severe malaria, all-cause hospital admissions, severe malaria anaemia and the need for blood transfusions. Compared to SMC, RTS,S/AS01 is non-inferior in reducing clinical malaria and severe malaria anaemia and may be superior in reducing hospitalization with severe malaria. The combination of RTS,S/AS01 and SMC is probably better than SMC alone in reducing all-cause mortality and clinical malaria, and may reduce the need for blood transfusions and all-cause hospital admissions. The pilot programme showed that delivery of RTS,S/AS01 through routine systems probably reduces hospital admissions with severe malaria.

The RCTs had too few cases to determine an association between the vaccine and meningitis but the pilot study showed that RTS,S/AS01 introduction was probably not associated with an increase in hospital admissions with meningitis. There was uncertainty whether RTS,S/AS01 was associated with an increase in cerebral malaria in the RCTs but the pilot programme showed that vaccine introduction was probably not associated with an increase in hospital admission with cerebral malaria. One RCT found that vaccination with RTS,S/AS01 may be associated with an increase in deaths in girls, but the other found no evidence that the effect of RTS,S/AS01 (alone or in combination with SMC) on mortality differed between girls and boys compared to SMC alone. The pilot programme found that the effect of the RTS,S/AS01 vaccine introduction on all-cause mortality probably did not differ between girls and boys.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Protective efficacy (%) against clinical malaria episodes; 4-doses of RTS,S/AS01 versus control [1] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	36.3 (CI 95% 31.8 — 40.5) Based on data from 5,950 participants in 1 studies. [2] (Randomized controlled) Follow up: 48 months.	Difference:	**1,774 fewer per 1000** (CI 95% 1,387 fewer — 2,186 fewer)	**High**	RTS,S/AS01 vaccination reduces clinical malaria.
Protective efficacy (%) against clinical malaria of vaccine alone versus SMC alone [3] Phase 3b randomized study 2017–2020; 3 years' follow-up 6 Important	7.9 (CI 99% -1 — 16) Based on data from 3,953 participants in 1 studies. [4] (Randomized controlled)	305 per 1000 Difference:	278 per 1000 **27 fewer per 1000** (CI 95% 13 fewer — 40 fewer)	**High**	RTS,S/AS01 vaccination is non inferior to SMC in reducing clinical malaria.
Protective efficacy (%) against clinical malaria of vaccine + SMC combination versus SMC alone [5] Phase 3b randomized study 2017–2020; 3 years' follow-up 6 Important	62.8 (CI 95% 58.4 — 66.8) Based on data from 3,932 participants in 1 studies. [6] (Randomized controlled)	305 per 1000 Difference:	113 per 1000 **192 fewer per 1000** (CI 95% 182 fewer — 200 fewer)	**High**	The combination of RTS,S/AS01 vaccination with SMC is superior to SMC alone in reducing clinical malaria.
Protective efficacy (%) against severe malaria episodes; 4 vaccine doses versus control [7] Ph 3 randomized trial 2009–2014	32.2 (CI 95% 13.7 — 46.9) Based on data from 5,950 participants in 1 studies. [8] (Randomized controlled) Follow up: 48 months.	Difference:	**19 fewer per 1000** (CI 95% 4 fewer — 35 fewer)	**High** [9]	RTS,S/AS01 vaccination reduces severe malaria.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
(month 0 to end of study); median of 48 months' follow-up 9 Critical					
Protective efficacy (%) against hospitalization due to severe malaria of vaccine alone versus SMC alone [10] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	-0.4 (CI 95% -60.2 — 37.1) Based on data from 3,953 participants in 1 studies. [11] (Randomized controlled)	6.8 per 1000 Difference:	6.7 per 1000 **0.1 fewer per 1000** (CI 95% 2 fewer — 2.4 more)	**Low** Due to very serious imprecision [12]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing hospitalization with severe malaria.
Protective efficacy (%) against hospitalization due to severe malaria of vaccine + SMC combination versus SMC alone [13] Phase 3b randomized study 2017–2020, 3 years' follow-up 9 Critical	70.5 (CI 95% 41.9 — 85) Based on data from 3,932 participants in 1 studies. [14] (Randomized controlled)	6.8 per 1000 Difference:	2 per 1000 **4.8 fewer per 1000** (CI 95% 3.2 fewer — 5.7 fewer)	**Moderate** Due to serious imprecision [15]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing hospitalization with severe malaria.
Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on hospitalization with severe malaria in implementing versus comparison areas [16] Pilot implementation study 2019–2021 (month 0 to	0.7 (CI 95% 0.54 — 0.92) Based on data from 27,678 participants in 1 studies. [17]			**Moderate** Due to serious imprecision [18]	RTS,S/AS01 vaccine introduction is probably associated with a reduction in incidence of hospital admissions with severe malaria.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
month 24) 9 Critical					
Protective efficacy (%) against severe malaria anaemia; 4 vaccine doses versus control [19] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	47.8 (CI 95% 11.6 — 69.9) Based on data from 5,950 participants in 1 studies. [20] (Randomized controlled) Follow up: 48 months.	Difference:	**11 fewer per 1000** (CI 95% 1 fewer — 24 fewer)	**Moderate** Due to serious imprecision [21]	RTS,S/AS01 vaccination probably reduces severe malaria anaemia.
Protective efficacy (%) against severe malaria anaemia of vaccine alone versus SMC alone [22] Phase 3b randomized study 2017–2020, 3 years' follow-up 6 Important	18.4 (CI 95% -39.3 — 52.2) Based on data from 3,953 participants in 1 studies. [23] (Randomized controlled)	5.69 per 1000 Difference:	4.52 per 1000 **1.17 fewer per 1000** (CI 95% 2.64 fewer — 0.99 more)	**Low** Due to very serious imprecision [24]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing severe malaria anaemia.
Protective efficacy (%) against severe malaria anaemia of vaccine + SMC combination versus SMC alone [25] Phase 3b randomized study 2017–2020, 3 years' follow-up 6 Important	67.9 (CI 95% 34.1 — 84.3) Based on data from 3,932 participants in 1 studies. [26] (Randomized controlled)	5.69 per 1000 Difference:	1.82 per 1000 **3.87 fewer per 1000** (CI 95% 2.32 fewer — 4.71 fewer)	**Moderate** Due to serious imprecision [27]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing severe malaria anaemia.
Protective efficacy (%) against blood transfusions; 4 vaccine doses	28.5 (CI 95% 3.5 — 47.2) Based on data from 5,950 participants in 1 studies. [29] (Randomized	Difference:	**15 fewer per 1000** (CI 95% 1 fewer — 31 fewer)	**Moderate** Due to serious imprecision [30]	RTS,S/AS01 vaccination probably reduces the need for blood transfusions.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
versus control [28] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 6 Important	controlled)				
Protective efficacy (%) against blood transfusion of vaccine alone versus SMC alone [31] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	8.27 (CI 95% -67.6 — 49.8) Based on data from 3,953 participants in 1 studies. [32] (Randomized controlled)	4.22 per 1000 Difference:	3.79 per 1000 **0.43 fewer per 1000** (CI 95% 1.75 fewer — 1.6 more)	**Low** Due to very serious imprecision [33]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing the need for blood transfusions.
Protective efficacy (%) against blood transfusions of vaccine + SMC combination versus SMC alone [34] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	65.4 (CI 95% 22.9 — 84.5) Based on data from 3,932 participants in 1 studies. [35] (Randomized controlled)	4.22 per 1000 Difference:	1.45 per 1000 **2.77 fewer per 1000** (CI 95% 1.32 fewer — 3.49 fewer)	**Low** Due to very serious imprecision [36]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing the need for blood transfusions.
Protective efficacy (%) against all-cause hospital admissions; 4 vaccine doses versus control [37] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 9 Critical	16.5 (CI 95% 7.2 — 24.9) Based on data from 5,950 participants in 1 studies. [38] (Randomized controlled)	Difference:	**59 fewer per 1000** (CI 95% 18 fewer — 103 fewer)	**High** [39]	RTS,S/AS01 vaccination reduces all-cause hospital admissions.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Protective efficacy (%) against all-cause hospital admissions of vaccine alone versus SMC alone [40] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	-22.3 (CI 95% -74.4 — 14.3) Based on data from 3,953 participants in 1 studies. [41] (Randomized controlled)	**11** per 1000 Difference:	**13.2** per 1000 **2.2 more per 1000** (CI 95% 0.5 fewer — 5.6 more)	**Low** Due to very serious imprecision [42]	There may be little or no difference between RTS,S/AS01 vaccination and SMC in reducing all-cause hospital admissions.
Protective efficacy (%) against all-cause hospital admissions of vaccine + SMC combination versus SMC alone [43] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	18.7 (CI 95% -19.4 — 44.7) Based on data from 3,932 participants in 1 studies. [44] (Randomized controlled)	**11** per 1000 Difference:	**8.9** per 1000 **2.1 fewer per 1000** (CI 95% 4.28 fewer — 0.8 more)	**Low** Due to very serious imprecision [45]	The combination of RTS,S/AS01 vaccination with SMC may be superior to SMC alone in reducing all-cause hospital admissions.
Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on all-cause hospital admissions in implementing versus comparison areas [46] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	0.92 (CI 95% 0.83 — 1.03) Based on data from 27,678 participants in 1 studies. [47]			**Moderate** Due to serious imprecision [48]	RTS,S/AS01 vaccine introduction probably has little or no difference on all-cause hospital admissions.
Incidence rate ratio for impact of routine RTS,S/AS01 vaccination on	0.79 (CI 95% 0.68 — 0.93) Based on data from 27,678 participants in 1 studies. [50]			**High** [51]	RTS,S/AS01 vaccine introduction is associated with reduced hospital admissions with a positive malaria test.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
hospital admissions with a positive malaria test in implementing versus comparison areas [49] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical					
Protective efficacy (%) against all-cause mortality; 3 or 4 vaccine doses versus control [52] Ph 3 randomized trial 2009–2014 (month 0 to end of study); median of 48 months' follow-up 9 Critical	Based on data from 8,922 participants in 1 studies. [53] (Randomized controlled)			**Low** Due to very serious imprecision [54]	There were too few deaths to determine the impact of RTS,S/AS01 vaccination on all-cause mortality.
Protective efficacy (%) against all-cause mortality; vaccine alone versus SMC alone [55] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	12.1 (CI 95% -55.7 — 50.4) Based on data from 3,953 participants in 1 studies. [56] (Randomized controlled)	4.59 per 1000 Difference:	3.97 per 1000 **0.62 fewer per 1000** (CI 95% 1.97 fewer — 1.45 more)	**Low** Due to very serious imprecision [57]	There may be little or no difference between the impact of RTS,S/AS01 vaccination and SMC administration on all-cause mortality.
Protective efficacy (%) against all-cause mortality of vaccine + SMC combination versus SMC alone [58] Phase 3b randomized study 2017–2020; 3	52.3 (CI 95% 4.99 — 76) Based on data from 3,932 participants in 1 studies. [59] (Randomized controlled)	4.59 per 1000 Difference:	2.18 per 1000 **2.41 fewer per 1000** (CI 95% 0.75 fewer — 3.35 fewer)	**Moderate** Due to serious imprecision [60]	The combination of RTS,S/AS01 vaccination and SMC is probably associated with a reduction in all-cause mortality.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
years' follow-up 9 Critical					
Incidence rate ratio of meningitis; 3 or 4 vaccine doses versus control [61] Post-hoc analysis of Ph 3 randomized trial 2009–2014 9 Critical	10.5 (CI 95% 1.41 — 78) Based on data from 8,922 participants in 1 studies. [62]			**Low** Due to serious risk of bias, Due to serious imprecision [63]	There were too few meningitis cases to determine an association with RTS,S/AS01 vaccination.
Incidence rate ratio of meningitis in vaccine alone versus SMC alone versus combination of vaccine with SMC [64] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	Based on data from 6,861 participants in 1 studies. [65] (Randomized controlled)			**Low** Due to very serious imprecision [66]	There were no meningitis cases to determine an association with RTS,S/AS01 vaccination.
Incidence rate ratio of hospital admissions with meningitis; vaccine implementing versus comparison areas [67] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	0.81 (CI 95% 0.43 — 1.55) Based on data from 27,678 participants in 1 studies. [68]			**Moderate** Due to serious imprecision [69]	There is probably no evidence that RTS,S/AS01 vaccine introduction is associated with an increase in hospital admissions with meningitis.
Incidence rate ratio of possible cerebral malaria; 4-dose + 3-dose versus control	2.15 (CI 95% 1.1 — 4.3) Based on data from 8,922 participants in 1 studies. [71]			**Very low** Due to very serious risk of bias and serious imprecision [72]	There is uncertainty whether RTS,S/AS01 vaccination is associated with an increase in cerebral malaria cases.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
groups [70] Post-hoc analysis of Ph 3 randomized trial 2009–2014 9 Critical					
Incidence rate ratio of cerebral malaria in vaccine alone versus SMC alone vs combination of vaccine with SMC [73] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	Based on data from 5,920 participants in 1 studies. [74] (Randomized controlled)			**Low** Due to very serious imprecision [75]	There were too few cerebral malaria cases to determine an association with RTS,S/AS01 vaccination.
Incidence rate ratio of hospital admissions with cerebral malaria; vaccine implementing versus comparison areas [76] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	0.77 (CI 95% 0.44 — 1.35) Based on data from 27,678 participants in 1 studies. [77]			**Moderate** Due to serious inconsistency and serious imprecision [78]	There is probably no evidence that RTS,S/AS01 vaccine introduction is associated with an increase in hospital admissions with cerebral malaria.
Female:male risk ratio of vaccine impact on all-cause mortality; 4-dose + 3-dose versus control groups [79] Post-hoc analysis of Ph 3 randomized trial 2009–2014 9 Critical	1.5 (CI 95% 1.03 — 2.08) Based on data from 8,922 participants in 1 studies. [80]			**Low** Due to very serious imprecision [81]	RTS,S/AS01 vaccination may be associated with an increase in deaths in girls and a decrease in deaths in boys.

Outcome Timeframe	**Study results and measurements**	**Comparator** No vaccination	**Intervention** RTS,S/AS01 malaria vaccination	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Female:male rate ratio on vaccine impact on all-cause mortality; vaccine alone versus SMC alone [82] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	1.8 (CI 95% 0.56 — 5.79) Based on data from 3,953 participants in 1 studies. [83] (Randomized controlled)			**Low** Due to very serious imprecision [84]	There may be no evidence that the effect of RTS,S/AS01 vaccination differs between girls and boys.
Female:male rate ratio for all-cause mortality; combination of vaccine with SMC versus SMC alone [85] Phase 3b randomized study 2017–2020; 3 years' follow-up 9 Critical	0.35 (CI 95% 0.06 — 1.98) Based on data from 3,932 participants in 1 studies. [86] (Randomized controlled)			**Low** Due to very serious imprecision [87]	There may be no evidence that the effect of RTS,S/AS01 vaccination differs between girls and boys.
Female:male rate ratio of all-cause mortality ratio; vaccine implementing versus comparison areas [88] Pilot implementation study 2019–2021 (month 0 to month 24) 9 Critical	1.08 (CI 95% 0.93 — 1.25) Based on data from 13,682 participants in 1 studies. [89]			**Moderate** Due to serious imprecision because not yet powered to assess overall impact on all-cause mortality, however well powered to detect gender imbalance in all-cause mortality [90]	There is probably no evidence that the effect of RTS,S/AS01 vaccine introduction on all-cause mortality differs between girls and boys.

1. Clinical malaria episodes (from month 0 to end of study; median follow-up: 48 months) (modified ITT analysis) assessed with: illness in a child brought to a study facility with a measured temperature of 37.5°C and P. falciparum asexual = parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition = P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 (on a scale of 0 to = 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration); four-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control

group received comparator vaccine at months 0, 1, 2, and 20; Protective efficacy = (1-hazard ratio); Per Protocol analysis: VE 28.5% (95% CI 6.3 to 45.7)
2. Primary study[143]. The number of cases averted over time was calculated as the sum of 3-monthly differences in the estimated number of cases between the control and the RTS,S/AS01 groups (R3R and R3C combined up to the time of booster dose and R3R and R3C separately after the booster dose) and expressed per 1000 participants vaccinated. Among the older children, in the 12 months following administration of the first three doses, vaccine efficacy against clinical (uncomplicated and severe) malaria was 51% (95% CI 47-55) (per protocol analysis). **Baseline/comparator:** . **Supporting references:** [143],
3. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
4. Primary study[145]. The RTS,S vaccine alone group had 1,540 clinical malaria cases over 5535.7 total person-years at risk (PYAR) for an incidence rate of 278 cases (95% CI: 264.6 to 292.4) per 1000 PYAR; The SMC alone group had 1,661 cases over 5449.9 total PYAR for an incidence rate of 305 cases (95% CI: 290.5 to 319.8) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145], The 90, 95, and 99% CIs for the hazard ratio (HR) all excluded the pre-specified non-inferiority margin of 1.20..
5. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
6. Primary study[145]. The RTS,S + SMC combined group had 624 clinical malaria cases over 5508.0 total PYAR for an incidence rate of 113 cases (95% CI: 104.7 to 122.5) per 1000 PYAR; The SMC alone group has 1,661 cases over 5449.9 total PYAR for an incidence rate of 305 cases (95% CI: 290.5 to 319.8) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145],
7. Assessed with P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of acoexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 (on a scale of 0 to = 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration). 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio). Per Protocol analysis: VE 28.5% (95%CI: 6.3 to 45.7)
8. Primary study[143]. Among the older children, in the 12 months following administration of the first three doses, vaccine efficacy against severe malaria was 45% (95% CI 22-60) (per protocol analysis).. **Baseline/comparator:** . **Supporting references:** [143], PP analysis VE: 28.5% (95% CI: 6.3 to 45.7); The number of cases averted overtime was calculated as the sum of 3-monthly differences in the estimated number of cases between the control and the RTS,S/AS01 groups (R3R and R3C combined up to the time of booster dose and R3R and R3C separately after the booster dose) and expressed per 1000 participants vaccinated..
9. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
10. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
11. Primary study[145]. The RTS,S vaccine alone group had 37 severe malaria cases (of which 25 were severe malaria anaemia) over 5535.7 total PYAR for an incidence rate of 6.7 severe malaria cases (95% CI: 4.8 to 9.2) per 1000 PYAR; The SMC alone group had 37 cases (of which 31 were severe malaria anaemia) over 5449.9 total PYAR for a rate of 6.8 cases (95% CI: 4.9 to 9.4) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145], Most cases of severe malaria were severe malaria anaemia (vaccine: 25/37; SMC: 31/37).
12. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
13. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
14. Primary study[145]. Combination group of RTS,S + SMC had 11 severe malaria cases (of which 10 were severe malaria anaemia) over 5508 total PYAR for an incidence rate of 2.0 severe malaria cases (95% CI: 1.1 to 3.6) per 1000 PYAR; The

SMC alone group has 37 cases (of which 31 were severe malaria anaemia) over 5449.9 total PYAR for a rate of 6.8 cases (95% CI: 4.9 to 9.4) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145],

15. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**

16. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there was a total of 27 678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementating areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas

17. [155]. Among children eligible to have received all three primary doses of RTS,S/AS01, there was a total of 1107 admissions with severe malaria (out of 9,994 total age-eligible admissions), 418 from implementation areas and 689 from comparison areas. Among children who were not eligible there were 2,703 total admissions with severe malaria (out of 17,684 total age-ineligible admissions) to have received any doses of RTS,S/AS01: 1313 from implementation areas and 1390 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementing and comparison areas was 0.70 (95%CI 0.54 to 0.92), a reduction of 30% (95%CI 8% to 46%); there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria. **Baseline/comparator:** .

18. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggestthere is no evidence that the introduction of RTS,S/AS01 had a negative effect on the uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level for imprecision: few events and large CI. **Publication bias: no serious.**

19. Assessed with: a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a P. falciparum parasitaemia at a density of > 5000 parasites per cubic millimetre. 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).

20. Primary study[143]. **Baseline/comparator:** .

21. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder within the project; however, it has not been downgraded for ROB as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large confidence interval. **Publication bias: no serious.**

22. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

23. Primary study[145]. The RTS,S vaccine group had 25 severe malaria anemia cases over 5535.7 total PYAR for an incidence rate of 4.52 cases (95% CI: 3.05 to 6.68) per 1000 PYAR; The SMC alone group has 31 cases over 5449.9 total PYAR for a rate of 5.69 cases (95% CI: 4.00 to 8.09) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145],

24. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm. **Publication bias: no serious.**

25. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

26. Primary study[145]. The RTS,S vaccine and SMC combination group had 10 severe malaria anaemia cases over 5508 total PYAR for an incidence rate of 1.82 cases (95% CI: 0.977 to 3.37) per 1000 PYAR; The SMC alone group had 31 cases over 5449.9 total PYAR for a rate of 5.69 cases (95% CI: 4.00 to 8.09) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145],

27. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and a very large CI. **Publication bias: no serious.**

28. 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).

