Malaria Policy Advisory Committee Meeting

13—14 May 2020, Geneva, Switzerland
Background document for Session 5

WHO technical consultation to review the role of drugs in malaria prevention for people living in endemic settings

Meeting report, 16–17 October 2019, Geneva, Switzerland

Summary

On 16–17 October 2019, the World Health Organization (WHO) convened a Technical Consultation to review the use of medicines for malaria prevention in endemic countries and to identify opportunities to increase their impact through review of the flexibility of the recommendations for their deployment. Experts reviewed the policies and use of chemoprevention as currently endorsed by WHO, including intermittent preventive treatment in pregnancy (IPTp), intermittent preventive treatment in infants (IPTi), seasonal malaria chemoprevention (SMC) and mass drug administration (MDA) for the reduction of disease burden in emergency situations. By reviewing these strategies side-by-side for the first time, the meeting was able to consider opportunities for optimization. Additional potential applications of chemoprevention were also reviewed, and key considerations identified to develop a broader role for malaria chemoprevention in malaria-endemic populations.

Key conclusions of the meeting included:

- **There is a need for general guidance on the broader use of chemoprevention.** Chemoprevention is an important approach in the package of strategies that countries may use to decrease their malaria burden and/or move towards malaria elimination. Development of broader, more flexible guidance that builds on existing chemoprevention recommendations in specific populations is expected to support the greater, more rational use of chemoprevention and enhance its impact.
- **Chemoprevention strategies may be tailored to country-specific needs.** Guidance should be flexible enough to enable adaptation of strategies according to the needs of different countries and settings. Adaptations should consider the safety profile, biological rationale, epidemiological setting and delivery method. There should be rigorous evaluation of implementation activities that go beyond previously evaluated approaches.
- **Integration of chemoprevention into existing platforms** is encouraged wherever possible (e.g., IPTi and immunization services, IPTp and antenatal care packages). Early engagement of relevant partners, such as the Expanded Programme on Immunization (EPI) and reproductive health programmes, is encouraged. It is important to ensure that clear roles are agreed upon among partners for the delivery, monitoring and evaluation of the strategy.
- **Additional approaches to boost coverage** should be considered if there is no fit-for-purpose platform and to extend coverage to those not accessible through existing platforms. Methods of intervention delivery (such as the EPI, or through integrated community case management) may be setting-specific. The use of alternative delivery methods supports flexibility and should not be viewed as a deviation from policy. The system and cost implications of different delivery channels should be considered and documented.

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- **Countries should be supported to tailor strategies and adapt the mix of interventions according to their malaria control/elimination needs and context**. Support should be provided as countries develop and review their national strategic plans.
- **Monitoring the impact of chemoprevention strategies is critical** to understand their value and to inform the development of future guidance. Clear target outcomes will inform the design of specific evaluations. Impact may be monitored through collection of quality-assured routine data at health facilities and hospitals and the targeted collection of non-routine data. Operational and implementation research should be appropriately supported and involve both the national malaria control programme and local research partners; the results should be disseminated widely.
- **Research and development of new malaria drugs should place greater emphasis on their potential use for chemoprevention.** Important factors for different use cases should be considered early: e.g., dosage, pharmacokinetics and safety in infants and pregnancy, long-acting drugs, co-formulation with drugs of similar half-lives (to avoid exposure to a single drug), effects of co-administration with other interventions (e.g., vaccines), and impact on transmission.

Background

The 2017 and 2018 World Health Organization (WHO) world malaria reports *(1,2)* document that progress in malaria control has stalled. The trends showing encouraging reductions in malaria disease and death documented in the period 2000–2015 have faltered and, in some settings, begun to reverse. In the context of population increases, finite resources and a lack of immediately available new tools, the use of current tools needs to be maximized to get back on track to meet the targets of the *Global technical strategy for malaria 2016–2030* (GTS) *(3).*

Case management with highly effective antimalarial drugs has contributed to the decrease in malaria morbidity and mortality. Routine administration of antimalarial drugs has also been recommended for use in selected high-risk populations, irrespective of malaria infection status, both to treat any unrecognized *Plasmodium* infections and to prevent new ones. This meeting was convened to consider how to optimize the use of antimalarial drugs to prevent malaria disease and death.

The use of antimalarial drugs for prevention can broadly be termed *chemoprevention*. Multiple current interventions fit under this umbrella although they target different populations, utilize different delivery methods and are designed to achieve different outcomes (Table 1). In some use cases, mass drug administration (MDA) may also be considered a form of chemoprevention.

Table 1. Current routine uses of chemoprevention

TYPE	TARGET POPULATION	TRANSMISSION SETTING	DRUG	DELIVERY MECHANISM	TIMING
Intermittent preventive treatment in pregnancy (IPTp)	Pregnant women	Areas of moderate to high transmission in Africa	SP	Antenatal care clinics	Year-round
Intermittent preventive treatment in infants (IPTi)	Infants (<12 months of age)	Areas of moderate to high transmission in Africa	SP	Routine vaccination visits	Year-round
Seasonal malaria chemoprevention (SMC)	Children 3–59 months old	Highly seasonal transmission areas	SP+AQ	Mass delivery campaigns	During each transmission season

SP: sulfadoxine-pyrimethamine, AQ: amodiaquine

Additional chemoprevention approaches are under evaluation, such as IPT post-discharge from hospital and IPT in schoolchildren.

The adoption and implementation of chemoprevention policies has been fragmented. According to the 2019 *World malaria report (4)*, in 2018, only 31% of women in sub-Saharan Africa received three or more doses of IPTp; only one country had adopted IPTi; and even though 31 million children received SMC, just six years after WHO recommended this strategy, an additional 12 million children could have benefited from this intervention.

The GTS *(3)* encourages endemic countries to set their own targets and to tailor and prioritize the use of interventions to suit their needs. The extent to which they can do this may, however, be limited by the prescriptive nature of existing recommendations and/or their accompanying guidance. For example, some presentations of the existing SMC recommendation refer to the definition of "highly seasonal" (60% of malaria cases occurring within four consecutive months), indicate the frequency (monthly) and maximum number of doses (four) of a single recommended drug combination (SP+AQ), state the age range of the target group (3–59 months) and define the minimum disease burden (incidence of ≥0.1 episodes per child per season).

Meeting attendees were asked to consider how guidance could be presented in a way that enhances a country's ability to set policies as part of a problem-solving approach to malaria control. This requires clarity and agreement on what is meant by the term intervention. SMC, IPTp, IPTi and MDA all distribute antimalarial drugs to individuals at risk without knowing their malaria infection status. The aim is to clear any existing infections and prevent new ones. Therefore, they could be considered a range of strategies to deliver the same intervention, despite targeting different groups and using different drugs and delivery approaches. In this context, when developing guidance, it may be useful to consider the concept of transferability, i.e., the degree to which evidence generated in one context or target group can be used to inform decisions in another.

The aims of this Technical Consultation were to identify: i) strategies to maximize the impact of malaria chemoprevention on mortality, morbidity (including anaemia) and/or transmission; and ii) evidence gaps and priority implementation research needed to update WHO policies on malaria chemoprevention. The meeting began by considering the age patterns of different manifestations of malaria, followed by a brief review of the history and current uses of chemoprevention. Discussions then focused on the individual recommended chemoprevention strategies – SMC, IPTp, IPTi and MDA – and opportunities to optimize them; potential new use cases in schoolchildren and among children discharged from hospital; and issues around the choice of drugs for chemoprevention.

Age patterns of malaria disease

The risk and consequences of malaria infection are influenced by a large number of factors, including transmission intensity, health-seeking behaviour, accessibility and quality of health services, which are in turn influenced by socioeconomic and cultural factors, conflict and emergencies, and genetic factors (e.g., haemoglobinopathies). An understanding of the age group(s) most seriously affected by malaria in specific epidemiological situations is important in order to effectively target malaria chemoprevention.

In settings with stable malaria transmission, the more severe consequences of *P. falciparum* infection tend to occur in younger age groups. This may reflect the more rapid acquisition of immunity against severe forms of malaria than against less severe forms. In effect, protection against death due to malaria develops before protection against uncomplicated malaria. However, this understanding comes from data generated in the 1990s and early 2000s, before the scale-up of malaria control.

An unpublished, ongoing review of data from hospitals with individual patient-level information has enabled the calculation of endemicity- and age-specific rates of different clinical presentations

before and after the scale-up of malaria control efforts. Data from over 50 hospitals in eight countries in sub-Saharan African show that, before 2006, the mean age of malaria hospitalization was lower in more intense transmission settings than in less intense transmission settings. This pattern persisted between 2006 and 2018, when control efforts had been scaled-up, even though the absolute incidence of malaria admission decreased. Since the scale-up of control efforts, across the range of malaria transmission settings in Africa, severe disease presenting to hospital has continued to be a predominantly paediatric problem, affecting children under 5 years of age. In areas with medium and high transmission, severe malaria admission rates are particularly high among children in their first two to three years of life. Severe malaria anaemia remains the most common presentation among severe malaria admissions and is common up to 5 years of age. In comparison, cerebral malaria is a relatively rare cause of admission among children under 15 years of age. In most transmission settings, including settings with very low transmission, severe malaria in children aged 10–15 years is rare.

The severe disease risks in populations over 15 years of age in Africa remain poorly defined, including risks in those with underlying morbidities, such as HIV on treatment (antiretroviral therapy, cotrimoxazole), diabetes, etc. The morbidity consequences of malaria infection among non-pregnant adults and school-age children, including indirect effects (e.g., on cognition in schoolchildren), require further empirical investigation.

The observations that severe malaria in Africa remains primarily a problem in children under 5 years of age and that cerebral malaria is markedly less common than severe anaemia have implications for the age-targeting of chemoprevention and underscore that anaemia is an important outcome measure that should be monitored.

Historical perspective on malaria chemoprevention

There is a long history of antimalarial drug use for prevention. Chemoprophylaxis of travellers, traders, sailors and soldiers has been used since the 1700s. The first test of malaria drug use for control at the population level was by Robert Koch, who used quinine in Papua in the early 1900s. This was poorly tolerated. Medicated salt programmes in South America, Asia and Africa in the 1950s and 1960s had better outcomes, although they likely accelerated the development of resistance to antimalarials such as chloroquine and pyrimethamine when introduced in salt. The 1960s saw chemoprophylaxis programmes in schoolchildren in several West, East and Southern African countries, and quinine was made available and widely used during the successful elimination of malaria from southern Italy.

In the early 1970s, the Garki project evaluated the ability of intensive malaria control, including the combination of mass treatment with malarial drugs and indoor residual spraying, to interrupt malaria transmission in a high-transmission area of northern Nigeria. Two years of intervention reduced the prevalence of infection from over 60% to less than 1% and likely had a marked effect on morbidity, although this was not the focus of the evaluation. Transmission was not interrupted, however, and resurged when interventions were stopped, quickly returning to pre-intervention levels. This result led to pessimism about the potential value of available tools to interrupt transmission. Together with concerns about accelerating the development of drug resistance, the costs and feasibility of providing chemoprophylaxis to whole populations, and the possibility of impairing the development of naturally acquired immunity, the subsequent decades were characterized by neglect of chemoprevention strategies for malaria control.

Interest was rekindled in the 1990s, starting with the first policy on using IPT in pregnant women for malaria prevention. Reducing the frequency of drug administration, using full treatment doses and targeting specific high-risk groups ameliorated concerns over chemoprevention's feasibility, costs, and effects on the development of drug resistance and naturally acquired immunity.

Antimalarial drugs used for preventive treatment in pregnant women, infants and young children have now been shown to decrease malaria-related morbidity. Clinical trials and modelling have also shown the potential of MDA, in conjunction with other control measures, to reduce transmission and disease. In contrast with the Garki era, there is now a commitment and a financing mechanism in place to sustain at least a subset of interventions to control malaria in endemic countries over the longer term. More drugs are available to treat and prevent malaria, and vector control tools are deployed at a larger scale. These interventions, complemented by broad improvements in economic conditions, have delivered massive progress in malaria control in recent decades. Nevertheless, the burden of malaria remains high in many parts of sub-Saharan Africa. With over 400 000 deaths attributed to malaria every year, there is an urgency to reconsider how best to use antimalarial drugs for prevention.