29. Primary study[143]. **Baseline/comparator:** .

30. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**

31. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S +

SMC = combination group).
32. Primary study[145]. The RTS,S vaccine group had 21 blood transfusion events over 5535.7 total PYAR for an incidence rate of 3.79 events (95% CI: 2.47 to 5.82) per 1000 PYAR; The SMC alone group had 23 events over 5449.9 total PYAR for an incidence rate of 4.22 events (95% CI: 2.80 to 6.35) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145],
33. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
34. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
35. Primary study[145]. The RTS,S vaccine and SMC combination group had 8 blood transfusion events over 5508.0 total PYAR for an incidence rate of 1.45 events (95% CI: 0.726 to 2.90) per 1000 PYAR; The SMC alone group has 23 events over 5449.9 total PYAR for an incidence rate of 4.22 events (95% CI: 2.80 to 6.35) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145],
36. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
37. 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).
38. Primary study[143]. **Baseline/comparator:** .
39. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
40. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
41. Primary study[145]. The RTS,S vaccine group had 73 events over 5535.7 total PYAR for an incidence rate of 13.2 events (95% CI: 10.5 to 16.6) per 1000 PYAR; The SMC alone group had 60 events over 5449.9 total PYAR for an incidence rate of 11.0 events (95% CI: 8.55 to 14.2) per 1000 PYAR;. **Baseline/comparator:** .
42. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
43. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
44. Primary study[145]. The RTS,S vaccine and SMC combination group had 49 events over 5508 total PYAR for an incidence rate of 8.90 events (95% 6.72 to 11.8) per 1000 PYAR; The SMC alone group had 60 events over 5449.9 total PYAR for an incidence rate of 11.0 events (95% CI: 8.55 to 14.2) per 1000 PYAR;. **Baseline/comparator:** . **Supporting references:** [145],
45. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm. **Publication bias: no serious.**
46. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementating areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
47. [155]. Severe malaria represented 19% of all admissions to sentinel hospitals (with at least one overnight stay) in comparison areas among children who were eligible to receive three doses of malaria vaccine. In this age group, there was a total of 3196 admissions to sentinel hospitals in implementation areas and 3569 in comparison areas. The rate ratio comparing the incidence of all-cause hospital admission between implementation and comparison areas, for this age group, was 0.92 (95%CI 0.83 to 1.03), a reduction of 8% (95%CI -3% to 17%).. **Baseline/comparator:** .
48. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile

illness.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI that incorporates the possibility of benefit and harm. Study was powered for a pooled analysis only, country estimates vary but confidence intervals are wide and consistent with pooled effect.. **Publication bias: no serious.**
49. Pilot implementation study designed to be analysed using cluster randomized control methodology. Across the three countries, there were a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas.
50. [155]. Patients admitted to sentinel hospitals were routinely tested for malaria infection by rapid diagnostic test (RDT) or microscopy. Out of a total of 27,678 patients admitted, test results were available for 88%. Among children eligible to have received three vaccine doses, the number of patients admitted with a positive malaria test was 2630-- 1075 from implementation areas and 1555 from comparison areas. The rate ratio comparing the incidence of hospital admission with a positive malaria test between implementation and comparison areas was 0.79 (95%CI 0.68 to 0.93), a reduction of 21% (95%CI 7% to 32%).. **Baseline/comparator:** .
51. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.; . **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
52. 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a comparator vaccine at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).
53. [143]. Four dose group: 61 deaths (13 malaria)/2976 children + Three dose group: 51 deaths (17 malaria) / 2972 children vs Control group: 46 deaths (13 malaria) / 2974 children.. **Baseline/comparator:** .
54. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**
55. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
56. Primary study[145]. In the RTS,S vaccine alone group there were 22 deaths total/1734 participants or 3.97 deaths (95% CI 2.92 to 6.04) per 1000 PYAR. In the SMC alone group, there were 25 deaths total/1716 participants or 4.59 deaths (95% CI 3.10 to 6.79) per 1000 PYAR.. **Baseline/comparator:** .
57. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**
58. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
59. Primary study[145]. In the RTS,S vaccine + SMC combination group there were 12 deaths total/1740 children or 2.18 deaths (95% CI 1.24 to 3.84) per 1000 PYAR. In the SMC alone group, there were 25 deaths total/1716 children or 4.59 deaths (95% CI 3.10 to 6.79) per 1000 PYAR.. **Baseline/comparator:** .
60. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI.. **Publication bias: no serious.**
61. mITT analysis; 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a comparator vaccine at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20. Protective efficacy = (1-hazard ratio).
62. [143]. 4-dose group 11/2976 + 3-dose group 10/2972 vs Control group 1/2974. **Baseline/comparator:** .
63. **Risk of Bias: serious.** This outcome was not pre-specified in the protocol (post-hoc analysis). Study was rated as unclear risk of bias due to heavy involvement of the funder within the project.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large confidence interval; . **Publication bias: no serious.**
64. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
65. Primary study[145]. Eight cases of clinically suspected meningitis (four in the SMC-alone group, three in the RTS,S

vaccine-alone group, and one in the RTS,S + SMC combined group) were investigated with the use of lumbar puncture, but none showed proven meningitis.. **Baseline/comparator:** .
66. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels for imprecision: no events reported in any groups. **Publication bias: no serious.**
67. Pilot implementation study designed to be analysed using cluster randomized control methodology; to be able to rule out an association with meningitis of the magnitude seen in the Phase 3 trial it would therefore be necessary to exclude rate ratios of about 10.5 (4.5 allowing for coverage and contamination) or more. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas
68. Primary study[155]. A total of 4,311 suspected cases of meningitis were investigated. Lumbar punctures were performed in 2,652 (62%) of these patients, and PCR analysis of samples of cerebrospinal fluid (CSF) was available for 2,249 patients (52%). A total of 51 cases of probable or confirmed meningitis were seen in sentinel hospitals among age groups of children eligible for the malaria vaccine: 27 from implementation areas and 24 from comparison areas. Among the age groups that were not eligible for the malaria vaccine, there were 79 probable or confirmed cases of meningitis: 44 from implementation areas and 35 from comparison areas. The incidence rate ratio comparing rates of admission with meningitis in implementation and comparison areas, among vaccine-eligible children, was 0.81 (95%CI 0.43 to 1.55). There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with meningitis. There were sufficient cases and high coverage of the vaccine to detect an excess of the magnitude observed in the Phase 3 trial if it had occurred. Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received the RTS,S/AS01 vaccine, compared to 53% (2491/4672) of all other hospital admissions in this age group from implementation areas (odds ratio, adjusted for country and age: 0.73 (95%CI 0.31,1.71). The PCR results showed that only 15% (8/55) of samples from confirmed cases, were of vaccine serotypes preventable by Hib or pneumococcus vaccines (i.e. Haemophilus influenzae type b, or vaccine serotypes of Streptococcus pneumoniae).. **Baseline/comparator:** .
69. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI that incorporates the possibility of benefit and harm. It was only downgraded by 1 level because the result excludes an effect of the magnitude observed in the Phase 3 trial (RR = 4.5-10.5), after allowing for vaccine uptake levels in the pilot.. **Publication bias: no serious.**
70. Unplanned sub-group analysis of participant groups: 4-dose group received three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group received three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20; Control group received a comparator vaccine at months 0, 1, 2, and 20 (control group).
71. [143]. In the context of an overall decrease in severe malaria, in an unplanned subgroup analysis from study months 0 to 20, 13 cases of possible cerebral malaria by record review and expert opinion occurred in the combined 3- and 4-dose RTS,S/AS01 group compared to 7 in the control group (2:1 randomization). From study month 21 until trial end, there were 7 cerebral malaria cases in the 4-dose RTS,S/AS01 group, 8 cases in the 3-dose RTS,S/AS01 group, and 2 cases in the control group. **Baseline/comparator:** .
72. **Risk of Bias: very serious.** Downgraded two levels for risk of bias: This was a post-hoc analysis based on an imprecise algorithm, followed by record review and expert panel review. Cerebral malaria is a difficult diagnosis to make in real time, and more difficult through record review Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias for this reason. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: few events and large CI. **Publication bias: no serious.**
73. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
74. Primary study[145]. Due to the absence of cases in the reference group, it was not possible to calculate the incidence rate ratio in vaccine recipients. There were no cases of cerebral malaria in the SMC alone group, 4 cases in the RTS,S vaccine alone group (0.723 cases per 1000 PYAR; 95%CI 0.271 to 1.93), and 1 case in the combination of RTS,S vaccine + SMC group (0.182 cases per 1000 PYAR; 95%CI 0.026 to 1.29).. **Baseline/comparator:** .
75. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: very few events and 0 events in the control arm; . **Publication bias: no serious.**
76. Pilot implementation study designed to be analysed using cluster randomized control methodology; to be able to rule out an association with cerebral malaria of the magnitude seen in the Phase 3 trial it would therefore be necessary to

exclude rate ratios of about 2.2 (1.6 allowing for 60% coverage and 5% contamination) or more. Across the three countries, there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months during the period from vaccine introduction until 30 April 2021: 4,853 were vaccine-eligible based on their date of birth out of 13,918 total admissions in areas where the vaccine was provided (implementing areas); 5,141 were vaccine-eligible out of 13,760 total admissions in comparison areas

77. [155]. There were 55 cases of cerebral malaria, in whom lumbar puncture was performed to exclude cases with probable meningitis): 25 from implementation areas and 30 from comparison areas. Among age groups of children not eligible to receive the malaria vaccine, there were 241 cases of cerebral malaria, 115 from implementation areas and 126 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.77 (95%CI 0.44 to 1.35). The incidence rate ratio for admission with other forms of severe malaria excluding cerebral malaria was 0.70 (95%CI 0.54 to 0.89). There was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (95%CI 0.57 to 1.56; and test of interaction p-value: 0.808). When the analysis was broadened to include cases meeting the criteria for cerebral malaria but in whom lumbar puncture was not performed, there was a total of 103 cases in age-groups eligible to have received at least one dose of the malaria vaccine: 49 from implementation areas and 54 from comparison areas. There were 455 cases in non-eligible age groups: 230 from implementing areas and 225 from comparison areas. The incidence rate ratio comparing rates of admission to hospital with cerebral malaria (with the broader case definition) in implementation areas relative to comparison areas, among children eligible for the malaria vaccine, was 0.96 (95%CI 0.61 to 1.52). Again there was no evidence that impact differed between cerebral malaria and other forms of severe malaria (test of interaction p-value: 0.470). Similar results were obtained when cerebral malaria was limited to cases defined as U (unresponsive) on the AVPU score. Among children eligible tohave received the vaccine, 20 of the cases from implementation areas and 25 from comparison areas met this stricter criterion, and the estimate of the rate ratio was 0.66 (95%CI: 0.31 to 1.43). Of the patients with cerebral malaria in vaccine-eligible age groups from implementation areas, 47% (23/49) had received RTS,S/AS01 vaccine, compared to 53% (2479/4650) of all other admissions in this age group from implementation areas (odds ratio, adjusted for country and age,1.03, 95%CI 0.56,1.90; the odds ratio among cases meeting the stricter definition requiring a lumbar puncture was 1.58; 95%CI: 0.66 to 3.80). There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria. The incidence rate ratio excludes an effect of the magnitude observed in the Phase 3 trial (RR = 2.2), after allowing for uptake of the vaccine in the pilot. **Baseline/comparator:** .

78. **Risk of Bias: no serious.** Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behaviour, or health worker behaviour in testing and treating for febrile illness.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level due to imprecision: large CI that incorporates the possibility of benefit and harm. Study was powered for a pooled analysis only; country estimates vary but CIs are wide and consistent with pooled effect; .

79. All-cause mortality (month 0 to study end) (modified ITT analysis); 4-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a booster dose at month 20; 3-dose group = three doses of RTS,S/AS01 at months 0, 1, and 2 and a comparator vaccine at month 20; Control group received = comparator vaccine at months 0, 1, 2, and 20.

80. [143]. Incidence rate ratio (IRR) of 4-dose group + 3-dose group vs Control group: Girls only IRR 2.0 (95% CI: 1.2 - 3.4) vs Boys only IRR 0.8 (95% CI 0.5 - 1.2). Girls only: 4-dose group 35 deaths (9 malaria)/1467 girls + 3-dose group 32 deaths (8 malaria) / 1500 girls vs Control group 17 deaths (4 malaria) / 1503 girls. Boys only 4-dose group 26 deaths (4 malaria) / 1509 boys + 3-dose group 19 deaths (9 malaria) / 1472 boys vs Control group 29 deaths (8 malaria) / 1471 boys. **Baseline/comparator:** .

81. **Risk of Bias: no serious.** Study was rated as unclear risk of bias due to heavy involvement of the funder in the project; however, it has not been downgraded for risk of bias as this was the only concern and the study was carefully scrutinized by independent experts and considered well conducted.. **Inconsistency: no serious. Indirectness: no serious.** For this safety outcome we have reported the combined results for children receiving 3 or 4 doses of the vaccine; however, it has not been downgraded for indirectness. **Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**

82. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).

83. Primary study[145]. Gender interaction parameter 1.80 (95%CI: 0.56 to 5.79); Girls only RTS,S vs SMC alone hazard ratio (HR) 1.23 (95% CI: 0.51 to 2.96); there were 11 deaths total or 4.15 deaths per 1000 PYAR (95% CI 2.30 to 7.49) among girls in the RTS,S alone group compared to 9 deaths total or 3.42 deaths per 1000 PYAR (95% CI 1.78 to 6.57) among girls in the SMC alone group. Boys only RTS,S vs SMC alone HR 0.68 (95% CI 0.32 to 1.47); there were 11 deaths total or 3.82 deaths per 1000 PYAR (95% CI 2.11 to 6.89) among boys in the RTS,S alone group compared to 16 deaths total or 5.68

deaths per 1000 PYAR (95% CI 3.48 to 9.27) among boys in the SMC alone group. **Baseline/comparator:** .
84. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm; . **Publication bias: no serious.**
85. Randomly assigned children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (SMC = chemoprevention-alone group), RTS,S/AS01E (RTS,S = vaccine-alone group), or chemoprevention and RTS,S/AS01E (RTS,S + SMC = combination group).
86. Primary study[145]. Gender interaction parameter 0.35 (95%CI 0.06 to 1.98). Girls only RTS,S+SMC combination group vs SMC alone group hazard ratio (HR) 0.22 (95% CI 0.05 to 1.02); there were 2 deaths total or 0.75 deaths per 1000 PYAR (95% CI 0.19 - 3.01) among girls in the RTS,S + SMC combination group compared to 9 deaths total or 3.42 deaths per 1000 PYAR (95% CI 1.78 - 6.57) among girls in the SMC alone group. Boys only RTS,S + SMC combination group vs SMC alone group HR 0.62 (95% CI 0.28 to 1.37); there were 10 deaths total or 3.51 deaths per 1000 PYAR (95% CI 1.89 - 6.52) among boys in the Combination group compared to 16 deaths total or 5.68 deaths per 1000 PYAR (95% CI 3.48 - 9.27) among boys in the SMC alone group.. **Baseline/comparator:** .
87. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Downgraded two levels due to imprecision: few events and a very large CI that incorporates the possibility of benefit and harm;. **Publication bias: no serious.**
88. Pilot implementation study designed to be analysed using cluster randomized control methodology. The evaluation was not powered at this time point to assess the overall impact of vaccine introduction on mortality but the evaluation was well powered to detect gender imbalance in all-cause mortality of the magnitude observed in the Phase 3 trial (mortality ratio = 1.4--1.6), in children up to about 2 years of age. A total of 13682 deaths among children 1-59 months of age were reported via community-based mortality surveillance across the three countries from the start of vaccinations on 23 April 2019 to 31 March 2021 (deaths in April 2021 were excluded because verbal autopsies have not all been completed).
89. [155]. There was no evidence that the effect of RTS,S/AS01 introduction on all-cause mortality differed between girls and boys in this age group. Excluding deaths due to injury in children eligible to have received three doses of RTS,S/AS01, there was a total of 2864 deaths reported, 1421 from implementing regions and 1443 from comparison regions. In children who were not eligible to have received the vaccine there were 4218 deaths in implementing regions and 3874 in comparison regions. The mortality ratio in the vaccine-eligible age group (eligible for three doses) between implementing and comparison regions, was 0.93 (95%CI: 0.84 to 1.03), a 7% reduction (95%CI: -3% to 16%). There was no evidence that the mortality ratio differed between girls and boys, the p-value for this interaction was 0.343. The mortality ratio in girls was 0.98 and in boys 0.90; the relative mortality ratio (girls:boys) was 1.08 (95%CI: 0.92 to 1.28). When analysis was extended to children eligible to have received at least one dose of the vaccine, similar results were obtained (ratio of mortality ratios: 1.08; 95%CI: 0.93 to 1.25; p-value for the interaction: 0.321). Similar results were also obtained when the analysis was repeated for different age groups of eligible children (mortality ratio girls:boys in eligible children under 18 months of age was 1.10 [95%CI: 0.94 to 1.29], and in eligible children aged 18 months and over it was 0.95 [95%CI: 0.70 to 1.31]). The vaccination status of vaccine-eligible children who died in implementation areas was similar in girls and boys (58.9% and 57.0% respectively). According to the household surveys in 12-23 month olds, coverage of the first dose of RTS,S/AS01 was slightly higher in girls than in boys (77.6% in girls and 73.0% in boys in Ghana; 75.1% in girls and 70.1% in boys in Malawi; and 79.0% in girls and 78.2% in boys in Kenya). Coverage was similar for the third dose.. **Baseline/comparator:** .
90. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Downgraded one level because the evaluation was not powered at this time point to assess overall impact of vaccine introduction on mortality. However the evaluation was well powered to detect gender imbalance in all-cause mortality of the magnitude observed in the Phase 3 trial (mortality ratio = 1.4 - 1.6), in children up to about 2 years of age.. **Publication bias: no serious.**

Attached Images

References

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5. CASE MANAGEMENT

5.1. Diagnosing malaria

5.2. Treating malaria

5.2.1. Treating uncomplicated malaria

5.2.1.1. Artemisinin-based combination therapy

Clinical Question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine once daily for 3 days
Comparator: Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Treatment failure - PCR unadjusted [1] 28 days	Relative risk 0.34 (CI 95% 0.3 — 0.39) Based on data from 6,200 participants in 9 studies. (Randomized controlled)	230 per 1000 Difference:	78 per 1000 **152 fewer per 1000** (CI 95% 161 fewer — 140 fewer)	High [2]	
Treatment failure - PCR adjusted [3] 28 days	Relative risk 0.42 (CI 95% 0.29 — 0.62) Based on data from 5,417 participants in 9 studies. (Randomized controlled)	30 per 1000 Difference:	13 per 1000 **17 fewer per 1000** (CI 95% 21 fewer — 11 fewer)	High [4]	
Treatment failure - PCR unadjusted [5]	Relative risk 0.71 (CI 95% 0.65 — 0.78) Based on data from 3,200 participants in 2	450 per 1000	320 per 1000	High [6]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
63 days	studies. (Randomized controlled)	Difference:	**130 fewer per 1000** (CI 95% 157 fewer — 99 fewer)		
Treatment failure - PCR adjusted [7] 63 days	Relative risk 0.72 (CI 95% 0.5 — 1.04) Based on data from 2,097 participants in 2 studies. (Randomized controlled)	60 per 1000 Difference:	43 per 1000 **17 fewer per 1000** (CI 95% 30 fewer — 2 more)	High [8]	

1. PCR unadjusted
2. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**
3. PCR adjusted
4. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** Although there is a benefit in favour of dihydroartemisinin + piperaquine, the PCR-adjusted treatment failure rate was < 5% with both drugs.. **Publication bias: no serious.**
5. PCR unadjusted
6. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** At this time, there is inconsistency between trials; both show a benefit with dihydroartemisinin + piperaquine, but the size of the benefit differs.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**
7. PCR adjusted
8. **Risk of Bias: no serious.** Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** The treatment failure rate with dihydroartemisinin + piperaquine was < 5% in both trials.. **Indirectness: no serious.** The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** Both ACTs performed well in these two trials, with low rates of treatment failure.. **Publication bias: no serious.**

Attached Images

Clinical Question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine once daily for 3 days
Comparator: Artesunate + mefloquine once daily for 3 days

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Dihydroartemisinin + piperaquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure - PCR unadjusted [1] 28 days	Relative risk 1.02 (CI 95% 0.28 — 3.72) Based on data from 3,487 participants in 8 studies. (Randomized controlled)	20 per 1000 Difference:	20 per 1000 **0 fewer per 1000** (CI 95% 14 fewer — 54 more)	**High** Due to serious inconsistency [2]	
Treatment failure - PCR adjusted [3] 28 days	Relative risk 0.41 (CI 95% 0.21 — 0.8) Based on data from 3,467 participants in 8 studies. (Randomized controlled)	10 per 1000 Difference:	4 per 1000 **6 fewer per 1000** (CI 95% 8 fewer — 2 fewer)	**High** Due to serious inconsistency [4]	
Treatment failure - PCR unadjusted [5] 63 days	Relative risk 0.84 (CI 95% 0.69 — 1.03) Based on data from 2,715 participants in 5 studies. (Randomized controlled)	120 per 1000 Difference:	101 per 1000 **19 fewer per 1000** (CI 95% 37 fewer — 4 more)	**Moderate** Due to serious inconsistency [6]	
Treatment failure - PCR adjusted [7] 63 days	Relative risk 0.5 (CI 95% 0.3 — 0.84) Based on data from 2,500 participants in 5 studies. (Randomized controlled)	30 per 1000 Difference:	15 per 1000 **15 fewer per 1000** (CI 95% 21 fewer — 5 fewer)	**High** Due to serious inconsistency [8]	