Chemoprevention current use cases

SMC

SMC is the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malaria illness and death. The objective of SMC is to maintain therapeutic drug concentrations in the blood throughout the period of greatest malaria risk. WHO has recommended SMC since 2012 and presents the following recommendation in the 2015 *Guidelines for the treatment of malaria (5)*:

> *"In areas with highly seasonal malaria transmission in the sub-Sahel region of Africa, provide seasonal malaria chemoprevention (SMC) with monthly amodiaquine + SP for all children < 6 years during each transmission season."*

Related statements indicate a minimum age of 3 months, the need to start at the beginning of the transmission season, a maximum of four doses during each malaria transmission season, a minimum incidence of 0.1 episodes per child per transmission season and a need for SP+AQ to have >90% efficacy.

SMC has been rapidly scaled up, with 31 million children in 12 countries receiving the intervention in 2018 *(4)*. Many countries implement SMC subnationally in areas meeting the various criteria. There is good operational experience (e.g., in northern Nigeria and Mali) with the delivery of SMC in areas of poor security. The successful replenishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria in 2019 is likely to provide a substantial boost for financing SMC programmes. Detailed assessments of the current status of SMC were discussed in a meeting immediately preceding the current meeting (details provided in a separate report).

An important challenge with current SMC programmes is their lack of adequate monitoring and evaluation, including assessment of coverage, adherence, pharmacovigilance and impact. The primary approach for impact monitoring should be through routine (health management information system [HMIS]) data. With careful analysis to account for time-varying factors, such data can be expected to document low morbidity in the target age group during the intervention period. Data from clinical trials show that SMC can reduce both malaria morbidity and severe morbidity by 75% in the target age group, including a reduction of 19 cases of severe anaemia and one death per 1000 SMC recipients per season *(6)*. Where the incidence rate is ≥0.2 cases per child per season, SMC is likely to be highly cost-effective. At an incidence rate of <0.1 cases per child per season, SMC is unlikely to be considered cost-effective.

Opportunities for optimization

The impact of the SMC strategy could be increased by expanding its implementation in places where SMC is currently deployed – e.g., by including additional rounds or extending the age range targeted. The impact of SMC could also be increased by introducing it in settings where SMC is not currently

used, such as places with less marked seasonality. Maximizing coverage of the standard, currently recommended strategy should be prioritized, as the benefits of this have been demonstrated in the vulnerable groups targeted. The intervention should not be expanded in an effort to compensate for inadequate implementation of the current SMC recommendation; however, expansion may be considered in settings where the recommended strategy has been implemented at scale, but there is an ongoing unmet need.

Additional round(s): A potential adaptation of the currently recommended intervention is to implement an additional round (or rounds) of drug distribution. Justification for this adaptation may be that, while the original seasonal transmission criterion is being met, i) there is annual variation in the exact timing of the onset of the transmission season (for example, rains may start in August in some years and in July in others), and thus the additional round could provide a buffer to cover this variability; or ii) the additional burden that lies just outside the peak transmission window can be targeted, thereby further reducing morbidity. Modelling shows that, in specific areas lying near the southern edge of the current SMC areas, an additional round of drug distribution would increase the percentage of the annual burden falling within the SMC window from around 60% to 80% (Cairns M, personal communication).

Once high-level coverage of the recommended SMC package has been attained, the committee supported piloting and evaluating additional round(s) of drug distribution, acknowledging that the understanding yielded by such evaluation is likely to be relatively transferable between settings.

Age group expansion: Another potential alteration to the currently recommended SMC intervention is to expand the age range to include older children. Where malaria is well controlled in children under 5 years of age, a substantial number of malaria episodes may still occur in children over 5. As noted in the discussion on the age patterns of malaria, hospital surveillance data from areas of sub-Saharan Africa with a wide range of perennial transmission intensities suggest that, in the highest transmission settings (prevalence >50%), the highest rates of hospital admissions and severe malaria are in children under 1 year of age. As transmission intensity decreases, the rates of hospitalization and severe malaria decrease and become more broadly distributed. However, the highest rates of severe disease remain concentrated in the youngest children (up to 5 years). It is not clear whether intense seasonality of transmission disrupts this pattern or whether the pattern persists in areas that have maintained low transmission for long enough that older children have only ever experienced low-intensity transmission.

In settings where SMC has been effectively implemented, the rates of malaria in young children should be dramatically reduced. Although the proportion of remaining burden that occurs in older children would be expected to rise, it is not clear that incidence rates, including the incidence of severe disease, would increase in older children.

If countries decide to prioritize the targeting of disease in older age groups, then the expansion of SMC to include them is likely to be an effective approach. Based on surveillance data showing the burden of malaria in this older age group, and after conducting a pilot study showing the benefit of this strategy in their setting, Senegal has implemented this expansion. The committee supported this approach as a component for implementation if the impact of such an adaptation is carefully monitored and found to provide value for money.

Implementation in less seasonal settings: Implementation of SMC in areas that do not meet the criterion of 60% of the malaria morbidity occurring within a four-month period was recognized as another possible extension. Committee members encouraged prioritization of SMC implementation in areas fulfilling the seasonality criterion before encouraging implementation in other settings. See also the discussion regarding more general guidance on chemoprevention below.

Research/evaluation needs for SMC

The following opportunities were identified during the SMC discussion. Many of these areas can be addressed as implementation research, with modifications to the operational approach evaluated using good routine surveillance data.

Implementation research to expand current guidelines

- Coverage: What approaches (e.g., to community engagement) can enhance coverage and sustain participation in rounds two to four?
- Adherence: What approaches can enhance adherence to treatment on days two and three?
- Optimal timing: Given year-to-year variations in peak transmission seasons, what approaches can optimize the timing of SMC programmes?
- How might SMC be deployed outside the Sahel? Some settings outside the Sahel experience marked seasonality and have a considerable disease burden, but drug resistance is a concern. There is a lack of empirical evidence to inform resistance thresholds beyond which SMC loses efficacy. Documentation of the impact of SMC in the context of a range of SP and AQ resistance levels is encouraged.
- What methods are most appropriate to monitor the protective effectiveness of SMC?
- SMC in children over 5 years of age may have a relatively modest impact on the burden of severe disease compared to SMC in younger children, but can likely reduce uncomplicated malaria. In addition, an evaluation in Senegal suggests that SMC given to children aged up to 10 years is associated with a ~30% reduction in malaria risk in untargeted age groups *(7)*. To what extent can SMC reduce transmission? What are the drivers of this effect? What is the value of expanding the age group targeted with SMC? What outcome measures should be evaluated?
- How should the relative efficacy, cost, feasibility and acceptability of SMC and other malaria interventions be used to inform resource allocation?
- When should SMC programmes stop? The current guideline indicates that, with an attack rate lower than 0.1 episodes per child per season, SMC is unlikely to be considered cost-effective. An effective SMC programme may reduce the attack rate below this level, but termination of the programme is likely to result in an upswing of cases. What measures of transmission intensity (e.g., parasite prevalence in children, including schoolchildren) can provide a firm basis on which to decide when to start or stop an SMC programme?

Exploring the delivery system

- Recognizing that perennial transmission settings have seasonal variation in transmission intensity, how can children under 5 years living in perennial transmission settings benefit from chemoprevention?
- IPTi is delivered through the routine immunization platform and SMC is 'owned' by the malaria programme. Is it possible to make more use of health-facility-based or outreach-based delivery of SMC? Could SMC be linked with other health contacts, e.g., immunization, nutrition, healthy child visits, school health?
- How can the longer-term sustainability of SMC be assured? It currently depends on a community cadre for delivery. Can SMC be integrated into the formal health system?

Research on drugs

- Does the use of low-dose primaquine in conjunction with artemisinin-based combination therapies (ACTs) and/or SMC impact transmission intensity?

- What is the optimal timing (low- versus high-transmission season)?
- How does any impact on transmission compare with that associated with the expansion of SMC to older children?

- Drugs for SMC: Is it possible to identify or develop a simpler drug regimen, e.g., one that does not require administration over three days or monthly treatments?

IPTp

In 1998, IPTp became the first intermittent chemoprevention strategy to be recommended by WHO. Although the policy has been updated to incorporate evolving evidence (e.g., evidence on the frequency of dosing), the aim of IPTp continues to be the reduction of malaria's contribution to adverse pregnancy outcomes, including maternal anaemia, and low birth weight due to premature delivery and/or intrauterine growth retardation. IPTp with SP has been integrated into routine antenatal care (ANC) services, but implementation has generally been suboptimal; only 31% of eligible pregnant women in Africa received the recommended three or more doses of IPTp in 2018 *(4)*.

In 2004, the recommended frequency of dosing was increased such that women should receive at least two doses of IPT after quickening, based on data from four clinical trials and an effectiveness study. In 2007, a WHO technical review group recognized the continued effectiveness of IPTp with SP in East and West Africa, despite the failing efficacy of SP for the treatment of clinical malaria. A 2013 Evidence Review Group (ERG), on the basis of a meta-analysis, concluded that IPTp with SP can provide benefit even in areas where the quintuple mutation frequency (i.e., *P. falciparum* parasites carrying the triple *pfdhfr* and double *pfdhps* mutations) reaches 95%. The same ERG was unable to establish a threshold level of malaria transmission below which IPTp with SP was no longer cost-effective, but considered the evidence insufficient to support a general recommendation for the use of IPTp with SP outside of Africa.

The current IPTp recommendation was made in 2012 and was reiterated in the 2015 *Guidelines for the treatment of malaria (5):*

> *"In malaria-endemic areas, give sulfadoxine-pyrimethamine to all pregnant women in their first or second pregnancy monthly from the start of the second trimester."*

This recommendation was based on a systematic review of seven randomized trials of IPTp in Africa, which directly compared two doses of SP with three or more doses. The increased dose frequency reduced the risk of low birth weight (RR 0.80 (95% CI: 0.69–0.94)), placental infection (RR 0.51 (0.38–0.68)) and maternal peripheral blood infection (RR 0.68 (0.52–0.89)), with no statistical evidence of variation in these effects between studies. No differences in serious adverse events were documented between the groups.

A 2019 review *(8)* of the association between SP resistance markers and IPTp effectiveness found that, although IPTp with SP can reduce low birth weight and anaemia in settings with a quintuple mutation frequency of >90%, the effect size is less than in settings with lower frequencies of these markers. For example, the reduction in low birth weight associated with IPTp with SP in high-resistance settings (quintuple mutation frequency >90%) was 7% compared to 27% in low-resistance settings (quintuple mutation frequency ≤30%) and 21% in intermediate-resistance settings (quintuple mutation frequency 30–90%). IPTp with SP did not protect against low birth weight in settings with a sextuple mutation (*pfdhps*-A581G) frequency of 37%.

WHO encourages the use of IPTp in areas of moderate to high malaria transmission in Africa, and its use in pregnant women at each scheduled ANC visit, starting as early as possible in the second trimester, provided that the doses of SP are given at least one month apart. The objective is to ensure that at least three doses are received.

Guidance has been provided on how to adapt implementation of the recommendations in response to the expanded eight-visit ANC schedule endorsed in 2016. This guidance is presented in the Adaptation Toolkit *(9)*, which was developed to support the 2016 WHO ANC recommendations *(10)*.

Opportunities for optimization

The following are primary challenges for IPTp:

- Coverage remains low, with only 31% of eligible women receiving the recommended three doses in 2018 *(4)*. This is disappointing given the solid evidence that this simple, inexpensive strategy reduces maternal anaemia, reduces the incidence of low birth weight and may improve infant survival.
- There are concerns about the impact of drug resistance on the effectiveness of SP.

In addition, there is a need to optimize malaria control in HIV-positive women who are at increased risk of malaria compared to HIV-negative women. This is especially pressing for those in whom the use of SP is contraindicated because they are taking daily cotrimoxazole.

Six reviews published to date on the barriers to and facilitators of IPTp deployment through ANC highlight that many factors have been identified and that these factors vary by country, emphasizing the importance of operational and implementation research at country level.

Consideration of alternative drugs has been included in IPTp evidence reviews since 2007 and remains an opportunity to enhance the impact of IPTp. However, despite the increasing prevalence of molecular markers of resistance to SP and its decreased curative efficacy, no drug has been shown to be superior to SP in reducing the incidence of low birth weight. It has been postulated that this may be in part due to non-malaria effects of SP, e.g., on reproductive tract infections. Continued evaluation of alternative regimens – e.g., SP+azithromycin or dihydroartemisinin-piperaquine (DHA-PPQ) – is ongoing. Clear definitions of outcomes are essential. Careful consideration should be given to composite outcomes (both maternal and neonatal), which may drive decision-making and increase the power of studies to detect differences.