1. PCR unadjusted
2. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** In six trials, very few recurrences of parasitaemia were found in both groups. Two trials conducted mainly in areas in Thailand with multi-drug resistance showed increased risks for recurrent parasitaemia with artesunate + mefloquine.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.. **Imprecision: no serious.** Overall, no significant difference between treatments; however, dihydroartemisinin + piperaquine may be superior where P. falciparum is resistant to mefloquine.. **Publication bias: no serious.**
3. PCR adjusted
4. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** In six trials, very few recurrences of parasitaemia were found in both groups. Two trials conducted mainly in areas in Thailand with multi-drug resistance showed increased risks for recurrent parasitaemia with artesunate + mefloquine.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.. **Imprecision: no serious.** Overall, a statistically significant benefit with dihydroartemisinin + piperaquine, although the benefit may be present only where there is resistance to mefloquine.. **Publication bias: no**

serious.
5. PCR unadjusted
6. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Of the five trials, one in Thailand in 2005 showed a statistically significant benefit with dihydroartemisinin + piperaquine, one in Myanmar in 2009 showed a benefit with dihydroartemisinin + piperaquine, and three found no difference.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.. **Publication bias: no serious.**
7. PCR adjusted
8. **Risk of Bias: no serious.** Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Slight variation among trials, only one showing a statistically significant benefit with dihydroartemisinin + piperaquine.. **Indirectness: no serious.** The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.. **Publication bias: no serious.**

Attached Images

Clinical Question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine
Comparator: Artemether + lumefantrine

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Serious adverse events (including deaths)	Based on data from 7,022 participants in 8 studies. (Randomized controlled)	6 per 1000 Difference:	10 per 1000 **4 more per 1000**	Moderate Due to serious imprecision [1]	
Early vomiting	Based on data from 2,695 participants in 3 studies. (Randomized controlled)	20 per 1000 Difference:	30 per 1000 **10 more per 1000**	Moderate Due to serious risk of bias [2]	
Vomiting	Based on data from 6,761 participants in 9 studies. (Randomized controlled)	90 per 1000 Difference:	90 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [3]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Nausea	Based on data from 547 participants in 2 studies. (Randomized controlled)	20 per 1000 Difference:	20 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [4]	
Diarrhoea	Based on data from 4,889 participants in 7 studies. (Randomized controlled)	120 per 1000 Difference:	120 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [5]	
Abdominal pain	Based on data from 911 participants in 5 studies. (Randomized controlled)	190 per 1000 Difference:	160 per 1000 **30 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [6]	
Anorexia	Based on data from 3,834 participants in 5 studies. (Randomized controlled)	150 per 1000 Difference:	140 per 1000 **10 fewer per 1000**	Moderate Due to serious risk of bias [7]	
Headache	Based on data from 309 participants in 2 studies. (Randomized controlled)	270 per 1000 Difference:	330 per 1000 **60 more per 1000**	Low Due to serious risk of bias and serious imprecision [8]	
Sleeplessness	Based on data from 547 participants in 2 studies. (Randomized controlled)	10 per 1000 Difference:	30 per 1000 **20 more per 1000**	Low Due to serious risk of bias and serious imprecision [9]	
Dizziness	Based on data from 547 participants in 2 studies. (Randomized controlled)	30 per 1000 Difference:	40 per 1000 **10 more per 1000**	Low Due to serious risk of bias and serious imprecision [10]	
Sleepiness	Based on data from 384 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [11]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Weakness	Based on data from 1,812 participants in 5 studies. (Randomized controlled)	170 per 1000 Difference:	180 per 1000 **10 more per 1000**	Moderate Due to serious risk of bias [12]	
Cough	Based on data from 4,342 participants in 5 studies. (Randomized controlled)	420 per 1000 Difference:	420 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [13]	
Coryza	Based on data from 832 participants in 2 studies. (Randomized controlled)	680 per 1000 Difference:	660 per 1000 **20 fewer per 1000**	Low Due to serious imprecision [14]	
Prolonged QT interval (adverse event)	Based on data from 1,548 participants in 1 studies. (Randomized controlled)	30 per 1000 Difference:	20 per 1000 **10 fewer per 1000**	Low Due to serious imprecision and serious risk of bias [15]	
Prolonged QT interval (Bazett correction)	Based on data from 1,548 participants in 1 studies. (Randomized controlled)	70 per 1000 Difference:	90 per 1000 **20 more per 1000**	Low Due to serious imprecision and serious risk of bias [16]	
Prolonged QT interval (Fridericia correction)	Based on data from 1,548 participants in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [17]	
Pruritus	Based on data from 2,033 participants in 5 studies. (Randomized controlled)	20 per 1000 Difference:	40 per 1000 **20 more per 1000**	Moderate Due to serious risk of bias [18]	
Facial oedema	Based on data from 384 participants in 1	0 per 1000	0 per 1000	Low Due to serious risk of bias and	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	studies. (Randomized controlled)	Difference:	**0 fewer per 1000**	serious imprecision [19]	

1. **Risk of Bias: no serious.** All but one of the trials were open label; however, we did not downgrade for this outcome.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** No statistically significant difference was detected between treatments; however the sample size does not exclude the possibility of rare but clinically important differences..
2. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the absolute effects exclude clinically important differences..
3. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the absolute effects exclude clinically important differences..
4. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: There are limited data..
5. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the absolute effects exclude clinically important differences..
6. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** The result does not reach statistical significance..
7. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the absolute effects exclude clinically important differences..
8. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** The result does not reach statistical significance..
9. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** There are limited data..
10. **Risk of Bias: serious.** The majority of trials were open label.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** There are limited data..
11. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** There are limited data..
12. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the absolute effects exclude clinically important differences..
13. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the

absolute effects exclude clinically important differences..
14. **Risk of Bias: no serious.** All but one of the trials were open label; however, we did not downgrade for this outcome.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** The result does not reach statistical significance..
15. **Risk of Bias: serious.** This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious. Indirectness: no serious.** This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** The result does not reach statistical significance..
16. **Risk of Bias: serious.** This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious. Indirectness: no serious.** This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** The result does not reach statistical significance..
17. **Risk of Bias: serious.** This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious. Indirectness: no serious.** This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** The result does not reach statistical significance..
18. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No effect found, and the CIs around the absolute effects exclude clinically important differences..
19. **Risk of Bias: serious.** The majority of trials were open label.. **Inconsistency: no serious.** The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** There are limited data..

Attached Images

Clinical Question/ PICO

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine
Comparator: Artesunate + mefloquine

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Serious adverse events (including deaths)	Based on data from 3,522 participants in 8 studies. (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000**	Moderate Due to serious imprecision [1]	
Nausea	Based on data from 4,531 participants in 9 studies. (Randomized controlled)	20 per 1000 Difference:	14 per 1000 **6 fewer per 1000**	Moderate Due to serious risk of bias [2]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Early vomiting	Based on data from 4,114 participants in 9 studies. (Randomized controlled)	7 per 1000 Difference:	6 per 1000 **1 fewer per 1000**	Moderate Due to serious risk of bias [3]	
Vomiting	Based on data from 2,744 participants in 5 studies. (Randomized controlled)	13 per 1000 Difference:	8 per 1000 **5 fewer per 1000**	Moderate Due to serious risk of bias [4]	
Anorexia	Based on data from 3,497 participants in 6 studies. (Randomized controlled)	15 per 1000 Difference:	13 per 1000 **2 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [5]	
Diarrhoea	Based on data from 2,217 participants in 5 studies. (Randomized controlled)	6 per 1000 Difference:	8 per 1000 **2 more per 1000**	Moderate Due to serious risk of bias [6]	
Abdominal pain	Based on data from 3,887 participants in 7 studies. (Randomized controlled)	11 per 1000 Difference:	11 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [7]	
Headache	Based on data from 2,039 participants in 4 studies. (Randomized controlled)	12 per 1000 Difference:	10 per 1000 **2 fewer per 1000**	Low Due to serious risk of bias and serious inconsistency [8]	
Dizziness	Based on data from 4,531 participants in 9 studies. (Randomized controlled)	36 per 1000 Difference:	26 per 1000 **10 fewer per 1000**	Moderate Due to serious risk of bias [9]	
Sleeplessness	Based on data from 2,551 participants in 6 studies. (Randomized controlled)	21 per 1000 Difference:	10 per 1000 **11 fewer per 1000**	Moderate Due to serious risk of bias [10]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue	Based on data from 872 participants in 2 studies. (Randomized controlled)	8 per 1000 Difference:	3 per 1000 **5 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [11]	
Nightmares	Based on data from 220 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	1 per 1000 **9 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [12]	
Anxiety	Based on data from 522 participants in 1 studies. (Randomized controlled)	11 per 1000 Difference:	1 per 1000 **10 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [13]	
Blurred vision	Based on data from 464 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [14]	
Tinnitus	Based on data from 220 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000**	Low Due to serious risk of bias and serious indirectness [15]	
Palpitations	Based on data from 1,175 participants in 3 studies. (Randomized controlled)	18 per 1000 Difference:	11 per 1000 **7 fewer per 1000**	Moderate Due to serious risk of bias [16]	
Cough	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	10 per 1000 Difference:	8 per 1000 **2 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [17]	
Dyspnoea	Based on data from 220 participants in 1 studies. (Randomized controlled)	9 per 1000 Difference:	3 per 1000 **6 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [18]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prolonged QT interval (adverse event)	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	5 per 1000 **1 more per 1000**	Low Due to serious risk of bias and serious imprecision [19]	
Prolonged QT interval (Bazett correction)	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	9 per 1000 **5 more per 1000**	Low Due to serious risk of bias and serious imprecision [20]	
Prolonged QT interval (Fridericia correction)	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	5 per 1000 Difference:	4 per 1000 **1 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [21]	
Arthralgia	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **1 fewer per 1000**	Moderate Due to serious risk of bias [22]	
Myalgia	Based on data from 1,148 participants in 1 studies. (Randomized controlled)	6 per 1000 Difference:	6 per 1000 **0 fewer per 1000**	Moderate Due to serious risk of bias [23]	
Urticaria	Based on data from 719 participants in 2 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [24]	
Pruritus	Based on data from 872 participants in 2 studies. (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000**	Low Due to serious risk of bias and serious imprecision [25]	
Rash	Based on data from 220 participants in 1	1 per 1000	0 per 1000	Low Due to serious risk of bias and	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	studies. (Randomized controlled)	Difference:	**1 fewer per 1000**	serious imprecision [26]	

1. **Risk of Bias: no serious.** Only eight of the 11 reports made any comment on serious adverse events. None of these eight trials was blinded. . **Inconsistency: no serious.** None of the eight trials found statistically significant differences.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** These trials do not exclude the possibility of rare but clinically important adverse effects..
2. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
3. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** None of the eight trials found statistically significant differences.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The 95% CI around the absolute effect is narrow and excludes clinically important differences..
4. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
5. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** This result does not reach statistical significance..
6. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
7. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No difference was found between treatments, and the sample is large enough for detection of any differences..
8. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: serious.** There is moderate heterogeneity among trials.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
9. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
10. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
11. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: serious.** Only two trials assessed this outcome.. **Imprecision: no serious.**
12. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: serious.** Only two trials assessed this outcome.. **Imprecision: no serious.**
13. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: serious.** Only two trials assessed this outcome.. **Imprecision: no serious.**

14. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: serious.** Only two trials assessed this outcome.. **Imprecision: no serious.**
15. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: serious.** Only two trials assessed this outcome.. **Imprecision: no serious.**
16. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious.** This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
17. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** This result does not reach statistical significance..
18. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Limited data available, and the result is not statistically significant..
19. **Risk of Bias: serious.** This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious. Indirectness: no serious.** This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** This result does not reach statistical significance..
20. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious.** This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** This result does not reach statistical significance..
21. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious.** This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** This result does not reach statistical significance..
22. **Risk of Bias: serious.** All trials were open label. This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear. 15 . **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** No difference was found between treatments, and the sample is large enough for detection of any differences..
23. **Risk of Bias: serious.** All trials were open label. This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** No difference was found between treatments, and the sample is large enough for detection of any differences..
24. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Limited data available, and the result is not statistically significant..
25. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Limited data available, and the result is not statistically significant..
26. **Risk of Bias: serious.** All trials were open label.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Limited data available, and the result is not statistically significant..

Attached Images

Clinical Question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria-endemic settings)
Intervention: Artemisinin + naphthoquine; 1-day course
Comparator: Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Artemisinin + naphthoquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Treatment failure on day	Relative risk 1.54 (CI 95% 0.27 — 8.96)	10	15	**Very low** Due to serious	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Artemisinin + naphthoquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
28 (PCR-unadjusted)	Based on data from 297 participants in 2 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **5 more per 1000** (CI 95% 7 fewer — 80 more)	indirectness and very serious imprecision [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 3.25 (CI 95% 0.13 — 78.69) Based on data from 295 participants in 2 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	Very low Due to serious indirectness and very serious imprecision [2]	
Fever clearance: fever on day 2	Relative risk 5.9 (CI 95% 0.73 — 47.6) Based on data from 123 participants in 1 studies. (Randomized controlled)	20 per 1000 Difference:	118 per 1000 **98 more per 1000** (CI 95% 5 fewer — 932 more)	Very low Due to serious indirectness and very serious imprecision [3]	
Parasite clearance: parasitaemia on day 2	Relative risk 0.15 (CI 95% 0.01 — 2.92) Based on data from 297 participants in 2 studies. (Randomized controlled)	20 per 1000 Difference:	3 per 1000 **17 fewer per 1000** (CI 95% 20 fewer — 38 more)	Very low Due to serious indirectness and very serious imprecision [4]	
Gametocytaemia on day 7	Relative risk 1.97 (CI 95% 0.18 — 21.14) Based on data from 123 participants in 1 studies. (Randomized controlled)	20 per 1000 Difference:	39 per 1000 **19 more per 1000** (CI 95% 16 fewer — 403 more)	Very low Due to serious indirectness and very serious imprecision [5]	

1. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. Both trials are significantly underpowered.
2. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. Both trials are significantly underpowered.

3. **Risk of Bias: no serious.** This study adequately concealed allocation and thus had a low risk of selection bias. **Indirectness: serious.** Study in Cote d'Ivoire. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial was small and the result has a very wide 95% confidence interval, including appreciable benefit and harm.
4. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.
5. **Risk of Bias: no serious.** This study adequately concealed allocation and thus had a low risk of selection bias. **Indirectness: serious.** Study in Cote d'Ivoire. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial was small and the result has a very wide 95% confidence interval, including appreciable benefit and harm.

Attached Images

Clinical Question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria-endemic settings)
Intervention: Artemisinin + naphthoquine; 1-day course
Comparator: Dihydroartemisinin + piperaquine; 3-day course

Outcome Timeframe	**Study results and measurements**	**Comparator** Dihydroartemisinin + piperaquine	**Intervention** Artemisinin + naphthoquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Treatment failure on day 28 (PCR-unadjusted)	Based on data from 143 participants in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	**Very low** Due to serious indirectness and very serious imprecision [1]	
Treatment failure on day 28 (PCR-adjusted)	Based on data from 143 participants in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	**Very low** Due to serious indirectness and very serious imprecision [2]	
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.91 (CI 95% 0.13 — 6.26) Based on data from 143 participants in 1 studies. (Randomized controlled)	**30** per 1000 Difference:	**27** per 1000 **3 fewer per 1000** (CI 95% 26 fewer — 158 more)	**Very low** Due to serious indirectness and very serious imprecision [3]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Dihydroartemisinin + piperaquine	**Intervention** Artemisinin + naphthoquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Treatment failure on day 42 (PCR-adjusted)	Relative risk 0.19 (CI 95% 0.01 — 3.82) Based on data from 141 participants in 1 studies. (Randomized controlled)	30 per 1000 Difference:	6 per 1000 **24 fewer per 1000** (CI 95% 30 fewer — 85 more)	Very low Due to serious indirectness and very serious imprecision [4]	
Fever clearance: fever on day 2	Based on data from 144 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000	Very low Due to serious indirectness and very serious imprecision [5]	
Parasite clearance: parasitaemia on day 2	Relative risk 6.29 (CI 95% 0.33 — 119.69) Based on data from 144 participants in 1 studies. (Randomized controlled)	0 per 1000	40 per 1000	Very low Due to serious indirectness and very serious imprecision [6]	
Gametocytaemia: on day 7	Relative risk 1.38 (CI 95% 0.52 — 3.7) Based on data from 144 participants in 1 studies. (Randomized controlled)	80 per 1000 Difference:	110 per 1000 **30 more per 1000** (CI 95% 38 fewer — 216 more)	Very low Due to serious indirectness and very serious imprecision [7]	

1. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
2. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
3. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
4. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.

5. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial is small. No participants in either group had fever on day 2.
6. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.
7. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Inconsistency: no serious. Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.

Attached Images

Clinical Question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria in malaria transmission settings
Intervention: Artesunate-pyronaridine
Comparator: artemether-lumefantrine

Outcome Timeframe	**Study results and measurements**	**Comparator** AL	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Total failure: day 28 (PCR-adjusted)	Relative risk 0.59 (CI 95% 0.26 — 1.31) Based on data from 3,068 participants in 4 studies. [1] (Randomized controlled)	**15** per 1000 Difference:	**9** per 1000 **6 fewer per 1000** (CI 95% 11 fewer — 5 more)	**Low** Due to serious indirectness, Due to serious imprecision. Certainty of the evidence grade differs from the 2014 review version due to additional data: the previous review reported no substantial difference between ASPY and AL in reference to this outcome and therefore did not downgrade for imprecision. In this update we report a reduced rate in the ASPY arm. Because we concluded that there may be a difference, we necessarily	Compared to AL, ASPY may have fewer PCR-adjusted failures at day 28.

Outcome Timeframe	**Study results and measurements**	**Comparator** AL	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
				downgraded for the imprecision. [2]	
Total failure: day 42 (PCR-adjusted)	Relative risk 0.86 (CI 95% 0.49 — 1.51) Based on data from 2,575 participants in 4 studies. [3] (Randomized controlled)	23 per 1000 Difference:	20 per 1000 **3 fewer per 1000** (CI 95% 12 fewer — 12 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	There may be little or no difference in PCR-adjusted failures at day 42 between ASPY and AL.
Total failure: day 28 (unadjusted)	Relative risk 0.27 (CI 95% 0.13 — 0.58) Based on data from 3,149 participants in 4 studies. [5] (Randomized controlled)	126 per 1000 Difference:	34 per 1000 **92 fewer per 1000** (CI 95% 110 fewer — 53 fewer)	**Low** Due to serious indirectness, Due to serious inconsistency, Certainty of the evidence grade differs from the 2014 review version due to additional data: the introduction of more data increased the heterogeneity between the included trials. [6]	Compared to AL, ASPY may have fewer unadjusted failures at day 28.
Total failure: day 42 (unadjusted)	Relative risk 0.61 (CI 95% 0.46 — 0.82) Based on data from 3,080 participants in 4 studies. [7] (Randomized controlled)	254 per 1000 Difference:	155 per 1000 **99 fewer per 1000** (CI 95% 137 fewer — 46 fewer)	**Low** Due to serious inconsistency, Due to serious indirectness, Certainty of the evidence grade differs from the 2014 review version due to additional data: the introduction of more data increased the heterogeneity between the included trials. [8]	Compared to AL, ASPY may have fewer unadjusted failures at day 42.
Serious adverse events (42 days)	Relative risk 1.16 (CI 95% 0.3 — 4.5) Based on data from 2,004 participants in 3 studies. [9] (Randomized controlled)	3 per 1000 Difference:	3 per 1000 **0 fewer per 1000** (CI 95% 2 fewer — 11 more)	**Low** Due to very serious imprecision [10]	We do not know if there is a difference in serious adverse events between ASPY and AL.

Outcome Timeframe	**Study results and measurements**	**Comparator** AL	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
First treatment, abnormal ALT increase (42 days)	Relative risk 3.34 (CI 95% 1.33 — 8.39) Based on data from 3,415 participants in 4 studies. [11] (Randomized controlled)	3 per 1000 Difference:	10 per 1000 **7 more per 1000** (CI 95% 1 more — 22 more)	**Low** Due to serious indirectness, Due to serious imprecision [12]	Compared to AL, ASPY may lead to higher events of abnormal ALT increase. (Aggregate analysis indicates this estimate may be accurate).
First treatment, AST increase (42 days)	Relative risk 3.12 (CI 95% 1.23 — 7.94) Based on data from 3,415 participants in 4 studies. [13] (Randomized controlled)	3 per 1000 Difference:	9 per 1000 **6 more per 1000** (CI 95% 1 more — 21 more)	**Low** Due to serious indirectness, Due to serious imprecision [14]	Compared to AL, ASPY may lead to higher events of abnormal AST increase.
First treatment, abnormal bilirubin increase (42 days)	Relative risk 0.82 (CI 95% 0.33 — 2.04) Based on data from 3,130 participants in 3 studies. [15] (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **1 fewer per 1000** (CI 95% 4 fewer — 6 more)	**Low** Due to serious indirectness, Due to serious imprecision [16]	We do not know if there is a difference in bilirubin between ASPY and AL.

1. Systematic review [184] with included studies: Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali), Tshefu 2010, Sagara 2018 (Bougoula, Mali), Roth 2018a, Kayentao 2012, Sagara 2018 (Sotuba, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CIs are wide and include both almost no effect and clinically significant effect..
3. Systematic review [184] with included studies: Sagara 2018 (Kolle, Mali), Roth 2018a, Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Sotuba, Mali), Kayentao 2012, Sagara 2018 (Bougoula, Mali), Tshefu 2010. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CIs are wide and include both almost no effect and clinically significant effect..
5. Systematic review [184] with included studies: Tshefu 2010, Roth 2018a, Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Kayentao 2012, Sagara 2018 (Sotuba, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: serious.** There was quantitative heterogeneity between studies.. **Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: no serious.**
7. Systematic review [184] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Tshefu 2010, Roth 2018a, Kayentao 2012, Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: serious.** There was quantitative heterogeneity between studies.. **Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: no serious.**

9. Systematic review [184] with included studies: Tshefu 2010, Kayentao 2012, Roth 2018a. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** The low number of events recorded in the studies is insufficient for confidently estimating the effect size. .
11. Systematic review [184] with included studies: Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Roth 2018a, Sagara 2018 (Sotuba, Mali), Tshefu 2010, Sagara 2018 (Kolle, Mali), Sagara 2018 (Bougoula, Mali), Kayentao 2012. **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: no serious. Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CIs are wide and include both almost no effect and clinically significant effect..
13. Systematic review [184] with included studies: Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Bougoula, Mali), Tshefu 2010, Kayentao 2012, Roth 2018a, Sagara 2018 (Kolle, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: no serious. Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CIs are wide and include both almost no effect and clinically significant effect..
15. Systematic review [184] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Kayentao 2012, Tshefu 2010, Sagara 2018 (Sotuba, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
16. **Inconsistency: no serious. Indirectness: serious.** The trials included adults and children and had sites in Africa and Asia. However, across the trials, only 115 children and 0 adults were randomized to ASPY in Asia. Further adequately powered studies in adults and children in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CIs include both no effect and clinically significant effect.