Enhancing the uptake of IPTp is essential for optimization of impact. Review of the barriers to and facilitators of IPTp uptake has revealed both health system and recipient-level challenges. It is important to recognize sociocultural and individual-level factors when addressing ANC coverage and attendance issues. However, it has also been repeatedly reported that uptake of IPTp with SP remains poor, even in places with high ANC coverage, indicating a gap between ANC and IPTp coverage. It may be necessary to cultivate an awareness of and confidence in IPTp with SP among women and in their communities. At the same time, health facilities need to be adequately stocked with commodities and staffed by skilled, motivated health workers who can establish gestational age and start IPTp in the second trimester. The 2016 WHO *Recommendations on antenatal care for a positive pregnancy experience* aim to address some of these issues *(10)*.

Community-based delivery of IPTp is currently being evaluated. The aim is to have community health workers deliver IPTp without reducing ANC attendance. Integration of IPTp into the formal health system by utilizing the ANC platform for delivery is generally seen as a strength for the long-term sustainability of the strategy. However, even though ANC attendance may be high, the first visit often happens well into the second trimester, and coverage is lower for subsequent ANC visits. These issues contribute to lower coverage of IPTp and have stimulated consideration of community delivery as a means of complementing ANC. Engagement of multiple groups of actors to implement and monitor interventions can be challenging. IPTp is largely implemented by reproductive health teams, but delivery is monitored as an indicator of malaria control programmes. As general guidance on chemoprevention is developed, approaches to the engagement of other actors and sectors should be considered early in the design and implementation phases.

Prevention of malaria in pregnancy for those ineligible for IPTp-SP: IPTp with SP is not recommended in the first trimester of pregnancy and the intervention is contraindicated in HIV-positive women taking daily cotrimoxazole. Although cotrimoxazole has some antimalarial efficacy, protection is not optimal. These high-risk groups are therefore inadequately protected from malaria.

Intermittent screening and treatment (IST): IST in pregnancy is not as cost-effective as IPTp in terms of malaria and low birth weight prevention. The potential of highly sensitive rapid diagnostic tests to reduce the frequency of false-negative test results is being evaluated. When considering the cost-effectiveness of IST approaches, the value of the information generated by the screening tests should be considered. For example, in low-transmission settings, women attending ANC may form a sentinel group, drawing attention to areas with ongoing focal transmission and enabling the targeting of resources.

Methods to track low birth weight: Improved methods are needed to monitor low birth weight, ideally by capturing relevant data in routine HMIS.

IPTi

IPTi is the administration, at pre-specified times, of a full course of an effective antimalarial treatment to infants at risk of malaria, regardless of whether or not they are infected. The objective is to reduce the burden of malaria disease and death in infants. In 2010, WHO provided the following policy recommendation *(11)*:

> *"In areas of moderate-to-high malaria transmission where SP is still effective, provide intermittent preventive treatment with SP to infants (< 12 months of age) (SP-IPTi) at the time of the second and third rounds of vaccination against diphtheria, tetanus and pertussis (DTP) and vaccination against measles."*

The 2015 *Guidelines for the treatment of malaria (5)* recognized the potential of the routine immunization services within the Expanded Programme on Immunization (EPI) to deliver IPTi as part of the routine health system and defined resistance as "not high" when the prevalence of the *pfdhps540* mutation is $\leq$50%.

Prior to the policy recommendation, pilot implementation by UNICEF in districts of six countries concluded that IPTi could be easily scaled up to near universal coverage, had an acceptable safety profile and was highly cost-effective (US$ 2.50/disability-adjusted life year [DALY] averted). However, to date, only Sierra Leone has implemented IPTi at a national scale. The country adopted the intervention in 2016, piloting it in two then four districts before national roll-out in 2018. A cross-departmental technical working group brought together Ministry of Health (MoH) staff from the immunization, malaria, health education and planning departments. Implementation data are now routinely captured in the district health information system (DHIS2). A drop in coverage between the second and third IPTi doses has been documented.

Implementation was considered in the Democratic Republic of the Congo in 2016, but plans were halted when it was confirmed that the sites targeted for the intervention had a *pfdhps*540 mutation frequency over 50%. High prevalence of molecular markers of SP resistance across East and Southern Africa has likely limited consideration of IPTi implementation in these regions. Large areas in West Africa, where SP resistance profiles are more favourable, have seasonal transmission and have adopted SMC to decrease disease burden in infants and young children. Nevertheless, IPTi should still be considered as a strategy in parts of West Africa where SMC is not implemented. Other barriers to IPTi implementation have included the lack of an infant-friendly formulation of SP and the challenge of coordinating stakeholders in malaria and child health more broadly.

Opportunities for optimization

Increasing implementation: The main opportunity to enhance the impact of IPTi is to increase its implementation. The recommendation that IPTi should not be implemented in areas with high prevalence of molecular markers of SP resistance was seen as the primary barrier to its implementation for two reasons. First, the requirement for countries to measure molecular markers to determine the applicability of IPTi in their setting may be a barrier, as markers of SP resistance are no longer routinely monitored. Second, the prevalence of molecular markers of drug resistance may not correlate with the effectiveness of chemoprevention, as has been acknowledged with IPTp. However, caution is required in extrapolating findings from semi-immune pregnant women to non-immune infants.

Meeting participants recognized that the prevention of infection is likely to require less drug activity than clearing an established infection, and that the duration of prevention following treatment is likely to decrease as resistance increases. The cut-off of 50% prevalence of *pfdhps540* mutants was originally recommended, as this was the highest prevalence at which IPTi-SP had been shown to have a protective effect *(12)*. A study done in a setting where ~90% of the parasites carried the *pfdhps540* mutation showed that IPTi had no efficacy *(13)*. However, the relationship between IPTi efficacy and *pfdhps540* mutation frequencies between 50% and 90% remains unknown.

The relationship between therapeutic and preventive efficacy is unclear; since SP is no longer recommended for malaria treatment, its therapeutic efficacy is not routinely monitored. Evaluating the efficacy of SP to clear infections in parasitaemic but asymptomatic children might be considered in some settings. The development of approaches to assess the preventive efficacy of SP – for example, by monitoring the timing of malaria episodes after doses of IPTi – may be feasible in routine settings and useful in guiding countries on the likely effectiveness of IPTi.