Attached Images

References

184. Pryce J, Taylor M, Fox T, Hine P : Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6): Pubmed Journal

Clinical Question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria transmission settings)
Intervention: Artesunate-pyronaridine
Comparator: Artesunate-amodiaquine

Outcome Timeframe	**Study results and measurements**	**Comparator** AS-AQ	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Total failure: day 28 (PCR-adjusted)	Relative risk 0.55 (CI 95% 0.11 — 2.77) Based on data from 1,245 participants in 1 studies. [1] (Randomized controlled)	8 per 1000 Difference:	4 per 1000 **4 fewer per 1000** (CI 95% 7 fewer — 14 more)	**Low** Due to serious indirectness, Due to serious imprecision [2]	Compared to AS-AQ, ASPY may have fewer PCR-adjusted failures at day 28.

Outcome Timeframe	**Study results and measurements**	**Comparator** AS-AQ	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Total failure: day 42 (PCR-adjusted)	Relative risk 0.98 (CI 95% 0.2 — 4.83) Based on data from 1,091 participants in 1 studies. [3] (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **0 fewer per 1000** (CI 95% 5 fewer — 23 more)	Low Due to serious indirectness, Due to serious imprecision [4]	There may be little or no difference in PCR-adjusted failures at day 42 between ASPY and AS-AQ.
Total failure: day 28 (unadjusted)	Relative risk 0.49 (CI 95% 0.3 — 0.81) Based on data from 1,257 participants in 1 studies. [5] (Randomized controlled)	75 per 1000 Difference:	37 per 1000 **38 fewer per 1000** (CI 95% 52 fewer — 14 fewer)	Moderate Due to serious indirectness [6]	Compared to AS-AQ, ASPY probably has fewer unadjusted failures at day 28.
Total failure: day 42 (unadjusted)	Relative risk 0.98 (CI 95% 0.78 — 1.23) Based on data from 1,235 participants in 1 studies. [7] (Randomized controlled)	195 per 1000 Difference:	192 per 1000 **4 fewer per 1000** (CI 95% 43 fewer — 45 more)	Moderate Due to serious indirectness [8]	There is probably little or no difference in unadjusted failures at day 42 between ASPY and AS-AQ.
First treatment, abnormal ALT increase (42 days)	Relative risk 1.41 (CI 95% 0.28 — 7.09) Based on data from 1,317 participants in 1 studies. [9] (Randomized controlled)	1 per 1000 Difference:	1 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 6 more)	Low Due to serious indirectness, Due to serious imprecision [10]	Compared to AL, ASPY may lead to higher events of abnormal ALT increase. (Aggregate analysis indicates this estimate may be accurate).
First treatment, abnormal AST increase (42 days)	Relative risk 0.43 (CI 95% 0.08 — 2.07) Based on data from 1,317 participants in 1 studies. [11] (Randomized controlled)	4 per 1000 Difference:	2 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 4 more)	Very low Due to serious indirectness, Due to very serious imprecision [12]	We do not know if there is a difference in AST between ASPY and AS-AQ.
First treatment, abnormal bilirubin increase (42 days)	Relative risk 0.99 (CI 95% 0.06 — 15.76) Based on data from 1,317 participants in 1 studies. [13] (Randomized controlled)	1 per 1000 Difference:	1 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 15 more)	Very low Due to serious indirectness, Due to very serious imprecision [14]	We do not know if there is a difference in bilirubin between ASPY and AS-AQ
Serious					Serious adverse events data were not available

Outcome Timeframe	**Study results and measurements**	**Comparator** AS-AQ	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
adverse events [15]					disaggregated by site to allow inclusion in this comparison.

1. Systematic review [184] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Ouagadougou, Burkina Faso). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects..
3. Systematic review [184] with included studies: Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Ouagadougou, Burkina Faso). **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: serious.** The effect estimate is close to no effect, but the CI is wide..
5. Systematic review [184] with included studies: Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Djoliba, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: no serious.**
7. Systematic review [184] with included studies: Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Ouagadougou, Burkina Faso). **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: no serious.**
9. Systematic review [184] with included studies: Sagara 2018 (Kolle, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso). **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: serious.** The low number of events recorded in the study is insufficient for confidently estimating the effect size. However, aggregate analysis of ALT increase across different comparator drugs provides indirect evidence that the point estimate may be accurate..
11. Systematic review [184] with included studies: Sagara 2018 (Djoliba, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bougoula, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: very serious.** The CI is very large and includes both no effect and clinically important effects..
13. Systematic review [184] with included studies: Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Kolle, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: no serious. Indirectness: serious.** The data are drawn from one study, conducted in six sites in three countries in West Africa. Further studies in Asia would be needed to fully apply this result.. **Imprecision: very serious.** The CI is very large and includes both no effect and clinically important effects..
15. Serious adverse events data were not available disaggregated by site to allow inclusion in this comparison.

Attached Images

References

184. Pryce J, Taylor M, Fox T, Hine P : Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6): Pubmed Journal

Clinical Question/ PICO

Population: Adults and children with uncomplicated P. falciparum malaria (malaria transmission settings)
Intervention: Artesunate-pyronaridine
Comparator: Mefloquine plus artesunate

Outcome Timeframe	**Study results and measurements**	**Comparator** MQ+AS	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Total failure: day 28 (PCR-adjusted)	Relative risk 0.37 (CI 95% 0.13 — 1.05) Based on data from 1,117 participants in 1 studies. [1] (Randomized controlled)	22 per 1000 Difference:	8 per 1000 **14 fewer per 1000** (CI 95% 19 fewer — 1 more)	**Low** Due to serious indirectness, Due to serious imprecision, Certainty of the evidence grade differs from the 2014 review version due to alterations in the data extraction protocol: the CI has become less precise, and our decision has greater consistency with other outcome certainty grades. [2]	Compared to MQ+AS, ASPY may have fewer PCR-adjusted failures at day 28.
Total failure: day 42 (PCR-adjusted)	Relative risk 1.8 (CI 95% 0.9 — 3.57) Based on data from 1,037 participants in 1 studies. [3] (Randomized controlled)	29 per 1000 Difference:	52 per 1000 **23 more per 1000** (CI 95% 3 fewer — 75 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	Compared to MQ+AS, ASPY may have more PCR-adjusted failures at day 42.
Total failure: day 28 (unadjusted)	Relative risk 0.36 (CI 95% 0.17 — 0.78) Based on data from 1,120 participants in 1 studies. [5] (Randomized controlled)	41 per 1000 Difference:	15 per 1000 **26 fewer per 1000** (CI 95% 34 fewer — 9 fewer	**Moderate** Due to serious indirectness [6]	Compared to MQ+AS, ASPY probably has fewer unadjusted failures at day 28.

Outcome Timeframe	**Study results and measurements**	**Comparator** MQ+AS	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			)		
Total failure: day 42 (unadjusted)	Relative risk 0.84 (CI 95% 0.54 — 1.31) Based on data from 1,059 participants in 1 studies. [7] (Randomized controlled)	**83** per 1000 Difference:	**70** per 1000 **13 fewer per 1000** (CI 95% 38 fewer — 26 more)	**Low** Due to serious indirectness, Due to serious imprecision, Certainty of the evidence grade differs from the 2014 review version due to alterations in the data extraction protocol: the CI has become less precise, and our decision has greater consistency with other outcome certainty grades. [8]	There is probably little or no difference in unadjusted failures at day 42 between ASPY and MQ+AS.
Serious adverse events (42 days)	Relative risk 1 (CI 95% 0.25 — 3.97) Based on data from 1,271 participants in 1 studies. [9] (Randomized controlled)	**7** per 1000 Difference:	**7** per 1000 **0 fewer per 1000** (CI 95% 5 fewer — 21 more)	**Low** Due to serious indirectness, Due to serious imprecision [10]	There may be little or no difference in serious adverse events between ASPY and MQ+AS
Adverse events leading to withdrawal	Relative risk 0.62 (CI 95% 0.17 — 2.31) Based on data from 1,271 participants in 1 studies. [11]	**9** per 1000 Difference:	**6** per 1000 **3 fewer per 1000** (CI 95% 7 fewer — 12 more)		
First treatment, abnormal ALT increase (42 days)	Relative risk 7.48 (CI 95% 0.99 — 56.45) Based on data from 1,271 participants in 1 studies. [12] (Randomized controlled)	**2** per 1000 Difference:	**18** per 1000 **13 more per 1000** (CI 95% 0 fewer — 111 more)	**Low** Due to serious indirectness, Due to serious imprecision [13]	Compared to MQ+AS, ASPY may lead to higher events of abnormal ALT increase. (Aggregate analysis indicates this estimate may be accurate).
First treatment, abnormal AST increase (42 days)	Relative risk 9.49 (CI 95% 0.55 — 162.64) Based on data from 1,271 participants in 1 studies. [14] (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Very low** Due to very serious imprecision, Due to serious indirectness [15]	We do not know if there is a difference in AST between ASPY and MQ+AS.

Outcome Timeframe	**Study results and measurements**	**Comparator** MQ+AS	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
First treatment, abnormal bilirubin increase (42 days)	Relative risk 3.49 (CI 95% 0.43 — 28.29) Based on data from 1,271 participants in 1 studies. [16] (Randomized controlled)	2 per 1000 Difference:	7 per 1000 **5 more per 1000** (CI 95% 1 fewer — 55 more)	**Very low** Due to serious indirectness, Due to very serious imprecision [17]	We do not know if there is a difference in bilirubin between ASPY and MQ+AS.

1. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects.
3. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects..
5. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: no serious.**
7. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects..
9. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The CI is large and includes both no effect and clinically important effects..
11. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
12. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
13. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: serious.** The low number of events recorded in the study is insufficient for confidently estimating the effect size. However, aggregate analysis of ALT increase across different

comparator drugs provides indirect evidence that the point estimate may be accurate..
14. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
15. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: very serious.** The CI is very large and includes both no effect and clinically important effects..
16. Systematic review [184] with included studies: Rueangweerayut 2012. **Baseline/comparator:** Control arm of reference used for intervention.
17. **Inconsistency: no serious. Indirectness: serious.** Of the 1271 children and adults aged greater than 5 years enrolled in this trial, 81.3% (1033) were enrolled and treated in trial sites in Asia (Cambodia, India, Thailand, and Vietnam), and only 18.7% (237) in Africa (Burkina Faso, Ivory Coast, and Tanzania). Further studies in African children are necessary to fully apply this result.. **Imprecision: very serious.** The CI is very large and includes both no effect and clinically important effects..

Attached Images

References

184. Pryce J, Taylor M, Fox T, Hine P : Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6): Pubmed Journal

Clinical Question/ PICO

Population: Adults and children with uncomplicated malaria (high and low transmission settings for P. falciparum and P. vivax malaria)

Intervention: Artesunate-pyronaridine

Comparator: other antimalarials for all malaria subtypes (safety outcomes only)

Outcome Timeframe	**Study results and measurements**	**Comparator** other antimalarials	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Serious adverse events	Relative risk 1.24 (CI 95% 0.54 — 2.84) Based on data from 3,941 participants in 7 studies. [1] (Randomized controlled)	5 per 1000 Difference:	7 per 1000 **1 more per 1000** (CI 95% 2 fewer — 9 more)	**Moderate** Due to serious imprecision [2]	There is probably little or no difference in the rate of serious adverse events with ASPY compared to other antimalarials.
First treatment, abnormal ALT increase	Relative risk 3.59 (CI 95% 1.76 — 7.33) Based on data from 6,669 participants in 8 studies. [3] (Randomized controlled)	2 per 1000 Difference:	7 per 1000 **5 more per 1000** (CI 95% 2 more — 13 more)	**High** [4]	Abnormal ALT increase is more frequent with ASPY compared to other antimalarials.

Outcome Timeframe	**Study results and measurements**	**Comparator** other antimalarials	**Intervention** ASPY	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
First treatment, abnormal AST increase	Relative risk 2.22 (CI 95% 1.12 — 4.41) Based on data from 6,669 participants in 14 studies. [5] (Randomized controlled)	3 per 1000 Difference:	7 per 1000 **4 more per 1000** (CI 95% 0 fewer — 10 more)	**Moderate** Due to serious imprecision [6]	There is probably an increased risk of abnormal AST increase with ASPY compared to other antimalarials.
First treatment, abnormal bilirubin increase	Relative risk 1.03 (CI 95% 0.49 — 2.18) Based on data from 6,417 participants in 7 studies. [7] (Randomized controlled)	4 per 1000 Difference:	4 per 1000 **0 fewer per 1000** (CI 95% 2 fewer — 5 more)	**Moderate** Due to serious imprecision [8]	There is probably little or no difference for bilirubin between ASPY and other antimalarials.
Subsequent treatment(s), abnormal ALT increase	Relative risk 2.18 (CI 95% 0.76 — 6.27) Based on data from 1,649 participants in 1 studies. [9] (Randomized controlled)	4 per 1000 Difference:	8 per 1000 **5 more per 1000** (CI 95% 1 fewer — 21 more)	**Low** Due to serious indirectness, Due to serious imprecision [10]	There may be an increased risk of raised ALT with subsequent treatments with ASPY compared to other antimalarials.
Subsequent treatment(s), abnormal AST increase	Relative risk 1.82 (CI 95% 0.74 — 4.44) Based on data from 1,649 participants in 1 studies. [11] (Randomized controlled)	6 per 1000 Difference:	11 per 1000 **5 more per 1000** (CI 95% 2 fewer — 21 more)	**Low** Due to serious indirectness, Due to serious imprecision [12]	There may be an increased risk of raised AST with subsequent treatments with ASPY compared to other antimalarials.
Subsequent treatment(s), abnormal bilirubin increase	Relative risk 1.13 (CI 95% 0.42 — 3.01) Based on data from 1,649 participants in 1 studies. [13] (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000** (CI 95% 5 fewer — 16 more)	**Low** Due to serious indirectness, Due to serious imprecision [14]	There may be little or no difference for bilirubin between ASPY and other antimalarials.

1. Systematic review [184] with included studies: Roth 2018a, Kayentao 2012, Nelwan 2015, Tshefu 2010, Rueangweerayut 2012, Shin 2011, Poravuth 2011. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The CI includes both no effect and clinically important effects..
3. Systematic review [184] with included studies: Sagara 2018 (Sotuba, Mali), Sagara 2018 (Mafrinyah, Guinea), Rueangweerayut 2012, Sagara 2018 (Kolle, Mali), Tshefu 2010, Shin 2011, Nelwan 2015, Kayentao 2012, Sagara 2018 (Bougoula, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Poravuth 2011, Sagara 2018 (Djoliba, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali), Roth 2018a. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Although the CI is wide, there were few events..
5. Systematic review [184] with included studies: Nelwan 2015, Poravuth 2011, Sagara 2018 (Mafrinyah, Guinea),

Sagara 2018 (Kolle, Mali), Roth 2018a, Shin 2011, Kayentao 2012, Sagara 2018 (Bougoula, Mali), Tshefu 2010, Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Djoliba, Mali), Rueangweerayut 2012, Sagara 2018 (Bougoula, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The CI includes both almost no effect and clinically important effects.
7. Systematic review [184] with included studies: Tshefu 2010, Sagara 2018 (Kolle, Mali), Shin 2011, Rueangweerayut 2012, Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Sotuba, Mali), Poravuth 2011, Nelwan 2015, Sagara 2018 (Bougoula, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Ouagadougou, Burkina Faso), Kayentao 2012, Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
8. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The CI includes both no effect and clinically important effects..
9. Systematic review [184] with included studies: Sagara 2018 (Sotuba, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bougoula, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** The CI includes both no effect and clinically important effects.. **Imprecision: serious.**
11. Systematic review [184] with included studies: Sagara 2018 (Sotuba, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Bobo-Doiulasso, Burkina Faso), Sagara 2018 (Kolle, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Djoliba, Mali). **Baseline/comparator:** Control arm of reference used for intervention.
12. **Inconsistency: no serious. Indirectness: serious. Imprecision: serious.**
13. Systematic review [184] with included studies: Sagara 2018 (Bougoula, Mali), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Mafrinyah, Guinea), Sagara 2018 (Djoliba, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Bougoula, Mali), Sagara 2018 (Kolle, Mali), Sagara 2018 (Ouagadougou, Burkina Faso), Sagara 2018 (Sotuba, Mali), Sagara 2018 (Bobo-Doiulasso, Burkina Faso). **Baseline/comparator:** Control arm of reference used for intervention.
14. **Inconsistency: no serious. Indirectness: serious. Imprecision: serious.**

Attached Images

References

184. Pryce J, Taylor M, Fox T, Hine P : Pyronaridine-artesunate for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database Syst Rev 2022;6(6): Pubmed Journal

5.2.1.1.1. Duration of treatment

Clinical Question/ PICO

Population:	Adults and children with uncomplicated malaria (malaria-endemic settings)
Intervention:	Artesunate 4 mg/kg bw once daily for 3 days plus sulfadoxine–pyrimethamine on day 1
Comparator:	Artesunate 4 mg/kg bw once daily for 1 day plus sulfadoxine–pyrimethamine on day 1

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate 1 day plus sulfadoxine-pyrimethamine	**Intervention** Artesunate 3 days plus sulfadoxine-pyrimethamine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Parasitological failure 14 days	Relative risk 0.36 (CI 95% 0.27 — 0.5) Based on data from 1,276 participants in 4 studies. (Randomized controlled)	**19** per 1000 Difference:	**7** per 1000 **12 fewer per 1000** (CI 95% 14 fewer — 9 fewer)	**High** 1	
Parasitological failure - PCR-unadjusted 28 days	Relative risk 0.62 (CI 95% 0.54 — 0.71) Based on data from 1,260 participants in 4 studies. (Randomized controlled)	**47** per 1000 Difference:	**29** per 1000 **18 fewer per 1000** (CI 95% 22 fewer — 14 fewer)	**High** 2	*Corresponding risk calculated is different than what is reported in WHO document*
Parasitological failure - PCR-adjusted 28 days	Relative risk 0.45 (CI 95% 0.36 — 0.55) Based on data from 1,202 participants in 4 studies. (Randomized controlled)	**33** per 1000 Difference:	**15** per 1000 **18 fewer per 1000** (CI 95% 21 fewer — 15 fewer)	**High** 3	*Corresponding risk calculated is different than what is reported in WHO document*
Gametocytaemia 7 days	Relative risk 0.74 (CI 95% 0.58 — 0.93) Based on data from 1,260 participants in 4 studies. (Randomized controlled)	**20** per 1000 Difference:	**15** per 1000 **5 fewer per 1000** (CI 95% 8 fewer — 1 fewer)	**High** 4	
Gametocytaemia 14 days	Relative risk 0.8 (CI 95% 0.57 — 1.14) Based on data from 1,199 participants in 4 studies. (Randomized controlled)	**11** per 1000 Difference:	**9** per 1000 **2 fewer per 1000** (CI 95% 5 fewer — 2 more)	**High** 5	*Corresponding risk calculated is different than what is reported in WHO document*
Gametocytaemia 28 days	Relative risk 0.36 (CI 95% 0.14 — 0.92) Based on data from 898 participants in 4 studies. (Randomized controlled)	**3** per 1000 Difference:	**1** per 1000 **2 fewer per 1000**	**Moderate** Due to serious imprecision [6]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate 1 day plus sulfadoxine-pyrimethamine	**Intervention** Artesunate 3 days plus sulfadoxine-pyrimethamine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			(CI 95% 3 fewer — 0 fewer)		

1. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Indirectness: no serious.** The four trials were conducted in children with uncomplicated P. falciparum malaria in the Gambia, Kenya, Malawi and Uganda. The same screening methods and inclusion criteria were used. Sulfadoxine–pyrimethamine was the partner antimalarial drug in all four trials. Resistance to sulfadoxine–pyrimethamine was noted at three study sites, parasitological failure with sulfadoxine–pyrimethamine alone being seen in 10–13% of participants in the Gambia, 27% in Kenya and 25% in Uganda. **Imprecision: no serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. No serious imprecision: The confidence intervals are narrow and do not include no effect.
2. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Indirectness: no serious.** The four trials were conducted in children with uncomplicated P. falciparum malaria in the Gambia, Kenya, Malawi and Uganda. The same screening methods and inclusion criteria were used. Sulfadoxine–pyrimethamine was the partner antimalarial drug in all four trials. Resistance to sulfadoxine–pyrimethamine was noted at three study sites, parasitological failure with sulfadoxine–pyrimethamine alone being seen in 10–13% of participants in the Gambia, 27% in Kenya and 25% in Uganda. **Imprecision: no serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. No serious imprecision: The confidence intervals are narrow and do not include no effect.
3. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Indirectness: no serious.** The four trials were conducted in children with uncomplicated P. falciparum malaria in the Gambia, Kenya, Malawi and Uganda. The same screening methods and inclusion criteria were used. Sulfadoxine–pyrimethamine was the partner antimalarial drug in all four trials. Resistance to sulfadoxine–pyrimethamine was noted at three study sites, parasitological failure with sulfadoxine–pyrimethamine alone being seen in 10–13% of participants in the Gambia, 27% in Kenya and 25% in Uganda. **Imprecision: no serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. No serious imprecision: The confidence intervals are narrow and do not include no effect.
4. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Indirectness: no serious.** The four trials were conducted in children with uncomplicated P. falciparum malaria in the Gambia, Kenya, Malawi and Uganda. The same screening methods and inclusion criteria were used. Sulfadoxine–pyrimethamine was the partner antimalarial drug in all four trials. Resistance to sulfadoxine–pyrimethamine was noted at three study sites, parasitological failure with sulfadoxine–pyrimethamine alone being seen in 10–13% of participants in the Gambia, 27% in Kenya and 25% in Uganda. **Imprecision: no serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. No serious imprecision: The confidence intervals are narrow and do not include no effect.
5. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Imprecision: no serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. No serious imprecision: The confidence intervals are narrow and do not include no effect.
6. **Inconsistency: no serious.** All four studies found reductions with 3 days of artesunate, although there was some variation in the size of this effect. **Imprecision: serious.** The confidence intervals are narrow, and the intervals comprise clinically important effects. Downgraded by 1 for serious imprecision: As gametocytaemia at this time was rare in both groups, the studies have inadequate power to confidently detect important differences.

Attached Images

5.2.1.1.2. Dosing of ACTs

5.2.1.2. Recurrent falciparum malaria

5.2.1.3. Reducing the transmissibility of treated P. falciparum infections in areas of low-intensity transmission

Clinical Question/ PICO

Population: People with symptomatic malaria in malaria-endemic areas
Intervention: Short-course primaquine plus malaria treatment including an artemisinin derivative
Comparator: Malaria treatment with an artemisinin derivative alone

Outcome Timeframe	**Study results and measurements**	**Comparator** ACT	**Intervention** ACT + primaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Malaria incidence, prevalence or entomological inoculation rate	Relative risk Based on data from 0 participants in 0 studies.		CI 95%		
People infectious to mosquitoes	Relative risk Based on data from 0 participants in 0 studies.		CI 95%		Limited observational data from mosquito feeding studies suggests that 0.25 mg/kg bw may rapidly reduce the infectivity of gametocytes to mosquitoes.
Participants with gametocytes on microscopy or PCR (day 8) (dose < 0.4 mg/kg bw) [1]	Relative risk 0.67 (CI 95% 0.44 — 1.02) Based on data from 223 participants in 1 studies. (Randomized controlled)	34 per 1000 Difference:	23 per 1000 **11 fewer per 1000** (CI 95% 19 fewer — 1 more)	**Low** Due to very serious imprecision [2]	
Participants with gametocytes on microscopy or PCR (day 8) (dose 0.4–0.6	Relative risk 0.3 (CI 95% 0.16 — 0.56) Based on data from 219 participants in 1 studies. (Randomized controlled)	35 per 1000 Difference:	11 per 1000 **24 fewer per 1000** (CI 95% 29	**Low** Due to serious imprecision and serious indirectness [4]	

Outcome Timeframe	Study results and measurements	Comparator ACT	Intervention ACT + primaquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
mg/kg bw) [3]			fewer — 15 fewer)		
Participants with gametocytes on microscopy or PCR (day 8) (dose > 0.6 mg/kg bw) [5]	Relative risk 0.29 (CI 95% 0.22 — 0.37) Based on data from 1,380 participants in 7 studies. (Randomized controlled)	30 per 1000 Difference:	9 per 1000 **21 fewer per 1000** (CI 95% 23 fewer — 19 fewer)	High [6]	
Mean percentage change in haemoglobin (Hb) [7]	Based on data from 101 participants in 1 studies. (Randomized controlled)			Low Due to very serious indirectness [8]	ACT: 15% mean drop in Hb from baseline in the control group. ACT + primaquine: Mean drop in Hb from baseline in the intervention groups was 3% lower (10% lower to 4% higher).

1. AUC estimates (log10 AUC for days 1–43) are included as footnotes for each dosing stratum.
2. **Risk of Bias: no serious.** Includes one trial with no risk of bias detected. **Imprecision: very serious.** One small trial with CIs that include 50% reduction and no effect.
3. AUC estimates (log10 AUC for days 1–43) are included as footnotes for each dosing stratum.
4. **Risk of Bias: no serious.** Includes one trial with no risk of bias detected. **Indirectness: serious.** This is a single trial in a single setting. **Imprecision: serious.** A single trial with few events.
5. AUC estimates (log10 AUC for days 1–43) are included as footnotes for each dosing stratum.
6. **Indirectness: no serious.** While there is marked quantitative heterogeneity, the studies with no demonstrable effect had few events. Not downgraded.
7. One trial reported a relative decrease in haemoglobin against baseline in both groups on days 8, 15, 29 and 43 in all participants irrespective of G6PD status. No difference at any time between participants receiving primaquine and those that not did not. We present the data for day 43 in this table.
8. **Indirectness: very serious.** The percentage of people with large drops in haemoglobin, not the mean change in the population, is the important safety outcome, and the estimates are averages in a small population (N = 99) that includes people with normal G6PD function. The study is therefore unlikely to detect effects in a small subgroup with a relatively uncommon adverse event.

Attached Images

5.2.1.4. Special risk groups

5.2.1.4.1. Pregnant and lactating women

Clinical Question/ PICO

Population: Treating malaria in pregnancy during their first trimester in prospective cohort studies
Intervention: artemisinin derivatives
Comparator: antimalarial not including artemisinin derivative and recommended in the first trimester

Outcome Timeframe	**Study results and measurements**	**Comparator** antimalarial not including artemisinin derivative and recommende	**Intervention** artemisinin derivatives	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Composite	Relative risk 0.71 (CI 95% 0.49 — 1.03) Based on data from 1,810 participants in 12 studies. (Observational (non-randomized))	89 per 1000 Difference:	64 per 1000 **25 fewer per 1000** (CI 95% 45 fewer — 3 more)	Low	ABT may reduce adverse fetal events
Miscarriage	Relative risk 0.74 (CI 95% 0.47 — 1.17) Based on data from 1,739 participants in 12 studies.	71 per 1000 Difference:	53 per 1000 **18 fewer per 1000** (CI 95% 37 fewer — 12 more)	Low	ABT may reduce miscarriage
Stillbirth	Relative risk 0.71 (CI 95% 0.32 — 1.57) Based on data from 1,389 participants in 12 studies.	16 per 1000 Difference:	11 per 1000 **5 fewer per 1000** (CI 95% 11 fewer — 9 more)	Low	ABT may reduce stillbirth
Fetal loss	Relative risk 0.7 (CI 95% 0.47 — 1.02) Based on data from 1,810 participants in 12 studies.	82 per 1000 Difference:	58 per 1000 **24 fewer per 1000** (CI 95% 43 fewer — 2 more)	Low	ABT may reduce fetal loss
Major congenital anomalies	Relative risk 0.6 (CI 95% 0.13 — 2.87) Based on data from 1,810 participants in 12 studies.	7 per 1000 Difference:	4 per 1000 **3 fewer per 1000** (CI 95% 6 fewer — 14	Low	ABT may reduce congenital abnormalities

Outcome Timeframe	**Study results and measurements**	**Comparator** antimalarial not including artemisinin derivative and recommende	**Intervention** artemisinin derivatives	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			more)		

Attached Images

Clinical Question/ PICO

Population: Treating malaria in pregnancy during their first trimester in prospective cohort studies
Intervention: Artemether-lumefantrine
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether-lumefantrine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Composite	Relative risk 0.58 (CI 95% 0.36 — 0.92) Based on data from 1,439 participants in 12 studies.	92 per 1000 Difference:	54 per 1000 **37 fewer per 1000** (CI 95% 58 fewer — 7 fewer)	Low	AL may reduce adverse fetal events
Miscarriage	Relative risk 0.67 (CI 95% 0.37 — 1.23) Based on data from 1,377 participants in 12 studies.	74 per 1000 Difference:	51 per 1000 **24 fewer per 1000** (CI 95% 46 fewer — 16 more)	Low	AL may reduce miscarriage
Stillbirth	Relative risk 0.53 (CI 95% 0.22 — 1.24) Based on data from 1,078 participants in 12 studies.	20 per 1000 Difference:	11 per 1000 **10 fewer per 1000** (CI 95% 16 fewer — 5 more)	Low	AL may reduce stillbirth
Fetal loss	Relative risk 0.56 (CI 95% 0.35 — 0.9)	87	50	Low It is not	AL may reduce fetal loss

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether-lumefantrine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		per 1000 Difference:	per 1000 **37 fewer per 1000** (CI 95% 56 fewer — 8 fewer)	appropriate to upgrade here. Whilst very large effects may “upgrade” by one point, this is only when the CI do not overlap with smaller effects, which is not the case here. Indeed, GRADE state that a large effect is only considered with the RR is <0.5, and this is based on direct evidence with no plausible confounders.	
	Based on data from 1,439 participants in 12 studies.				
Major congenital anomalies	Based on data from 1,439 participants in 12 studies.	4 per 1000		**Low**	AL may reduce congenital abnormalities

Attached Images

5.2.1.4.2. Young children and infants

5.2.1.4.3. Patients co-infected with HIV

5.2.1.4.4. Non-immune travellers

5.2.1.4.5. Uncomplicated hyperparasitaemia

5.2.1.5. Uncomplicated malaria caused by P. vivax, P. ovale, P. malariae or P. knowlesi

Clinical Question/ PICO

Population: Adults and children with uncomplicated P. vivax malaria (Malaria-endemic areas in which chloroquine is still effective for the first 28 days)

Intervention: Artemisinin-based combination therapy

Comparator: Chloroquine

Outcome Timeframe	**Study results and measurements**	**Comparator** Chloroquine	**Intervention** ACT	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Remaining parasitaemia at 24 h	Relative risk 0.42 (CI 95% 0.36 — 0.5) Based on data from 1,652 participants in 4 studies. (Randomized controlled)	520 per 1000 Difference:	218 per 1000 **302 fewer per 1000** (CI 95% 333 fewer — 260 fewer)	High [1]	
Still febrile after 24 h	Relative risk 0.55 (CI 95% 0.43 — 0.7) Based on data from 990 participants in 2 studies. (Randomized controlled)	290 per 1000 Difference:	160 per 1000 **130 fewer per 1000** (CI 95% 165 fewer — 87 fewer)	Moderate Due to serious inconsistency [2]	
Effective treatment of blood-stage infection as assessed by recurrent parasitaemia before day 28	Relative risk 0.58 (CI 95% 0.18 — 1.9) Based on data from 1,622 participants in 5 studies. (Randomized controlled)	30 per 1000 Difference:	17 per 1000 **13 fewer per 1000** (CI 95% 25 fewer — 27 more)	High [3]	
Post-treatment prophylaxis as assessed by recurrent parasitaemia between day 28 and day 42, 56 or 63 - with primaquine	Relative risk 0.27 (CI 95% 0.08 — 0.94) Based on data from 376 participants in 1 studies. (Randomized controlled)	60 per 1000 Difference:	16 per 1000 **44 fewer per 1000** (CI 95% 55 fewer — 4 fewer)	Low Due to serious indirectness and serious imprecision [4]	
Post-treatment prophylaxis as assessed by	Relative risk 0.57 (CI 95% 0.4 — 0.82) Based on data from	400 per 1000	228 per 1000	Moderate Due to serious indirectness [5]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Chloroquine	**Intervention** ACT	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
recurrent parasitaemia between day 28 and day 42, 56 or 63 - without primaquine	1,066 participants in 3 studies. (Randomized controlled)	Difference:	**172 fewer per 1000** (CI 95% 240 fewer — 72 fewer)		
Serious adverse events	Relative risk 1 (CI 95% 0.14 — 7.04) Based on data from 1,775 participants in 5 studies. (Randomized controlled)	**0** per 1000 Difference:	**0** per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**High** [6]	

1. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT. **Publication bias: no serious.**
2. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: serious.** In one additional trial which could not be included in the meta-analysis, fever clearance was not significantly different between groups. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT.
3. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** No clinically important difference between ACTs and chloroquine. Although the 95% CI around the relative effect is very wide, recurrent parasitaemia before day 28 and serious adverse events were very rare; consequently, the 95% CI around the absolute effect is very narrow.
4. **Indirectness: serious.** This study delayed primaquine until day 28; therefore, the course was not completed until day 42, the last day of the trial. The effect might not be present if primaquine is given in the usual way (on completion of 3 days of ACT). The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes. **Imprecision: serious.** Although the result is statistically significant, the 95% CI is wide and includes the possibility of no appreciable benefit.
5. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: serious.** Both studies were conducted in Afghanistan where primaquine is not recommended because of a high prevalence of G6PD deficiency. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT.
6. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** No clinically important difference between ACTs and chloroquine. Although the 95% CI around the relative effect is very wide, recurrent parasitaemia before day 28 and serious adverse events were very rare; consequently, the 95% CI around the absolute effect is

very narrow.

Attached Images

Clinical Question/ PICO

Population: Adults and children with uncomplicated P. vivax malaria (Settings with high transmission of P. vivax (chloroquine resistance is also reported as high))

Intervention: Dihydroartemisinin + piperaquine

Comparator: Alternative ACTs

Outcome Timeframe	**Study results and measurements**	**Comparator** Alternative ACT	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Effective treatment of blood-stage parasites as assessed by recurrent parasitaemia before day 28	Relative risk 0.2 (CI 95% 0.08 — 0.49) Based on data from 334 participants in 3 studies. (Randomized controlled)	350 per 1000 Difference:	70 per 1000 **280 fewer per 1000** (CI 95% 322 fewer — 178 fewer)	Moderate Due to serious inconsistency [1]	
Post-treatment prophylaxis as assessed by recurrent parasitaemia between days 28 and 42 - with primaquine	Relative risk 0.21 (CI 95% 0.1 — 0.46) Based on data from 179 participants in 2 studies. (Randomized controlled)	340 per 1000 Difference:	71 per 1000 **269 fewer per 1000** (CI 95% 306 fewer — 184 fewer)	Low Due to serious risk of bias and serious indirectness [2]	
Post-treatment prophylaxis as assessed by recurrent parasitaemia between days 28 and 42 - without primaquine	Relative risk 0.4 (CI 95% 0.14 — 1.1) Based on data from 66 participants in 1 studies. (Randomized controlled)	330 per 1000 Difference:	132 per 1000 **198 fewer per 1000** (CI 95% 284 fewer — 33 more)	Very low Due to serious risk of bias, serious indirectness and serious imprecision [3]	

1. **Risk of Bias: no serious.** Allocation was adequately concealed in these studies, resulting in a low risk of bias.

Inconsistency: serious. There was some clinical heterogeneity between trials. Dihydroartemisinin + piperaquine did not perform as well in Papua New Guinea as it has elsewhere; however, it was still superior to artemether + lumefantrine and artesunate+sulfadoxine–pyrimethamine. **Indirectness: no serious.** Studies included adults and children and were conducted in areas where transmission is high and chloroquine resistance is well documented. **Imprecision: no serious.** Both limits of the 95% CI suggest an appreciable clinical benefit with dihydroartemisinin + piperaquine.

2. **Risk of Bias: serious.** Losses to follow-up were high (> 20% at this time). **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** One trial delayed administration of primaquine until day 28; therefore, the course will not have been completed until the last day of the trial. The second trial offered unsupervised primaquine to all participants on completion of ACT. This reflects normal practice, but it is not clear how many participants completed their course. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes.

3. **Risk of Bias: serious.** Losses to follow-up were high (> 20% at this time). **Indirectness: serious.** Only one study assessed this outcome. Recurrent parasitaemia was higher with all three ACTs than seen elsewhere, and the results are therefore not easily extrapolated to other sites. **Imprecision: serious.** The 95% CI of the effect estimate is wide and includes an important clinical benefit and no difference between treatments.

Attached Images

Clinical Question/ PICO

Population:	People with P. vivax malaria
Intervention:	Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
Comparator:	Chloroquine alone (25 mg/kg bw for 3 days)

Outcome Timeframe	**Study results and measurements**	**Comparator** No primaquine	**Intervention** Primaquine 14 days	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. vivax relapse defined as reappearance of P. vivax parasitaemia > 30 days after starting primaquine	Relative risk 0.6 (CI 95% 0.48 — 0.75) Based on data from 1,740 participants in 10 studies. (Randomized controlled)	80 per 1000 Difference:	48 per 1000 **32 fewer per 1000** (CI 95% 42 fewer — 20 fewer)	High [1]	
Serious adverse events	Based on data from 1,740 participants in 10 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			
Other adverse events	Based on data from 1,740 participants in 10 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			

1. **Risk of Bias: no serious.** No serious study limitations: Three studies were at high risk of bias; however, they contributed only 15.5% weight to the pooled effect estimates, and their removal from the sensitivity analysis did not alter the results appreciably. **Inconsistency: no serious.** Results were consistent within subgroups based on duration of follow-up < 6 months or > 6 months and whether treatment was supervised or not; the I2 value for the pooled effect estimate from the 10 trials was 30%. **Indirectness: no serious.** The trials included children and were done in transmission settings and countries representative of the vivax malaria burden. The outcome used was the best estimate currently available in the absence of widely available validated molecular techniques to differentiate relapse from new infections. **Imprecision: no serious.** The upper and lower limits of the 95% CI of the pooled relative risk indicate appreciable benefit with chloroquine + primaquine for 14 days. The total number of events was < 300, but the total sample size was larger than the optimal information size, given the magnitude of risk reduction.

Attached Images

Clinical Question/ PICO

Population: People with P. vivax malaria
Intervention: Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
Comparator: Primaquine (0.25 mg/kg bw) for 7 days plus chloroquine alone (25 mg/kg bw for 3 days)

Outcome Timeframe	**Study results and measurements**	**Comparator** 7 days primaquine	**Intervention** 14 days primaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
P. vivax relapse defined as reappearance of P. vivax parasitaemia > 30 days after starting primaquine	Relative risk 0.45 (CI 95% 0.25 — 0.81) Based on data from 126 participants in 1 studies. (Randomized controlled)	420 per 1000 Difference:	189 per 1000 **231 fewer per 1000** (CI 95% 315 fewer — 80 fewer)	**Low** Due to serious indirectness and serious imprecision [1]	
Severe adverse events	Based on data from 126 participants in 1 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			
Other adverse events	Based on data from 126 participants in 1 studies. (Randomized controlled)	No adverse events reported in either group. Relative effect cannot be estimated.			

1. **Indirectness: serious.** The trial authors did not include children < 15 years. Another trial in the same area by the same group of investigators immediately afterwards included children. The results for 3 days of primaquine versus 14 days of primaquine did not differ in children from that in adults. Duration of follow-up was 2 months. While this ensures detection of early relapse, it does not cover relapses after 2 months. The relapse rates at 6 months showed that most relapses occur by 2 months. The effects of 7 days of primaquine were assessed in only one trial. We therefore downgraded the evidence by 1. **Imprecision: serious.** Although the upper and lower limits of the 95% CI of the risk ratio in this trial showed statistically significant, clinically appreciable benefit with 14 days of primaquine over 7 days of primaquine, the total number of events was 38 and the sample size of the trial was 104. This is lower than the optimal information size. We downgraded the evidence by 1.

Attached Images

Clinical Question/ PICO

Population: Adults and children with confirmed clinical and parasitological P. vivax malaria (in India, Peru and Brazil)

Intervention: 0.5 mg/kg/day primaquine for 7 days (adult dose 30 mg/day, total dose 210 mg)

Comparator: Standard 14-day course of primaquine (0.25 mg/kg/day, adult dose 15mg/day; total dose 210mg) 14 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Standard 14-day course of primaquine	**Intervention** 0.5 mg/kg/ day primaquine for 7 days	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Recurrence of P. vivax parasitaemia 6 to 7 months of follow-up	Relative risk 0.96 (CI 95% 0.66 — 1.39) Based on data from 1,211 participants in 4 studies. [1] (Randomized controlled)	84 per 1000 Difference:	81 per 1000 **3 fewer per 1000** (CI 95% 29 fewer — 33 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	There may be little or no difference between 0.5 mg/kg/day primaquine for 7 days and the standard 14-day course.
Serious adverse events	Based on data from 1,427 participants in 5 studies. [3]				Not estimable. No events reported.
Adverse events that result in discontinuation of treatment	Relative risk 1.04 (CI 95% 0.15 — 7.38) Based on data from 1,427 participants in 5 studies. [4] (Randomized controlled)	3 per 1000 Difference:	3 per 1000 **0 fewer per 1000** (CI 95% 3 fewer — 19 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [5]	We do not know if there is any difference in adverse events that result in treatment discontinuation between 0.5 mg/kg/ day primaquine for 7 days and the standard 14-day course.
Anaemia or change in haemoglobin status	Relative risk 3 (CI 95% 0.12 — 72.91) Based on data from 240 participants in 1 studies. [6] (Randomized controlled)			**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [7]	We do not know if the occurrence of anaemia differs between the 2 treatment regimens.