The findings of market research assessing the drivers and barriers of IPTi implementation are consistent with the reported experiences of IPTi pilot implementation and full national implementation in Sierra Leone. At the central level, there is support to decrease the burden of malaria in infants, and implementation through routine immunization should ensure access for the target population. Integration of IPTi into immunization services, including outreach sessions, adds a preventive intervention and could increase coverage of both interventions in communities. However, careful coordination is required for training, supply and time management. As with IPTp, coordination is required between the established delivery platform, i.e., the routine immunization services, and the national malaria programme. The success of an IPTi programme will depend on strong leadership within the national and subnational EPI teams.

Extension to older age groups: A second opportunity to enhance the impact of IPTi is to consider extending the intervention to older age groups. By definition, use beyond the first year of life no longer targets infants. However, as discussed above, the burden of malaria extends beyond the first year of life, and the EPI is an evolving platform. Since the initial IPTi trials, various contacts have been added to the EPI schedule, for example, the administration of the second dose of the measles vaccine in the second year of life or later *(14)*, as well as booster doses of diphtheria and tetanus vaccines at 12–23 months, 4–7 years and 9–15 years *(15,16)*. At the same time, improvements in malaria control in many settings have been associated with a shift in the age pattern of malaria disease, although shifts in the peak ages of severe disease and malaria deaths are likely to be less marked than shifts in the ages of uncomplicated malaria cases. The ongoing RTS,S/AS01 malaria vaccine pilots have demonstrated the potential for strong partnership between the EPI and malaria control programmes, and the potential to integrate malaria control tools through new contacts. Taken together, there may be merit and opportunities for additional doses and reconsideration of the timing of chemoprevention.

The Immunization Agenda 2030 (IA2030) is being developed as a global strategy to support the ongoing evolution of the immunization programme. The intention is to enhance the reach – e.g., into

and beyond the second year of life – and impact of vaccines and vaccination platforms. Some countries already have additional contacts with children, supported by the EPI platform, for administration of non-vaccine interventions. For example, vitamin A supplementation is recommended in infants and children 6–59 months of age, and deworming is recommended for all young children (12–23 months of age), preschool (24–59 months of age) and school-age children living in areas where the baseline prevalence of any soil-transmitted infection is 20% or more. Many countries have weighing programmes where caregivers bring their children for a monthly weight check. In Sierra Leone, deworming and vitamin A are administered at 12 months. These could present additional opportunities for delivering chemoprevention.

The original IPTi studies extensively evaluated the potential of IPTi-SP to interfere with the serological response to routine vaccines. In the last decade, several new vaccines, e.g., those against pneumococcal and rotavirus disease, have been introduced in many malaria-endemic settings. The safety and immunogenicity of vaccines co-administered with IPTi-SP should be considered.

Paediatric drug formulation: The pilot implementation studies found that, although it was possible to cut and crush SP tablets for administration to young infants, this was a cumbersome process. A paediatric formulation has been developed for SMC, which would make for much easier administration. The importance of ensuring adequate dosing and of understanding the pharmacokinetics in the target age group was recognized.

The group welcomed the planned Unitaid investments in IPTi and the potential to act on these opportunities.

MDA

MDA is the delivery of malaria treatment to every member of a defined population or every person living in a defined geographic area (except to those for whom the medicine is contraindicated) at approximately the same time and often at repeated intervals. WHO recommendations in 2015 supported the use of MDA to accelerate progress towards interruption of transmission in pre-elimination settings and to ameliorate the worst effects of malaria in epidemics or complex emergencies. The outcomes of an Evidence Review Group in 2018 will be taken into consideration as part of the WHO guideline development process and may lead to updates to the current recommendations (see ERG meeting report *(17)*). Briefly, MDA has been shown to reduce transmission for one to three months across all transmission settings, although the evidence from settings with a *P. falciparum* prevalence >35% is less compelling than that from lower transmission settings. The effects of MDA are greatest when delivered with enhanced case management, surveillance and vector control. The coverage achieved is also a key driver of impact.

Population-wide MDA was employed in Sierra Leone in the setting of the Ebola epidemic in 2014–2015. The aims of the MDA were to decrease rates of fever due to illnesses other than Ebola, decrease burden on the health system, and decrease the potential exposure of malaria cases to Ebola during evaluation for fever. MDA was conducted using artesunate-amodiaquine in people over 6 months of age living in areas of high Ebola burden. Two rounds of MDA were conducted during the malaria transmission season using door-to-door distributions. Artesunate-amodiaquine (first-line treatment) was used for MDA because the combination was readily available, known to health care workers and trusted by the community. The intervention reached 2.6 million people with 95% coverage of the estimated population in the second round. One week after the first round of MDA, there was a 43% decrease in suspected malaria cases, a 47% decrease in RDT-positive malaria cases, and a 30% decrease in the number of Ebola alerts. There was no marked change in the number of non-malaria outpatient cases.

Age-targeted MDA was deployed in conflict-affected areas of Borno State in north-eastern Nigeria. An early warning alert and response system showed that malaria was the cause of 50% of reported

morbidity and mortality. Mapping was used to target areas with large populations and high numbers of internally displaced persons. Informed by modelling, it was decided to reduce the burden of malaria by targeting children under 5 years of age with MDA and to distribute long-lasting insecticidal nets (LLINs). Teams were trained and supplied using the Rapid Access Expansion Program (RAcE) for integrated community case management (iCCM). The activities were integrated with the polio teams for door-to-door delivery, data management and monitoring. In Borno State, four distributions of artesunate-amodiaquine to children 3–59 months were delivered in 2017–2019. In the first year, the campaign reached 1.1 million children with a coverage of 96% in targeted areas. Evaluation using routine data that were available from August 2016 onwards showed a 70% increase in confirmed malaria cases, pre- and post-MDA, in the target population (children under 5) in non-intervention areas, whereas intervention areas experienced only a 6% increase. Contemporaneous comparisons made in individuals over 5 years of age provided contextual information: In non-intervention areas, there was a 54% increase in malaria cases, and in intervention areas, there was a 45% increase. Though planned, LLIN distribution was not fully implemented. Population mobility in the area was high, which had particular implications for the effectiveness of LLIN distribution.

Overall, these examples illustrate the considerable potential impact of age-targeted MDA in complex situations. Cross-cutting challenges included coordination – both in initial consensus-building among stakeholders and in commodity procurement and distribution.

Opportunities for optimization

Given WHO's limited endorsement of MDA as an approach for disease burden reduction, specific opportunities to optimize MDA were not discussed in detail. However, relevant discussion of the general guidance on the use of chemoprevention (below) applies to MDA.