1. Systematic review [229] with included studies: Pareek 2015 IND, Abdon 2001 BRA, Durand 2014 PER, Rajgor 2014 IND. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** One study, which contributed the most weight to the meta-analysis, was at high risk of selection bias due to no allocation concealment and high risk of attrition bias. Although another study was at risk of selection bias as well as other bias for being funded and carried out by drug company, it only contributed a small amount of weight to the meta-analysis.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide CIs - may be 34% reduction in malaria recurrences or 40% increase with 0.5 mg/kg/day primaquine for seven days..
3. Systematic review [229] with included studies: Durand 2014 PER, Abdon 2001 BRA, Solari-Soto 2002 PER, Rajgor 2014 IND, Pareek 2015 IND. **Baseline/comparator:** Control arm of reference used for intervention.
4. Systematic review [229] with included studies: Rajgor 2014 IND, Solari-Soto 2002 PER, Durand 2014 PER, Pareek 2015 IND, Abdon 2001 BRA. **Baseline/comparator:** Control arm of reference used for intervention.
5. **Risk of Bias: serious.** One study was at high risk of selection bias due to no allocation concealment and high risk of attrition bias. Another study was at risk of selection bias as well as other bias for being funded and carried out by drug company.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Very few events (only four events occurring in one trial), very wide CIs..
6. Systematic review [229] with included studies: Pareek 2015 IND. **Baseline/comparator:** Control arm of reference used for intervention.

7. **Risk of Bias: serious.** One study was at risk of selection bias and other bias (funded and performed by drug company).. **Inconsistency: no serious. Indirectness: serious.** Only one study that excluded G6PD-deficient adults measured this safety outcome.. **Imprecision: very serious.** Only one event (in the 0.5 mg/kg/day primaquine for seven days group), very wide CIs..

Attached Images

References

229. Milligan R, Daher A, Villanueva G, Bergman H, Graves P : Primaquine alternative dosing schedules for preventing malaria relapse in people with Plasmodium vivax. Cochrane Database Syst Rev 2020; Pubmed Journal

Clinical Question/ PICO

Population: Adults and children with confirmed clinical and parasitological P. vivax malaria (in Afghanistan, Ethiopia, Indonesia, Thailand and Viet Nam)

Intervention: 1.0 mg/kg/day primaquine for 7 days (adult dose 60 mg/day; total dose 420 mg)

Comparator: High-standard 14-day course primaquine (0.5 mg/kg/day, adult dose 30 mg/day; total dose 420 mg) 14 days

Outcome Timeframe	**Study results and measurements**	**Comparator** high-standard 0.5 mg/kg/ day for 14 days	**Intervention** 1.0 mg/kg/ day primaquine for 7 days	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Recurrence of P. vivax parasitaemia with 12 months of follow-up	Relative risk 1.03 (CI 95% 0.82 — 1.3) Based on data from 2,526 participants in 2 studies. [1] (Randomized controlled)	**104** per 1000 Difference:	**107** per 1000 **3 more per 1000** (CI 95% 19 fewer — 31 more)	**Moderate** Due to serious risk of bias [2]	There is probably little or no difference between 1.0 mg/kg/ day primaquine for 7 days and the high-standard 0.5 mg/kg/ day for 14 days course.
Serious adverse events - Up to 42 days follow-up	Relative risk 12.03 (CI 95% 1.57 — 92.3) Based on data from 1,872 participants in 1 studies. [3] (Randomized controlled)	**1** per 1000 Difference:	**13** per 1000 **11 more per 1000** (CI 95% 1 more — 91 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	There may be a moderate to large increase in serious adverse events in the 1.0 mg/kg/day primaquine for 7 days compared with the high-standard 0.5 mg/ kg/day.
Adverse events that resulted in discontinuation of treatment	Relative risk 2.5 (CI 95% 0.49 — 12.87) Based on data from 2,526 participants in 2 studies. [5] (Randomized controlled)	**2** per 1000 Difference:	**5** per 1000 **3 more per 1000** (CI 95% 1 fewer — 24 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [6]	We do not know if there is any difference in adverse events resulting in treatment discontinuation between 1.0 mg/kg/ day primaquine for 7 days and the high-

Outcome Timeframe	**Study results and measurements**	**Comparator** high-standard 0.5 mg/kg/ day for 14 days	**Intervention** 1.0 mg/kg/ day primaquine for 7 days	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					standard 0.5 mg/kg/ day for 14 days course.
Anaemia follow-up between 3 and 42 days	Relative risk 0.93 (CI 95% 0.62 — 1.41) Based on data from 2,440 participants in 2 studies. [7]	35 per 1000 Difference:	33 per 1000 **2 fewer per 1000** (CI 95% 13 fewer — 14 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [8]	We do not know if there is any difference in anaemia between 1.0 mg/kg/day primaquine for 7 days and the high-standard 0.5 mg/kg/day for 14 days course.

1. Systematic review [229] with included studies: Taylor 2019 MULTI, Chu 2019 THA, Taylor 2019 MULTI, Chu 2019 THA. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** One study was an open-label trial with high risk of performance and detection bias; although drop-outs were balanced between groups the proportion of drop-outs after one year was high in both trials (30-40%).. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.**
3. Systematic review [229] with included studies: Taylor 2019 MULTI. **Baseline/comparator:** Control arm of reference used for intervention.
4. **Inconsistency: no serious. Indirectness: serious.** G6PD-deficient children and adults were excluded from the two trials that measured this outcome.. **Imprecision: serious.** Few events..
5. Systematic review [229] with included studies: Taylor 2019 MULTI, Chu 2019 THA. **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** One study was an open-label trial with high risk of performance and detection bias; although drop-outs were balanced between groups the proportion of drop-outs after one year was high in both trials (30-40%).. **Inconsistency: no serious. Indirectness: serious.** G6PD-deficient children and adults were excluded from the two trials that measured this outcome . **Imprecision: serious.** Few events..
7. Systematic review [229] with included studies: Taylor 2019 MULTI, Chu 2019 THA. **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** One study was an open-label trial with high risk of performance and detection bias; although drop-outs were balanced between groups the proportion of drop-outs after one year was high in both trials (30-40%).. **Inconsistency: no serious. Indirectness: serious.** G6PD-deficient children and adults were excluded from the two trials that measured this outcome. **Imprecision: serious.**

Attached Images

References

229. Milligan R, Daher A, Villanueva G, Bergman H, Graves P : Primaquine alternative dosing schedules for preventing malaria relapse in people with Plasmodium vivax. Cochrane Database Syst Rev 2020; Pubmed Journal

Clinical Question/ PICO

Population: Malaria-endemic areas
Intervention: Chloroquine prophylaxis
Comparator: Placebo

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Chloroquine prophylaxis	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Clinical malaria	Relative risk		CI 95%		
P. vivax parasitaemia	Relative risk 0.02 (CI 95% 0 — 0.26) Based on data from 951 participants in 1 studies. (Randomized controlled)	70 per 1000 Difference:	1 per 1000 **69 fewer per 1000** (CI 95% 70 fewer — 52 fewer)	Moderate Due to serious imprecision [1]	
Severe anaemia in third trimester	Relative risk		CI 95%		
Anaemia in third trimester	Relative risk 0.95 (CI 95% 0.9 — 1.01) Based on data from 951 participants in 1 studies. (Randomized controlled)	509 per 1000 Difference:	484 per 1000 **25 fewer per 1000** (CI 95% 51 fewer — 5 more)	Moderate Due to serious imprecision [2]	
Adverse events	Relative risk		CI 95%		

1. **Risk of Bias: no serious.** This study had a low risk of bias in all domains. **Indirectness: no serious.** This study was conducted in Thailand between 1998 and 2001. Chloroquine was administered as four tablets at enrolment, followed by two tablets once a week until delivery. **Imprecision: serious.** Although the intervention appeared to prevent all episodes of P. vivax malaria, there were few events, even in the control group.
2. **Risk of Bias: no serious.** This study had a low risk of bias in all domains. **Indirectness: no serious.** This study was conducted in Thailand between 1998 and 2001. Chloroquine was administered as four tablets at enrolment, followed by two tablets once a week until delivery. **Imprecision: serious.** The finding of a small clinical benefit did not reach statistical significance.

Attached Images

5.2.2. Treating severe malaria

5.2.2.1. Artesunate

Clinical Question/ PICO

Population: Children with severe malaria (malaria-endemic areas)
Intervention: Artesunate
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.76 (CI 95% 0.65 — 0.9) Based on data from 5,765 participants in 4 studies. (Randomized controlled)	109 per 1000 Difference:	83 per 1000 **26 fewer per 1000** (CI 95% 38 fewer — 11 fewer)	High [1]	
Neurological sequelae on day 28	Relative risk 1.23 (CI 95% 0.74 — 2.03) Based on data from 4,857 participants in 1 studies. (Randomized controlled)	11 per 1000 Difference:	14 per 1000 **3 more per 1000** (CI 95% 3 fewer — 11 more)	Moderate Due to serious risk of bias [2]	
Neurological sequelae at discharge	Relative risk 1.36 (CI 95% 1.01 — 1.83) Based on data from 5,163 participants in 3 studies. (Randomized controlled)	28 per 1000 Difference:	38 per 1000 **10 more per 1000** (CI 95% 0 fewer — 23 more)	Moderate Due to serious imprecision [3]	
Hypoglycaemia episodes	Relative risk 0.62 (CI 95% 0.45 — 0.87) Based on data from 5,765 participants in 4 studies. (Randomized controlled)	30 per 1000 Difference:	19 per 1000 **11 fewer per 1000** (CI 95% 16 fewer — 4 fewer)	High [4]	
Time to hospital discharge (days)	Based on data from 113 participants in 3 studies. (Randomized controlled)	See comment.		Moderate Due to serious imprecision [5]	

1. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: no serious.** Both limits of the 95% CI of the pooled effect imply an appreciable clinical benefit with artesunate. The number of people who must be treated to prevent one childhood death is 38.
2. **Risk of Bias: serious.** 41/170 (24%) patients with neurological sequelae at discharge were not available for assessment at day 28. **Indirectness: no serious.** This trial was conducted in 11 centres in Africa, with standard dosing

of artesunate and quinine. The nature of the neurological sequelae is not described. **Imprecision: no serious.** The 95% CI around the absolute effect is narrow. The worst-case scenario is a 1.2% increase in neurological sequelae at day 28.
3. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: serious.** The effect estimate indicates clinically important harm; however, the 95% CI includes the possibility of no clinically important difference between the two interventions.
4. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: no serious.** The result is statistically significantly in favour of artesunate. The sample size is adequate to detect a 40% risk reduction with 80% power and 95% confidence.
5. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** None of the trials found evidence of a large difference between the two treatment groups. **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: serious.** We were unable to pool the data as they were reported only as medians and range or intraquartile range. There is no evidence of a clinically important benefit with artesunate on this outcome.

Attached Images

Clinical Question/ PICO

Population: Adults with severe malaria (malaria-endemic areas)
Intervention: Artesunate
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.61 (CI 95% 0.5 — 0.75) Based on data from 1,664 participants in 5 studies. (Randomized controlled)	241 per 1000 Difference:	147 per 1000 **94 fewer per 1000** (CI 95% 120 fewer — 60 fewer)	High [1]	
Neurological	Relative risk				

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
sequelae at day 28			CI 95%		
Neurological sequelae at discharge	Relative risk 2.97 (CI 95% 0.6 — 14.64) Based on data from 1,259 participants in 1 studies. (Randomized controlled)	3 per 1000 Difference:	9 per 1000 **6 more per 1000** (CI 95% 1 fewer — 41 more)	Moderate Due to serious imprecision [2]	
Hypoglycaemia episodes	Relative risk 0.62 (CI 95% 0.45 — 0.87) Based on data from 5,765 participants in 4 studies. (Randomized controlled)	30 per 1000 Difference:	19 per 1000 **11 fewer per 1000** (CI 95% 16 fewer — 4 fewer)	High [3]	
Time to hospital discharge (days)	Based on data from 113 participants in 2 studies. (Randomized controlled)	See comment.		Moderate Due to serious imprecision [4]	

1. **Risk of Bias: no serious.** Two of the smaller studies did not conceal allocation, and none of the studies was blinded; however, most data are from studies in which allocation was concealed, and the lack of blinding is unlikely to introduce bias for an objective outcome such as death. **Inconsistency: no serious.** The point estimates of all five trials favoured artesunate. No significant statistical heterogeneity was detected (I^2 = 0%). **Indirectness: no serious.** All five trials were conducted in Asia but in a variety of settings (Bangladesh, India, Indonesia, Myanmar, Thailand and Viet Nam), and included age groups > 15–16 years. Of the four small trials, two did not give the loading dose of quinine, but there was no statistical heterogeneity between these two trials and the large multicentre trial, in which the loading dose was given. **Imprecision: no serious.** Both limits of the 95% CI imply a clinically important benefit with artesunate.
2. **Risk of Bias: no serious.** This trial was unblinded, but the nature of the sequelae makes observer or reporting bias unlikely. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: no serious.** This trial was conducted in sites in four countries in Asia with the standard doses of artesunate and quinine (with loading dose). Of the 10 sequelae that occurred in this trial (the additional two were in children), five were psychiatric sequelae, four were a persistent problem with balance, and two were hemiparesis. **Imprecision: serious.** Neurological sequelae appear to be rare after severe malaria in adults; however, the 95% CI includes the possibility of clinically important harm with artesunate.
3. **Risk of Bias: no serious.** The large multicentre study adequately concealed allocation and can be considered at low risk of bias. The smaller trial did not. Neither trial was blinded. **Inconsistency: no serious.** There was no statistical heterogeneity (I^2 = 0%). **Indirectness: no serious.** This evidence is from multiple sites in Asia (Bangladesh, India, Indonesia and Myanmar), and both trials used standard drug doses. **Imprecision: no serious.** This result is statistically significantly in favour of artesunate. The sample size was adequate to detect a 75% risk reduction with 80% power and 95% confidence..

4. **Risk of Bias: no serious.** The large multicentre study adequately concealed allocation and can be considered at low risk of bias. The smaller trial did not. Neither trial was blinded. **Inconsistency: no serious.** Neither trial found a statistically significant difference in time to hospital discharge. **Indirectness: no serious.** This evidence is from multiple sites in Asia (Bangladesh, India, Indonesia and Myanmar), and both trials used standard drug doses. **Imprecision: serious.** We were unable to pool data because of the way in which they were presented, but there is no evidence of a benefit on this outcome with artesunate.

Attached Images

5.2.2.2. Parenteral alternatives when artesunate is not available

Clinical Question/ PICO

Population: Adults with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular artesunate

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.55 (CI 95% 0.34 — 0.92) Based on data from 494 participants in 2 studies. (Randomized controlled)	148 per 1000 Difference:	81 per 1000 **67 fewer per 1000** (CI 95% 98 fewer — 12 fewer)	Moderate Due to serious imprecision [1]	
Neurological sequelae at discharge	Relative risk		CI 95%		
Coma resolution time	Based on data from 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Moderate Due to serious imprecision [2]	
Parasite clearance time	Based on data from 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Moderate Due to serious imprecision [3]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fever clearance time	Based on data from 494 participants in 2 studies. (Randomized controlled)	Not pooled.		Low Due to serious imprecision [4]	

1. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** There is no statistical heterogeneity. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These trials and the meta-analysis have inadequate power to detect a difference in mortality or to prove equivalence.
2. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** Both studies suggest an advantage with artesunate, although this was statistically significant only in the small trial. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.
3. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** Neither study found a difference between treatments. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.
4. **Risk of Bias: no serious.** The trials were generally well conducted and had a low risk of bias. **Inconsistency: no serious.** One trial found no statistically significant difference, and the other, small trial found a benefit with artesunate. **Indirectness: no serious.** The two studies were conducted in Thailand and Viet Nam; both compared intramuscular artemether with intravenous artesunate in adults. **Imprecision: serious.** These data could not be pooled.

Attached Images

Clinical Question/ PICO

Population: Children with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.96 (CI 95% 0.76 — 1.2) Based on data from 1,447 participants in 12 studies. (Randomized controlled)	170 per 1000 Difference:	163 per 1000 **7 fewer per 1000** (CI 95% 41 fewer — 34 more)	Moderate Due to serious imprecision [1]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Neurological sequelae at discharge	Relative risk 0.84 (CI 95% 0.66 — 1.07) Based on data from 968 participants in 7 studies. (Randomized controlled)	220 per 1000 Difference:	185 per 1000 **35 fewer per 1000** (CI 95% 75 fewer — 15 more)	**Low** Due to very serious imprecision [2]	
Coma resolution time	Based on data from 358 participants in 6 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 17.4 to 42.4 h. Artemether: The mean time was 5.45 h shorter in the intervention groups (7.90 to 3.00 h shorter).		**Low** Due to very serious risk of bias [3]	
Parasite clearance time	Based on data from 420 participants in 7 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 22.4 to 61.3 h. Artemether: The mean time was 9.03 h shorter in the intervention groups (11.43 to 6.63 h shorter).		**Moderate** Due to serious inconsistency [4]	
Fever clearance time	Based on data from 457 participants in 8 studies. (Randomized controlled)	Quinine: The mean time in control groups ranged from 18 to 61 h. Artemether: The mean time was 3.73 h shorter in the intervention groups (6.55 to 0.92 h shorter).		**Low** Due to serious risk of bias and serious inconsistency [5]	

1. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: no serious.** None of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: serious.** These trials and the meta-analysis had inadequate power to detect a difference or to prove equivalence.
2. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: no serious.** None of the individual trials found statistically significant effects, and there was no statistical heterogeneity between trials. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: very serious.** These trials and the meta-analysis have inadequate power to detect a difference or to prove equivalence. The 95% CI is very wide and includes clinically important differences and no effect.
3. **Risk of Bias: very serious.** Four of the six trials had unclear risk of selection bias. When these four trials are excluded, the result becomes nonsignificant. **Inconsistency: no serious.** Statistically significant differences were seen in only two of the six trials; however, statistical heterogeneity between trials was low, and the result of the meta-analysis is significant. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect.
4. **Risk of Bias: no serious.** Various risks of bias, but exclusion of trials with high or unclear risk of selection bias did not change this result. **Inconsistency: serious.** The mean difference in parasite clearance time ranged from a 2 h increase with artemether to a 15 h decrease. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of

intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis has adequate power to detect this effect.
5. **Risk of Bias: serious.** Four of the seven trials had unclear risks of selection bias. When these four trials are excluded, the result becomes nonsignificant. **Inconsistency: serious.** The mean difference in fever clearance time ranged from a 25 h increase with artemether to an 18 h decrease. **Indirectness: no serious.** Trials were conducted in East and West Africa and India. All were in children with severe malaria (aged < 15 years), and most compared the standard dose of intramuscular artemether with the WHO recommended dose of intravenous quinine. **Imprecision: no serious.** The meta-analysis has adequate power to detect this effect. The result is statistically significant but may not be clinically important.

Attached Images

Clinical Question/ PICO

Population: Adults with severe malaria (malaria-endemic countries)
Intervention: Intramuscular artemether
Comparator: Intravenous or intramuscular quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artemether	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.59 (CI 95% 0.42 — 0.83) Based on data from 716 participants in 4 studies. (Randomized controlled)	208 per 1000 Difference:	123 per 1000 **85 fewer per 1000** (CI 95% 121 fewer — 35 fewer)	Moderate Due to serious imprecision [1]	
Neurological sequelae at discharge	Relative risk 2.92 (CI 95% 0.31 — 27.86) Based on data from 560 participants in 1 studies. (Randomized controlled)	4 per 1000 Difference:	12 per 1000 **8 more per 1000** (CI 95% 3 fewer — 107 more)	Moderate Due to serious imprecision [2]	
Coma resolution time	Based on data from 683 participants in 3 studies. (Randomized controlled)	Not pooled.		Low Due to serious inconsistency and serious imprecision [3]	
Parasite clearance time	Based on data from 716 participants in 4 studies.	Not pooled.		Moderate Due to serious imprecision [4]	

Outcome Timeframe	Study results and measurements	Comparator Quinine	Intervention Artemether	Certainty of the Evidence (Quality of evidence)	Plain language summary
Fever clearance time	Based on data from 716 participants in 4 studies.	Not pooled.		Moderate Due to serious imprecision [5]	

1. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** Statistically significant differences were seen in only one of the four studies; however, statistical heterogeneity among the trials was low, and the results of the meta-analysis are statistically significant. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** These trials and the meta-analysis had inadequate power to detect a difference in mortality or to prove equivalence.
2. **Risk of Bias: no serious.** This single trial had a low risk of bias. **Imprecision: serious.** Neurological sequelae in adults were uncommon. This trial had inadequate power to detect or exclude clinically important differences.
3. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: serious.** One trial found a shorter median coma resolution time with quinine, and one trial found no difference; the third trial reported mean coma recovery time incompletely. **Imprecision: serious.** The data could not be pooled.
4. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** The two largest studies both found shorter median clearance times with artemether. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** The data could not be pooled.
5. **Risk of Bias: no serious.** The trials were generally well conducted and with low risk of bias. **Inconsistency: no serious.** One trial found a shorter median fever clearance time with quinine, and two trials found a shorter time with artemether. **Indirectness: no serious.** All four trials compared intramuscular artemether with intravenous quinine in adults: two studies in Thailand, one each in Papua New Guinea and Viet Nam. **Imprecision: serious.** The data could not be pooled.

Attached Images

5.2.2.3. Pre-referral treatment options

Clinical Question/ PICO

Population: Children aged < 5 years with severe malaria (rural settings in Africa and Asia where parenteral treatment is not available)

Intervention: Rectal artesunate plus referral for definitive treatment

Comparator: Placebo plus referral for definitive treatment

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Rectal artesunate	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality (in Asia)	Relative risk 0.44 (CI 95% 0.23 — 0.82) Based on data from	31 per 1000	14 per 1000	Low Due to serious inconsistency	

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo	**Intervention** Rectal artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
7-30 days	2,010 participants in 1 studies. (Randomized controlled)	Difference:	**17 fewer per 1000** (CI 95% 24 fewer — 6 fewer)	and serious imprecision [1]	
All-cause mortality (in Africa) 7-30 days	Relative risk 0.81 (CI 95% 0.63 — 1.04) Based on data from 6,040 participants in 1 studies. (Randomized controlled)	44 per 1000 Difference:	36 per 1000 **8 fewer per 1000** (CI 95% 16 fewer — 2 more)	**Low** Due to serious inconsistency and serious imprecision [2]	
All-cause mortality (overall) 7-30 days	Relative risk 0.74 (CI 95% 0.59 — 0.93) Based on data from 8,050 participants in 1 studies. (Randomized controlled)	41 per 1000 Difference:	30 per 1000 **11 fewer per 1000** (CI 95% 17 fewer — 3 fewer)	**Moderate** Due to serious inconsistency [3]	

1. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: serious.** The number of events was low.
2. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: serious.** The 95% confidence interval is wide and includes no difference.
3. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** In Asia, older children and adults were also randomized to artesunate or placebo, and mortality was significantly higher in those given rectal artesunate; the cause is unclear. **Indirectness: no serious.** This trial was conducted in community settings in Bangladesh, Ghana and the United Republic of Tanzania. **Imprecision: no serious.** The result is statistically significant, and the study had adequate power to detect this effect.

Attached Images

Clinical Question/ PICO

Population: Children aged > 6 years and adults with severe malaria (rural settings where parenteral treatment is not available)

Intervention: Rectal artesunate plus referral for definitive treatment

Comparator: Placebo plus referral for definitive treatment

Outcome Timeframe	Study results and measurements	Comparator Placebo	Intervention Rectal artesunate	Certainty of the Evidence (Quality of evidence)	Plain language summary
All-cause mortality 7-30 days	Relative risk 2.21 (CI 95% 1.18 – 4.15) Based on data from 4,018 participants in 1 studies. (Randomized controlled)	7 per 1000 Difference:	15 per 1000 **8 more per 1000** (CI 95% 1 more – 22 more)	Low Due to serious inconsistency and serious imprecision [1]	

1. **Risk of Bias: no serious.** Allocation was concealed, and trial participants and staff were blinded to treatment allocation. **Inconsistency: serious.** Rectal artesunate appears beneficial in children < 5 years and harmful in older children and adults. This finding is difficult to explain. **Indirectness: no serious.** This trial was conducted in a single setting in Bangladesh. **Imprecision: serious.** There were few deaths in adults in this trial: 31/2009 in treated and 14/2009 in controls.

Attached Images

5.2.3. Other considerations in treating malaria

5.2.3.1. Management of malaria cases in special situations

5.2.3.2. Quality of antimalarial drugs

5.2.3.3. Monitoring efficacy and safety of antimalarial drugs and resistance

5.3. National adaptation and implementation

6. INTERVENTIONS IN THE FINAL PHASE OF ELIMINATION AND PREVENTION OF RE-ESTABLISHMENT

6.1. Interventions recommended for mass implementation in delimited geographical areas

6.1.1. Mass testing and treatment (MTaT)

Clinical Question/ PICO

Population: Adults and children in a delimited geographic area
Intervention: Mass testing and treatment
Comparator: No MTaT

Summary

Seven studies of MTaT were included in the systematic review: four cRCTs, conducted in Kenya, Indonesia, Zambia and Burkina Faso; and three NRSs in Senegal, Ghana and India (Bhamani *et al* *unpublished evidence*).

All four of the cRCTs conducted 2–3 rounds of MTaT over a period of up to one year, with the exception of the study in Kenya that carried out six rounds of MTaT over two years. The studies in Kenya and Burkina Faso were conducted in areas of moderate to high transmission while those in Indonesia and Zambia were areas of low transmission. The overall risk of bias for community-level outcomes in these studies was low. Meta-analyses of the results found little to no reductions in community-level incidence or prevalence of infection. However, there was a small reduction of the incidence of clinical malaria found in two studies.

The certainty of evidence from the NRSs was GRADEd as very low.

Outcome Timeframe	**Study results and measurements**	**Comparator** No MTaT	**Intervention** Mass testing and treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
2 months - Prevalence	Relative risk 0.93 (CI 95% 0.82 — 1.04) Based on data from 3,660 participants in 1 studies. (Randomized controlled) Follow up: one study with 2 cohorts (year 1 & 2). pooled for both the cohorts.	377 per 1000 Difference:	351 per 1000 **26 fewer per 1000** (CI 95% 68 fewer — 15 more)	High	MTaT does not reduce the prevalence of malaria at 2 months.
0 - 12 months - Incidence	Rate ratio 0.95 (CI 95% 0.87 — 1.04) Based on data from 857 participants in 1 studies. (Randomized controlled)	2,331 per 1000 Difference:	2,214 per 1000 **117 fewer per 1000** (CI 95% 303 fewer — 93 more)	High	MTaT does not reduce incidence of malaria infection between 0-12 months.
0 - 12 months - Incidence of clinical malaria	Relative risk 0.81 (CI 95% 0.7 — 0.95) Based on data from 332,454 participants in 2 studies. (Randomized controlled)	233 per 1000 Difference:	189 per 1000 **44 fewer per 1000** (CI 95% 70 fewer — 12 fewer)	High	MTaT reduces the incidence of clinical malaria between 0-12 months.
6 - 12 months - Incidence	Relative risk 1.27 (CI 95% 0.51 — 3.14) Based on data from 2,349 participants in 2 studies. (Randomized controlled) Follow up: One study has two intervention arms. Both intervention arms are pooled with another study and compared with the	4 per 1000 Difference:	5 per 1000 **1 more per 1000** (CI 95% 2 fewer — 11 more)	Moderate Due to serious imprecision [1]	MTaT likely results in little to no difference in the incidence of malaria infection between 6-12 months (outcome measured only in children).

Outcome Timeframe	**Study results and measurements**	**Comparator** No MTaT	**Intervention** Mass testing and treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	control. Control arm is inflated in value because it's the same comparison group for the two different intervention arm in one study.				
Adverse event (group targeted by the intervention)	Based on data from 6,373 participants in 1 studies. (Randomized controlled)		5 per 1000	Low Due to serious indirectness, and serious imprecision [2]	The evidence is very uncertain about the effect of MTaT on adverse events.
Serious adverse event (SAE) (group targeted by the intervention)	Based on data from 6,373 participants in 1 studies. (Randomized controlled) Follow up: not estimable.			Low Due to serious indirectness, and serious imprecision [3]	The evidence is very uncertain about the effect of MTaT on serious adverse events.
6 months - Prevalence (group targeted by the intervention)	Odds ratio 0.47 (CI 95% 0.24 — 0.9) Based on data from 1,024 participants in 1 studies. (Randomized controlled)	440 per 1000 Difference:	270 per 1000 **170 fewer per 1000** (CI 95% 281 fewer — 26 fewer)	Moderate Due to serious imprecision [4]	MTaT likely reduces prevalence of infection at six months among those receiving the intervention.
9 months - Prevalence (group targeted by the intervention)	Relative risk 0.91 (CI 95% 0.82 — 1.01) Based on data from 2,838 participants in 1 studies. (Randomized controlled)	378 per 1000 Difference:	344 per 1000 **34 fewer per 1000** (CI 95% 68 fewer — 4 more)	Moderate Due to serious imprecision [5]	MTaT likely does not reduce the prevalence of infection at nine months among the group targeted by the intervention.
2 months - Prevalence (group targeted by the intervention)	Odds ratio 0.03 (CI 95% 0.02 — 0.07) Based on data from 8,508 participants in 1 studies. (Observational (non-randomized))	34 per 1000	1 per 1000	Very low Due to serious inconsistency, serious indirectness, and serious imprecision [6]	The evidence is very uncertain about the effect of MTaT on the prevalence of infection at two months in the group receiving the intervention.
12 months - Prevalence (group targeted	Odds ratio 0.91 (CI 95% 0.67 — 1.38) Based on data from 416	438 per 1000	415 per 1000	Very low Due to serious inconsistency,	The evidence is very uncertain about the effect of MTaT on the

Outcome Timeframe	**Study results and measurements**	**Comparator** No MTaT	**Intervention** Mass testing and treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
by the intervention)	participants in 1 studies. (Observational (non-randomized))			serious indirectness, and serious imprecision [7]	prevalence of infection at 12 months in the group targeted by the intervention.
12 months - Prevalence (group targeted by the intervention)	Odds ratio 0.76 (CI 95% 0.67 — 0.85) Based on data from 8,907 participants in 1 studies. (Observational (non-randomized))	363 per 1000 Difference:	302 per 1000 **61 fewer per 1000** (CI 95% 87 fewer — 37 fewer)	**Very low** Due to serious inconsistency, serious indirectness, and serious imprecision [8]	The evidence is very uncertain about the effect of MTaT on the prevalence of infection in the group targeted by the intervention.
Adverse event (group targeted by the intervention)	Based on data from 6,373 participants in 1 studies. (Randomized controlled)	Most common AEs during treatment were fever (0.023/person-day), headache (0.008/person-day), vomiting (0.006/person-day), cough (0.004/person-day), shivering (0.003/person-day), and nasal congestion (0.002/person-day).		**Low** Due to serious risk of bias, and serious imprecision [9]	The evidence is very uncertain about the effect of MTaT on adverse events.
Prevalence (group targeted by the intervention)	Based on data from 633 participants in 1 studies. (Observational (non-randomized))	Three rounds of MTaT were conducted to determine prevalence in the asymptomatic reservoir. MTaT was compared with detection through passive surveillance prevalence. 1st round-moderate to high burden areas -50/28,527 i.e. 0.18% vs 0.06% from passive surveillance; 2nd round-low to high burden areas - 7/11,363 i.e. 0.06% vs 0.03% from passive surveillance; 3rd round- RCD of cryptic cases in 50 households -3/8,467 i.e. 0.03%.		**Very low** Due to serious risk of bias [10]	The evidence is very uncertain about the effect of MTaT on the prevalence of infection among the group targeted by the intervention.

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Used as a proxy for incidence of infection at the community level.
2. **Inconsistency: no serious. Indirectness: serious.** SAEs and AEs are not classified based on intervention and control arms; unable to calculate control measures in absence of control measure. **Imprecision: serious.** SAEs and AEs are not classified based on intervention and control arms; unable to calculate control measures in absence of control measure.
3. **Inconsistency: no serious. Indirectness: serious.** SAEs and AEs are not classified based on intervention and control arms; unable to calculate control measures in absence of control measure. **Imprecision: serious.** SAEs and AEs are not classified based on intervention and control arms; unable to calculate control measures in absence of control measure.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Used as a proxy for prevalence of infection at the community level.
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Used as a proxy for prevalence of infection at the community level.
6. **Inconsistency: serious.** Study did not control for one confounding domain and missing register from health facility in intervention village - the analysis is unlikely to have removed the risk of bias arising from the missing data. **Indirectness: serious.** Study did not control for one confounding domain and missing register from health facility in intervention village - the analysis is unlikely to have removed the risk of bias arising from the missing data. **Imprecision: serious.** Study did not control for one confounding domain and missing register from health facility in intervention village - the analysis is unlikely to have removed the risk of bias arising from the missing data.

7. **Inconsistency: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Indirectness: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Imprecision: serious.** Critical overall risk of bias due to inherent biases associated with study design.
8. **Inconsistency: serious.** Used as a proxy for prevalence of infection at the community level; critical overall risk of bias due to inherent biases associated with study design . **Indirectness: serious.** Used as a proxy for prevalence of infection at the community level; critical overall risk of bias due to inherent biases associated with study design. **Imprecision: serious.** Used as a proxy for prevalence of infection at the community level; critical overall risk of bias due to inherent biases associated with study design.
9. **Risk of Bias: serious.** Common AEs are reported for the whole study, however no break-up is provided for different arms. **Imprecision: serious.** Common AEs are reported for the whole study, however no break-up is provided for different arms.
10. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design.

Attached Images

6.2. Interventions targeting infections in people at higher-risk

6.2.1. Targeted drug administration (TDA)

Clinical Question/ PICO

Population: Adults and children at increased risk of malaria infection relative to the general population living in areas of very low to low transmission or post-elimination settings

Intervention: Targeted drug administration (TDA)

Comparator: no TDA

Summary

No studies from areas approaching elimination were identified in the systematic review (Tusell *et al* *unpublished evidence*). Two studies conducted in post-elimination settings identified imported infections in migrant workers with onward transmission to the local population. In both studies, the migrant workers were provided with a full therapeutic dose of chloroquine and 14 days of primaquine in a single round (the study from Greece conducted one round per year for three years). No additional infections among the migrant workers or the community were identified for five months (Sri Lanka) or two years (Greece) after the last round of TDA. Adverse events were monitored in both studies: a single serious case of haemolysis was identified in the study from Greece due to an incorrect G6PD test result; the remaining adverse events were relatively minor side effects.

Outcome Timeframe	**Study results and measurements**	**Comparator** no TDA	**Intervention** Targeted drug administration (TDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prevalence of malaria infection	Relative risk 0.85 (CI 95% 0.73 — 1) Based on data from 8,922 participants in 1 studies. (Randomized controlled)	**219** per 1000 Difference:	**186** per 1000 **33 fewer per 1000** (CI 95% 59 fewer — 0 more)	**High**	TDA results in little to no difference in the prevalence of malaria

Outcome Timeframe	**Study results and measurements**	**Comparator** no TDA	**Intervention** Targeted drug administration (TDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Serious Adverse Events (cRCTs)	Based on data from 10,079 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000	Very low Due to very serious risk of bias, Due to very serious imprecision [1]	The evidence is very uncertain about the effect of TDA on serious adverse events
Serious adverse events (cRCTs)	Relative risk 4.19 (CI 95% 1.43 — 12.31) Based on data from 4,916 participants in 1 studies. (Randomized controlled)	2 per 1000 Difference:	7 per 1000 **6 more per 1000** (CI 95% 1 more — 23 more)	Low Due to very serious imprecision [2]	TDA may result in little to no difference in serious adverse events
Serious adverse events (NRS)	Based on data from 31 participants in 1 studies. (Observational (non-randomized))	0 per 1000	0 per 1000	Very low Due to serious risk of bias, Due to serious imprecision [3]	The evidence is very uncertain about the effect of TDA on serious adverse events
Adverse events (cRCTs)	Relative risk 1.48 (CI 95% 0.12 — 18.02) Based on data from 4,916 participants in 1 studies. (Randomized controlled)	19 per 1000 Difference:	28 per 1000 **9 more per 1000** (CI 95% 17 fewer — 325 more)	Low Due to very serious imprecision [4]	TDA may have little to no effect on adverse events
Adverse events (NRS)	Based on data from 1,094 participants in 1 studies. (Observational (non-randomized))	0 per 1000	0 per 1000	Very low Due to serious risk of bias [5]	The evidence is very uncertain about the effect of TDA on adverse events
Prevalence among those targeted by the intervention (cRCTs)	Relative risk 0.15 (CI 95% 0.06 — 0.38) Based on data from 5,970 participants in 2 studies. (Randomized controlled)	406 per 1000 Difference:	61 per 1000 **345 fewer per 1000** (CI 95% 381 fewer — 251 fewer)	Moderate Due to serious indirectness [6]	TDA probably reduces the prevalence of malaria among those targeted by the intervention
Prevalence among those targeted by the intervention (NRS)	Relative risk 0.35 (CI 95% 0.22 — 0.57) Based on data from 348 participants in 1 studies. (Observational (non-randomized))	315 per 1000 Difference:	110 per 1000 **205 fewer per 1000** (CI 95% 246 fewer — 135 fewer)	Low Due to serious risk of bias, Due to serious indirectness [7]	TDA may reduce the prevalence of malaria among those targeted by the intervention

Outcome Timeframe	**Study results and measurements**	**Comparator** no TDA	**Intervention** Targeted drug administration (TDA)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Incidence of malaria in the community	Based on data from 0 participants in 2 studies. (Observational (non-randomized))	Both studies reported no malaria cases during the follow-up periods.		Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [8]	The evidence is very uncertain about the effect of TDA on the prevalence of malaria among those targeted by the intervention

1. **Risk of Bias: very serious.** Outcome was collected in intervention arm only. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Unable to calculate effect measure in absence of control measures. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals. **Publication bias: no serious.**
3. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Few patients and few events. **Publication bias: no serious.**
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals. **Publication bias: no serious.**
5. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
6. **Inconsistency: no serious. Indirectness: serious.** Used as a surrogate for prevalence of infection at the community level. **Imprecision: no serious. Publication bias: no serious.**
7. **Risk of Bias: serious.** Moderate risk of bias due to bias due to confounding, bias due to deviations from intended interventions, and no information about bias in measurement of outcomes. **Inconsistency: no serious. Indirectness: serious.** Used as a surrogate for prevalence of infection at the community level. **Imprecision: no serious. Publication bias: no serious.**
8. **Risk of Bias: serious.** Critical overall risk of bias due to inherent biases associated with study design. **Inconsistency: no serious. Indirectness: serious.** Used as a surrogate for prevalence of infection at the community level. **Imprecision: serious.** Few patients and few events. **Publication bias: no serious.**

Attached Images

6.2.2. Targeted testing and treatment (TTaT)

Clinical Question/ PICO

Population: Adults and children at increased risk of malaria infection relative to the general population living in very low to low or post-elimination transmission settings

Intervention: Targeted testing and treatment

Comparator: No TTaT

Summary

The systematic review identified three studies for inclusion: two cRCTs in Ghana and Kenya and one NRS in Malawi (Allen *et al* unpublished evidence). No studies were conducted in very low to low transmission or post-elimination settings. The GDG determined that the TTaT strategy would be most relevant in very low to low transmission or post-elimination settings and, therefore, decided that the PICO question should be modified and the setting limited to such areas. As a result, the GDG did not consider any of the studies identified by the systematic review to fit the revised PICO.

Outcome Timeframe	**Study results and measurements**	**Comparator** No TTaT	**Intervention** Targeted testing and treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
0 - 24 months - Adverse events (group targeted by intervention)	Based on data from 2,030 participants in 1 studies. (Randomized controlled) Follow up: not estimable.		45 per 1000	Moderate Due to serious imprecision [1]	TTaT likely results in little to no difference in adverse events among the group targeted by intervention between 0-24 months.
0 - 24 months - Incidence	Rate ratio 1.13 (CI 95% 0.82 — 1.55) Based on data from 3,046 participants in 1 studies. (Randomized controlled)	666 per 1000	752 per 1000	Moderate Due to serious risk of bias [2]	TTaT probably results in little to no difference in the incidence of malaria infection between 0-24 months.
12 months - Prevalence (group targeted by intervention)	Relative risk 0.71 (CI 95% 0.46 — 1.11) Based on data from 4,382 participants in 1 studies. (Randomized controlled)	143 per 1000 Difference:	102 per 1000 **41 fewer per 1000** (CI 95% 77 fewer — 16 more)	Moderate Due to serious imprecision [3]	TTaT probably has little to no effect on malaria prevalence in the group targeted by the intervention at 12 months.
Mortality (group targeted by intervention)	Relative risk 0.73 (CI 95% 0.08 — 6.95) Based on data from 8,222 participants in 2 studies. (Randomized controlled)	7 per 1000 Difference:	5 per 1000 **2 fewer per 1000** (CI 95% 6 fewer — 42 more)	Moderate Due to serious imprecision [4]	TTaT likely results in little to no difference in severe adverse events among group targeted by intervention.
24 months - Prevalence (group targeted by intervention)	Relative risk 1.53 (CI 95% 0.89 — 2.62) Based on data from 4,140 participants in 1 studies. (Randomized controlled)	84 per 1000 Difference:	129 per 1000 **45 more per 1000** (CI 95% 9 fewer — 136 more)	Moderate Due to serious imprecision [5]	TTaT probably results in little to no difference in prevalence in the group targeted by intervention at 24 months.
6 weeks - Prevalence (group targeted by intervention)	Relative risk 0.43 (CI 95% 0.33 — 0.55) Based on data from 1,317 participants in 1 studies. (Observational (non-randomized))	255 per 1000 Difference:	110 per 1000 **145 fewer per 1000** (CI 95% 171 fewer — 115 fewer)	Moderate Due to serious risk of bias, serious imprecision, and large magnitude of effect [6]	TTAT reduces the prevalence of malaria among the group targeted by intervention at six weeks.

1. **Risk of Bias: serious.** Outcome not measured in control arm. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious.** Outcome not measured in control arm.

2. **Risk of Bias: serious.** High risk of bias for domain 5 of RoB2 assessment - Selection of reported result. Study assessed incidence of malaria; episodes of malaria and accounted for repeat illnesses, but did not assess number of children in intervention and control arms that had malaria. Incidence was instead categorized by all episodes, episodes after first fever and repeat malaria and prevalence or number of clinical cases was not reported. Conducted a multi-level poisson to calculate incidence and rate ratios for comparison in study arms, but did not perform a generalized model accounting for potential demographics and confounders to assess risk of malaria infection in study arms. Incidence among high-risk population within the community used as a surrogate for community level impact. **Inconsistency: no serious. Indirectness: no serious.** Incidence among high-risk population within the community used as a surrogate for community level impact. **Imprecision: no serious.**
3. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Absolute effect estimates both appreciable risk and appreciable benefit.
4. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Imprecision due to wide confidence intervals; crude data used for mortality unadjusted for additional criteria or potential confounders. Absolute effect estimates both appreciable risk and appreciable benefit.
5. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Absolute effect estimates both appreciable risk and appreciable benefit.
6. **Risk of Bias: serious.** Moderate risk of bias in D7 of ROBINS-I, bias in selection of the reported result. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Absolute effect estimates both appreciable risk and appreciable benefit. **Upgrade: large magnitude of effect.**

Attached Images

6.2.3. Testing and treatment at points of entry to reduce importation of malaria

Clinical Question/ PICO

Population: Adults and children arriving at points of entry (land, sea or air)
Intervention: Testing and treatment at points of entry
Comparator: no intervention

Summary

The systematic review identified seven NRSs in six countries (Cambodia, China, Equatorial Guinea, Greece, Myanmar and the United Arab Emirates that reported on TTaT at points of entry (Coma-Cros *et al* *unpublished evidence*). None of the studies provided information on the outcome considered critical by the GDG, i.e. the number of positive cases identified by the strategy as a proportion of all imported cases found in the country during the same period.