Updated handbooks for the use of chemoprevention in humanitarian emergencies are planned, based on the experiences described above.

Care is needed when considering the use of potentially cardiotoxic drugs where Chagas disease is co-endemic with malaria. Chagas disease induces abnormalities of myocardial repolarization, which predisposes individuals to cardiac arrhythmias.

Other potential chemoprevention use cases

Two other use cases of chemoprevention that do not fit into the above categories were discussed. Although the potential role of malaria chemoprevention was not discussed for children with other conditions (e.g., sickle cell disease, malnutrition, etc.) it was recognized that there may be specific situations in which the intervention should be contemplated.

IPT in schoolchildren (IPTsc)

This is an approach to decrease the burden of malaria in school-aged children. While rates of mortality and severe disease are low in this age group, prevalence of infection can be high, especially in Africa. Malaria has adverse effects on the health of students and their educational outcomes. School-age children are not specifically targeted by other malaria interventions and are less likely than others to benefit from vector control interventions. For example, they are the age group least likely to use LLINs. Nevertheless, school-age children are thought to be significant contributors to *P. falciparum* transmission. In some settings, schoolchildren benefit from screening for hearing and sight impairment, immunization, deworming and other health promotion activities that take place in schools and could present opportunities for malaria chemoprevention.

IPTsc has been shown to decrease infection, anaemia and clinical malaria in students, improve their educational attainment and possibly decrease transmission in the surrounding community. The

choice of drug is an important consideration. Monthly DHA-PPQ prevented 96% of clinical malaria episodes and was well tolerated in one study *(18)*. By contrast, SP+AQ was poorly tolerated, resulting in increased absenteeism due to abdominal pain and vomiting.

Schools are an attractive platform for the delivery of chemoprevention, as it could be integrated with other interventions. While this strategy is promising, there were concerns about the extent to which countries should prioritize interventions in this target group given the limited funds available for malaria control, and the need to balance the value of child health and survival, school achievement and transmission reduction outcomes.

IPT post-discharge (IPTpd)

Children under 5 years of age who were admitted to hospital for severe anaemia, including but not limited to severe anaemia associated with malaria, can experience high rates (e.g., five-fold increase) of mortality in the six months following hospital discharge *(19)*.

A randomized clinical trial of IPTpd evaluated the effect of lumefantrine-artemether administered one and two months after discharge to children under 5 years of age who had been admitted with severe malarial anaemia (haemoglobin of <5g/dl and parasitaemia). The intervention, sometimes referred to as post-discharge malaria chemoprevention (PMC), decreased the composite end point of death, severe anaemia or severe malaria by 31% (95% CI: 5–50) in Malawi. A study in Kenya and Uganda demonstrated that the administration of DHA-PPQ to children admitted for all-cause severe anaemia at two, six and 10 weeks after discharge reduced all-cause readmission or death by 35% (95% CI: 22–46%).

These studies draw attention to a vulnerable but accessible group of children who may benefit from a pragmatic intervention. Additional studies are needed to evaluate the role of iron supplements and/or antibiotics post-discharge, and the risk of bone marrow suppression associated with some antimalarial drugs. Measuring haemoglobin and other relevant clinical biomarkers during the immediate post-discharge intervention period may help to elucidate the mechanism of effects and anaemia etiology, and clarify the perceived risk of adverse events in the post-intervention period.

Choice of drug for chemoprevention

Chemoprevention currently depends heavily on SP (IPTp, IPTi) and SP and AQ (SMC), both of which benefit from widescale availability and familiarity, are generally affordable, are safe and are not used in first-line treatments. There is interest and some experience in the use of DHA-PPQ and pyronaridine-artesunate for chemoprevention, but there is a need for caution when considering the use of such drugs for chemoprevention. It would be counterproductive to accelerate the development and spread of resistance to potentially important therapeutic interventions.

The development and spread of drug resistance is likely to be an inevitable consequence of widespread drug use. The impact of chemoprevention on the emergence and spread of resistance is not well documented, although modelling studies and empirical observation suggest that the effect of IPTi on drug resistance is likely to be modest *(20)*. Although the level of drug activity required to prevent an infection is less than the level required to eliminate an existing infection, the duration of post-treatment prophylaxis decreases as resistance increases.

SP is widely used in chemoprevention and remains effective in settings where a high proportion of parasites carry molecular markers of SP resistance. The frequency of SP-resistant parasites has remained high even in places where SP has not been used widely for many years. By contrast, chloroquine sensitivity has been shown to return ~10 years following its replacement as first-line treatment in some countries (e.g., Malawi, Zambia), but not in others (Kenya). The potential use of chloroquine for malaria chemoprevention merits further consideration.

The use of antimalarial drugs with matched half-lives may retard the development and spread of resistance. Drugs with long half-lives may be expected to have the greatest benefit when used for chemoprevention, whereas short half-life drugs are generally adequate for treatment.

The addition of low-dose primaquine could potentially reduce the period of transmissibility of resistant parasites in individuals who receive chemoprevention, while ivermectin could potentially reduce the risk of onward transmission by affecting the longevity of biting *Anopheles* mosquitoes. These approaches could help to reduce the transmission of drug-resistant parasites.

Evidence is emerging that some drugs have opposing effects on the selection of parasites with markers of resistance to specific drugs. For example, lumefantrine in lumefantrine-artemether and amodiaquine (e.g., in SP+AQ or ASAQ) exert opposing selective effects on single-nucleotide polymorphisms in *pfcrt* and *pfmdr*. Lumefantrine and chloroquine also exert opposing selective pressures on these genes. This phenomenon raises the possibility that combinations – or sequential use – of some pairs of drugs may ameliorate the spread of resistance, which might otherwise be associated with their large-scale use for chemoprevention.

The choice between drugs with predominantly pre-erythrocytic versus blood-stage activity may influence the level of efficacy, risk of rebound[1] and impact on resistance of chemoprevention strategies. There may be less concern about possible rebound effects for drugs targeting blood-stage parasites, as these allow some exposure to infection and the development of naturally acquired immunity. This would be the case for DHA-PPQ. However, although the long half-life of PPQ leads to convenient once daily dosing, the mismatched half-lives of DHA and PPQ may contribute to the emergence of resistance, especially if the combination is used for both treatment and prevention.