Outcome Timeframe	**Study results and measurements**	**Comparator** no intervention	**Intervention** Testing and treatment at points of entry	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prevalence (group targeted by the intervention, test done at POE)	Based on data from 0 participants in 1 studies. (Observational (non-randomized))	Results indicate the highest prevalence in passengers younger than 15 years old travelling in the direction from the mainland to Bioko, 70.4% (95% CI 58.4 - 80.7; p-value 0.017). A lower prevalence was observed for the same age range in the opposite direction, 38.1% (95% CI 26.1 - 51.2; p-value 0.017). For		**Very low** Due to serious risk of bias [1]	

Outcome Timeframe	**Study results and measurements**	**Comparator** no intervention	**Intervention** Testing and treatment at points of entry	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		passengers older than 15 years a prevalence of 35.7% (95% CI 30.1 - 41.6; p-value 0.001) was observed between the mainland and Bioko and a prevalence of 22.6% (95% CI 17.3 - 28.6; p-value 0.001) in the opposite direction.			
Prevalence (positivity rate) (group targeted by the intervention, test done at POE)	Based on data from 0 participants in 4 studies. (Observational (non-randomized))	For UAE, where indigenous cases were zero, importation among arrivals applying for resident or work permits was between 4.6 and 9.1% for the study period. In Myanmar, among migrant workers, the positivity rate decreased over the years from 13.1% to 3.1%. In Cambodia, official border points identified different positivity rates depending on the neighbouring country, 0.6% with Thailand, 3.6% with Vietnam and 11.5% with Laos. Mobile malaria posts identified a decrease in the positivity rate over the years, from 9.2% to 0.09%.		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness [2]	
Prevalence (positivity rate) (group targeted by the intervention, test done after entry)	Based on data from 0 participants in 2 studies. (Observational (non-randomized))	Results in Shanglin County, China, showed a positivity rate of 21.6%. Targeted test and treat was done to persons with overseas travel history, mainly coming from Ghana where they work in the gold mining sector, within an 8-day median interval (range 0-28 days; interquartile range 4-18 days) between return date and diagnosis date. Results in Evrotas area in Greece, showed a positivity rate of 1.6% in 2012 and 2015, 1.4% in 2016 and 1.5% in 2017. During 2013 and 2014 there were no cases because an MDA was implemented in the area. The median time period from the migrants arriving in Greece to the day of their first contact with the field team and their registration in the database was much higher for the years 2012–2014 (90, 60 and 10 days respectively), compared with the years 2015–2017 (5, 15 and 7 days respectively).		**Very low** Due to serious risk of bias [3]	

1. **Risk of Bias: serious.** Observational study. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
2. **Risk of Bias: serious.** Observational study. **Inconsistency: serious.** Big differences among positivity rates (from 0.0 to 21.0). **Indirectness: serious.** Outcome expressed in positivity rate no prevalence. **Imprecision: no serious. Publication bias: no serious.**
3. **Risk of Bias: serious.** Observational study. **Inconsistency: no serious. Indirectness: no serious.** Outcome expressed in positivity rate no prevalence. **Imprecision: no serious. Publication bias: no serious.**

Attached Images

6.3. Interventions in response to detection of confirmed malaria cases

6.3.1. Reactive drug administration (RDA)

Clinical Question/ PICO

Population: Adults and children residing with or near a confirmed malaria case or having the same risk of acquiring infection as the index case in areas of very low to low transmission or in post-elimination settings

Intervention: Reactive drug administration

Comparator: No RDA

Summary

The systematic review identified six cRCTs assessing the impact of RDA in four countries of sub-Saharan Africa (Eswatini, Gambia, Namibia and Zambia) (Steinhardt *et al* *unpublished evidence (c)*). All studies used DP for treatment, with the exception of the study from Namibia that provided AL. One NRS assessing the impact of RDA was identified; the study, conducted in Peru, provided chloroquine plus seven days of primaquine at a dosage of 0.5mg/kg. All studies except for one were from low-transmission settings. Three of the cRCTs compared RDA to no RDA and three compared RDA to RACDT.

In the cRCTs, the people around the index case included in the RDA programme ranged from household and compound members (of the index case to people living within 500 meters of the index case.

Evidence of low to moderate certainty from the cRCTs suggested that RDA may reduce malaria prevalence and incidence slightly but probably results in little to no difference in the incidence of clinical malaria. Adverse events were often not measured in both arms, which complicated interpretation of the findings, but reported rates of adverse events or serious adverse events were low.

Outcome Timeframe	**Study results and measurements**	**Comparator** No RDA	**Intervention** Reactive drug administration	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prevalence of parasitemia - cRCTs	Odds ratio 0.76 (CI 95% 0.53 — 1.09) Based on data from 9,822 participants in 4 studies. (Randomized controlled)	20 per 1000 Difference:	16 per 1000 **5 fewer per 1000** (CI 95% 9 fewer — 2 more)	**Low** Due to serious indirectness, Due to serious imprecision [1]	RDA may reduce malaria prevalence
Incidence of parasitemia - cRCTs	Rate ratio 0.73 (CI 95% 0.36 — 1.47) Based on data from 18,354 participants in 2 studies. (Randomized controlled)	27 per 1000 Difference:	20 per 1000 **7 fewer per 1000** (CI 95% 17 fewer — 13 more)	**Moderate** Due to serious imprecision [2]	RDA probably reduces the incidence of malaria parasitaemia
Incidence of clinical malaria - cRCTs	Rate ratio 0.91 (CI 95% 0.8 — 1.03) Based on data from 3,013,320 participants in 6 studies. (Randomized controlled)	18 per 1000 Difference:	16 per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 1 more)	**Moderate** Due to serious indirectness [3]	The evidence is very uncertain about the effect of RDA on the incidence of clinical malaria
Incidence of	Rate ratio 0.59	6	3	**Very low**	The evidence is very

Outcome Timeframe	**Study results and measurements**	**Comparator** No RDA	**Intervention** Reactive drug administration	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
clinical malaria - NRS	(CI 95% 0.4 — 0.86) Based on data from 400,430 participants in 1 studies. (Observational (non-randomized))	per 1000 Difference:	per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 1 fewer)	Due to serious risk of bias [4]	uncertain about the effect of RDA on the incidence of clinical malaria
Adverse events (AEs) [5]	Based on data from participants in 4 studies. (Randomized controlled)	Four randomized trials reported on adverse events (AEs); however, AEs were typically only actively solicited from the RDA arm and not from the comparison or RACD arm. In the Zambia trial comparing RDA using dihydroartemisinin-piperaquine (DP) with RACD using artemether-lumefantrine (AL), 123 (6.9%) mild AEs occurred in 1,775 people treated with DP (Bridges 2021); all resolved. In the Namibia trial (Hsiang 2020) of RDA with AL compared to RACD with AL, 17 of 4,247 treated participants (0.4%) in the RDA arm experienced an AE versus 1 participant of 98 (1.0%) treated in the RACD arm; 11 AEs were considered unrelated, 6 possibly related, and 6 probably related. In The Gambia (Okebe 2021), 75 AEs (7.6%) among 979 participants receiving DP in the RDA arm reported AEs; 69 were considered mild and 6 moderate. In Eswati, 68 (3.8%) of 1,776 participants receiving RDA with DP experienced AEs; 54 were rated as mild and 14 as moderate.	Very low Most studies focused adverse event reporting only in the RDA arm; in three of the four studies no adverse events were reported from the comparison arm receiving RACD. We are unable to calculate an effect measure for AEs since they were measured in most studies only in the RDA arm	

1. **Inconsistency: no serious. Indirectness: serious.** Two studies (Hsiang 2020 and Okebe 2021) lack a true control group. The comparison in Hsiang 2020 is RACD and the comparison in Okebe 2021 is a modified version of RACD (testing and treating symptomatic household members of the index case). Although we rated down for indirectness, any bias would be towards the null if RACD has an effect on reducing malaria transmission., thus these effect sizes might underestimate the true effect of RDA. The pooled estimate ranges from averting 9 cases of parasitemia per 1,000 to having 2 more. **Imprecision: serious.** Two studies (Hsiang 2020 and Okebe 2021) lack a true control group. The comparison in Hsiang 2020 is RACD and the comparison in Okebe 2021 is a modified version of RACD (testing and treating symptomatic household members of the index case). Although we rated down for indirectness, any bias would be towards the null if RACD has an effect on reducing malaria transmission., thus these effect sizes might underestimate the true effect of RDA. The pooled estimate ranges from averting 9 cases of parasitemia per 1,000 to having 2 more.
2. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** The pooled effect estimate ranges from 0.36 (substantial benefit of RDA) to 1.47, indicating potential harm of RDA.
3. **Inconsistency: no serious. Indirectness: serious.** Only two studies (Eisele 2020--LOW and Eisele 2020--HIGH) had a true control group; three (Bridges 2021, Hsiang 2020, and VIlakati 2021) compared RDA to reactive case detection (RACD), and the fourth (Okebe 2021) compares RDA to a modified version of RACD (testing and treating symptomatic household members of the index case). Although we rated down for indirectness, any bias would be towards the null if RACD has an effect on reducing malaria transmission., thus these effect sizes might underestimate the true effect of RDA. **Imprecision: no serious.**
4. **Risk of Bias: serious.** There is a general lack of information about many aspects of this dissertation using data from Tumbes, Peru. We rated as 'Some concerns' most aspects of the study and consider the bias overall to be serious.
5. Four randomized trials reported on adverse events (AEs); however, AEs were typically only actively solicited from the RDA arm and not from the comparison or RACD arm. In the Zambia trial comparing RDA using dihydroartemisinin-

piperaquine (DP) with RACD using artemether-lumefantrine (AL), 123 (6.9%) mild AEs occurred in 1,775 people treated with DP (Bridges 2021); all resolved. In the Namibia trial (Hsiang 2020) of RDA with AL compared to RACD with AL, 17 of 4,247 treated participants (0.4%) in the RDA arm experienced an AE versus 1 participant of 98 (1.0%) treated in the RACD arm; 11 AEs were considered unrelated, 6 possibly related, and 6 probably related. In The Gambia (Okebe 2021), 75 AEs (7.6%) among 979 participants receiving DP in the RDA arm reported AEs; 69 were considered mild and 6 moderate. In Eswati, 68 (3.8%) of 1,776 participants receiving RDA with DP experienced AEs; 54 were rated as mild and 14 as moderate.

Attached Images

6.3.2. Reactive case detection and treatment (RACDT)

Clinical Question/ PICO

Population: Adults and children residing with or near a confirmed malaria case or having the same risk of acquiring infection as the index case in areas nearing elimination or in post-elimination settings

Intervention: Reactive case detection and treatment

Comparator: No RACDT

Summary

The systematic review identified three cRCTs in three countries of sub-Saharan Africa (Eswatini, Namibia and Zambia) (Steinhardt *et al* *unpublished evidence (d)*). However, all three studies were intended to evaluate the impact of RDA, and RACDT was the comparator. As RDA is likely to be a more effective strategy than RACDT, no conclusions could be drawn from these studies. The two NRSs identified from Brazil and Zambia reported on outcomes among those receiving the intervention, but did not evaluate impact at the community level.

Outcome Timeframe	**Study results and measurements**	**Comparator** No RACDT	**Intervention** Reactive case detection and treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prevalence of parasitemia	Odds ratio 1.85 (CI 95% 0.96 — 3.57) Based on data from 3,926 participants in 1 studies. (Randomized controlled)	31 per 1000 Difference:	56 per 1000 **26 more per 1000** (CI 95% 1 fewer — 80 more)	Very low Due to very serious indirectness, and serious imprecision [1]	The evidence is very uncertain about the effect of RACDT on the prevalence of malaria
Incidence of clinical malaria	Rate ratio 1.3 (CI 95% 0.94 — 1.79) Based on data from 215,146 participants in 3 studies. (Randomized controlled)	9 per 1000 Difference:	12 per 1000 **3 more per 1000** (CI 95% 1 fewer — 17 more)	Very low Due to very serious indirectness, and serious imprecision [2]	The evidence is very uncertain about the effect of RACDT on the incidence of clinical malaria
Parasitemia prevalence among those	Based on data from participants in 2 studies. (Observational (non-	Results from a difference-in-differences analysis of the Brazil study indicate a slight increase (by		Very low Due to serious risk of bias, and	The evidence is very uncertain about the effect or RACDT on

Outcome Timeframe	**Study results and measurements**	**Comparator** No RACDT	**Intervention** Reactive case detection and treatment	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
receiving the intervention	randomized))	0.8 percentage(%)-points, 3.8%-points, and 2.3%-points at 30, 60, and 180 days, respectively) in parasitemia over time in RACD households compared to control households. The Zambia study indicated a slight decrease (by 0.9%-points and 2.1%-points at 30 and 90 days after RACD, respectively) in parasitemia in RACD households, but no control households were included.		serious inconsistency [3]	parasite prevalence among people who participate in RACDT.
Adverse events	Based on data from participants in 3 studies. (Randomized controlled)	Three randomized trials reported on adverse events (AEs); however, AEs were typically only actively solicited from the RDA arm and not from the RACD arm. In the Zambia trial comparing RACD using artemether-lumefantrine (AL) with RDA using dihydroartemisinin-piperaquine (DP) (Bridges 2021(16)), 123 (6.9%) mild AEs occurred in 1,775 people treated with DP (all resolved); no events were reported from the RACD arm. In the Namibia trial (Hsiang 2020(23)) of RACD with AL compared to RDA with AL, the authors reported that 1 participant of 98 (1.0%) treated in the RACD arm experienced an AE compared to 17 of 4,247 treated participants (0.4%) in the RDA arm; 11 AEs were considered unrelated, 6 possibly related, and 6 probably related. In the Eswati trial (Vilakati 2021(18)), no AEs were reported from participants who received AL in the RACD arm and 68 (3.8%) of 1,776 participants receiving RDA with DP were reported to experience AEs; 54 were rated as mild and 14 as moderate.		Very low Due to very serious risk of bias, serious indirectness, and very serious imprecision [4]	The evidence is very uncertain about the effect of RACDT on adverse events.

1. **Inconsistency: no serious. Indirectness: very serious.** The study on which this effect estimate is based compared RACD to reactive drug administration (RDA), which is hypothesized to be a more effective intervention. Thus any effect favoring RACD (vs. RDA) is likely to be underestimated, and any effect favoring the comparison should not necessarily be interpreted as evidence that RACD has a harmful effect or no beneficial effect.. **Imprecision: serious.** The actual odds ratio for the effect size = 1.85 (95% CI: 0.96, 20.00) and is therefore quite imprecise, spanning no effect to a large harmful effect. (RevMan can only accommodate balanced confidence intervals but this effect size was calculated by study authors using non-linear model post-estimation combinations.).
2. **Inconsistency: no serious. Indirectness: very serious.** The studies on which this effect estimate is based all compared RACD to reactive drug administration (RDA), which is hypothesized to be a more effective intervention. Thus any effect favoring RACD (vs. RDA) is likely to be underestimated, and any effect favoring the comparison should not necessarily be interpreted as evidence that RACD has a harmful effect or no beneficial effect. **Imprecision: serious.** The pooled rate ratio spans no effect to a substantial absolute effect in a low-transmission setting.
3. **Risk of Bias: serious.** These data come from non-randomized studies. One of the studies has a before-and-after design with no control group. **Inconsistency: serious.** One study showed a slightly beneficial effect of RACD and the other study showed a slightly negative effect. **Indirectness: no serious. Imprecision: no serious.**
4. **Risk of Bias: very serious.** Two of the three studies included here focused adverse event reporting only in the RDA arm; in these studies no adverse events were reported from the RACD arm. **Indirectness: serious.** Two of the three

studies included here focused adverse event reporting only in the RDA arm; in these studies no adverse events were reported from the RACD arm. **Imprecision: very serious.** We are unable to calculate an effect measure for AEs since they were measured in most studies only in the RDA arm.

Attached Images

6.3.3. Reactive indoor residual spraying

Clinical Question/ PICO

Population: Adults and children residing with or near a confirmed malaria case in areas nearing elimination or in post-elimination settings

Intervention: Reactive indoor residual spraying

Comparator: no Reactive IRS

Summary

The systematic review identified two cRCTs in Namibia and South Africa (Gimnig *et al* *unpublished evidence*). The study from Namibia (superiority trial design) was conducted as a 2x2 factorial design with RACDT alone, RDA alone, RACDT plus RIRS, and RDA plus RIRS. The study from South Africa was designed as a non-inferiority trial comparing RIRS to standard IRS (used in defined priority areas) that reached one third of houses. The results below report the absolute effects (risk differences) of the intervention, as these were used by the GDG in its judgements; relative effect sizes are available in the Research evidence.

Beneficial outcomes

- RIRS results in a large reduction in the prevalence of malaria (RD: -27 per 1000 persons; 95% CI: -35 to -8 per 1000 persons; one cRCT [superiority design]; high-certainty evidence).
- RIRS may reduce the incidence of clinical malaria. However, the effects of RIRS on clinical malaria vary and it is possible that RIRS makes little or no difference (RD: -14 per 1000 p-y; 95% CI: -32 to 4 per 1000 p-y; one cRCT [superiority design]; moderate-certainty evidence).
- RIRS probably results in little to no difference in incidence of clinical malaria (mean difference: 0.1 per 1000 p-y; 95% CI: -0.38 to 0.59 per 1000 p-y; one cRCT [non-inferiority design]; moderate-certainty evidence).

Adverse events

- RIRS results in little to no difference in reported adverse events (RD: 2 per 1000 persons; 95% CI: -2 to 1 per 1000 persons; one cRCT [superiority design]; high-certainty evidence).
- RIRS results in little to no difference in serious adverse events (deaths) (one cRCT [non-inferiority design]; high-certainty evidence).

Outcome Timeframe	**Study results and measurements**	**Comparator** no Reactive IRS	**Intervention** Reactive indoor residual spraying	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Prevalence of malaria (superiority trial) 7 Critical	Odds ratio 0.32 (CI 95% 0.15 — 0.8) Based on data from 4,082 participants in 1 studies. (Randomized controlled)	41 per 1000 Difference:	13 per 1000 **28 fewer per 1000** (CI 95% 35	**High**	Reactive IRS reduces malaria prevalence

Outcome Timeframe	**Study results and measurements**	**Comparator** no Reactive IRS	**Intervention** Reactive indoor residual spraying	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
			fewer — 8 fewer)		
Incidence of clinical malaria (superiority design) 9 Critical	Relative risk 0.65 (CI 95% 0.19 — 1.11) Based on data from 2,000 participants in 1 studies. (Randomized controlled)	**39** per 1000 Difference:	**25** per 1000 **14 fewer per 1000** (CI 95% 32 fewer — 4 more)	**Moderate** Due to serious imprecision [1]	Reactive IRS probably reduces the incidence of clinical malaria
Adverse events (superiority trial)	Relative risk 0.48 (CI 95% 0.18 — 1.27) Based on data from 8,948 participants in 1 studies. (Randomized controlled)	**3** per 1000 Difference:	**1** per 1000 **2 fewer per 1000** (CI 95% 2 fewer — 1 more)	**High**	Reactive IRS results in little to no difference in adverse events
Serious adverse events (deaths, non-inferiority trial)	Relative risk 0.69 (CI 95% 0.29 — 1.6) Based on data from 393,387 participants in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	**High**	Reactive IRS results in little to no difference in serious adverse events (deaths) compared with standard IRS
Incidence of clinical malaria (non-inferiority design) 6 Important	High better Based on data from 0 participants in 1 studies. (Randomized controlled)	**0** (Mean) Difference:	**0.1** (Mean) **MD 0.1 higher** (CI 95% 0.38 lower — 0.59 higher)	**Moderate** Due to serious indirectness [2]	Reactive IRS probably results in little to no difference in incidence of clinical malaria compared with standard IRS
Adverse Events 5 Important	Based on data from 0 participants in 2 studies. (Randomized controlled)	One study (Hsiang 2020) reported adverse events among persons receiving reactive IRS versus those not receiving reactive IRS. A total of 23 adverse events were reported among 18 participants. In the the reactive IRS arm, 6/4579 participants (0.13%) reported an adverse event compared to 12/4369 participants (0.27%) in the arm that received reactive case detection alone. None of the adverse events were considered related to IRS. In the study by Bath 2021, comparing reactive IRS versus standard IRS over two years, 9 deaths due to malaria were reported in the reactive IRS arm out of a population of 204,237. In the standard IRS arm, a total of 12 malaria deaths were reported out of a population of 189,150.		**High**	

1. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Confidence interval of adjusted estimate overlaps 1. **Publication bias: no serious.**
2. **Inconsistency: no serious. Indirectness: serious.** Study was designed as a non-inferiority study compared to standard IRS. **Imprecision: no serious. Publication bias: no serious.**

Attached Images

7. SURVEILLANCE

8. METHODS

9. GLOSSARY

10. CONTRIBUTORS AND INTERESTS

10.1. Recommendations for vector control

10.2. Recommendations for chemoprevention

10.3. Malaria vaccine recommendation

10.4. Recommendations for treatment

10.5. Recommendations for interventions in the final phase of elimination and prevention of re-establishment