Routine monitoring of molecular markers of resistance is encouraged as an early warning of the spread of resistance and to enable monitoring of trends. These tests may be run on samples collected at baseline in routine in vivo therapeutic efficacy studies of other antimalarial drugs.

The Medicines for Malaria Venture is working to develop drugs for chemoprevention of vulnerable populations. Historically, the primary use case scenario for malaria medicines has been treatment, rather than prevention. Target candidate profiles (TCPs) are used to describe the characteristics of individual molecules or compounds undergoing formal pre-clinical or early clinical assessments, and target product profiles (TPPs) are used to guide the development of health products containing TCPs. The development of drugs for chemoprevention is drawing on TCPs targeting asexual blood stages and liver schizonts. Key considerations are simplicity of use (e.g., single dose) and duration of action. A drug providing several months' protection could conceivably be administered intramuscularly.

Antimalarial monoclonal antibodies (mAbs) could be another approach to protect people from malaria. First-in-man studies of mAbs designed to protect against infection for six months are expected to start in 2020.

General guidance on chemoprevention

The group agreed that overarching guidance on chemoprevention should be developed as an umbrella recommendation for the current policies. This should be a broad statement recommending chemoprevention as an important approach for malaria burden reduction on the pathway to elimination.

The broad guidance should allow for flexibility in its adaptation to specific country contexts based on i) the purpose of chemoprevention, in terms of reduction of morbidity and mortality, or of

[1] Rebound in malaria is a period of increased risk of malaria disease following the use of an intervention that effectively protects against malaria. This is thought to be due to impairment of the acquisition or maintenance of naturally acquired immunity against malaria.

transmission; and ii) the intended target group, defined by parameters that describe their risk factors (e.g., age, physiological or pathological condition, epidemiological setting, geographic or institutional location).

Specific guidance on IPTp, IPTi, SMC and MDA should give countries flexibility to adapt these strategies based on the country-specific epidemiology of malaria, the availability of appropriate delivery platforms and any other critical determinants, such as ecological factors, vulnerabilities, operational feasibility and community acceptance.

Global policy guidance should draw attention to specific issues (e.g., safety parameters relevant to individual drugs, pros and cons of different approaches to delivery in a range of settings), but should leave the choice of delivery platform to countries. If a specific delivery approach or platform is recommended, based on the available evidence at the time, the policy guidance should be open to other feasible and acceptable delivery approaches that maintain or improve the effectiveness and safety of the intervention.

Opportunities should be sought and taken to ensure that individuals in target groups receive the chemoprevention intended for them. For example, health staff should ensure that pregnant women attending the EPI with their children are up-to-date with their ANC, including IPTp. Similarly, children accompanying mothers to ANC present an opportunity to boost IPTi and SMC coverage. Missed opportunities for vaccination, chemoprevention and other interventions could also be reduced by screening children before discharge from hospital and maximizing coverage of key interventions in this particularly vulnerable population.

Adaptations of existing recommendations should be driven by data and introduced with the intention of optimizing effectiveness, while ensuring the safety of the intended recipients. Support should be available to countries as they adopt and adapt the suite of interventions to their country contexts. This includes flexibility and support from funders to adapt interventions from the current, more prescriptive policies. Formal evaluation of all adaptations is strongly encouraged.

Evidence needs will differ depending on the proposed adaptation. For instance, from a biological perspective, it is likely that a fifth round of SMC would have a predictable impact, depending on the burden of disease at the time of the additional round and the coverage achieved. It would be important to understand the factors affecting the feasibility and acceptability of delivery. In this case, a randomized controlled trial would not likely be necessary, as these questions can be addressed through programmatic evaluation. In addition, an RCT might not be particularly useful given the challenges of statistically powering a study to demonstrate an incremental impact of five versus four rounds of SMC. In such situations, it is important to ask if there is any reason to believe that safety issues would arise from the adaptation – in this instance, that five rounds of SMC would be less safe than four. It was noted that, in this particular instance, a cluster-randomized trial has been done *(21)*. It was also noted that there are precedents – such as the introduction of the Men A vaccination – for implementation in the absence of efficacy data which, as in the case of MenAfrivac, may be obtained following introduction.

It is important to ensure the design of robust assessments to enable monitoring, learning and evaluation. Countries may need support to develop frameworks for impact evaluation, ideally drawing on a model of impact. This is particularly important where substantial departures from previous experience are planned. Such evaluations may be done through effective use of competent routine surveillance or, depending on the situation, may require systematic collection of non-routine data (birth weight, anaemia, infection status, etc.) to generate evidence for future decision making. The WHO Global Malaria Programme (GMP) was encouraged to ensure clarity about the types of information and evaluation designs needed to inform different types of decisions. Linkages between national malaria control programmes and local researchers, and the availability of relevant expertise on evaluation, were identified as key facilitating factors. It will be important to discuss and share

evaluation designs and findings with WHO and other countries in order to facilitate learning across the malaria-endemic world.

There is a broad need to support capacity development in the conduct of impact evaluation, as well as implementation and operational research. Such work should feed into Malaria Programme Reviews, which, in turn, should inform the development of prioritized implementation research agendas.

Conclusions

There was general agreement that broader, less restrictive guidance on chemoprevention would be useful for facilitating the implementation of effective malaria control on the path to malaria elimination. In developing such guidance, it is important to specify the targeted outcome, as this will inform the design of the intervention strategy, including the target population, choice of drug, timing and delivery methods to be utilized. These components may not need to be specified in the broad guidance, but will need to be adapted by countries as they employ different approaches to achieve their country-specific malaria control targets. In the adaptation of chemoprevention strategies, the following aspects should be considered: Does the intervention apply to the local epidemiology? Are there reasons why additional safety concerns (including rebound phenomena) could arise? Does the biology of the drugs and parasites align with the intervention design? What are the optimal approaches to delivery? How will the intervention be evaluated to inform the development of future strategies and to document impact?

Countries, donors, implementing partners and WHO should work together to realize the full impact of more flexible and tailored chemoprevention strategies to reduce malaria burden and transmission.

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Annex 1. Breakout group discussions

Breakout groups discussed the following issues: i) potential innovations in implementation; ii) recommendations that merit development or review; iii) research needs; and iv) a synthesis of key issues.

Implementation innovations

Before taking steps to deviate from established practice, all efforts should be made to optimize implementation of existing policies, for example, through improved health promotion, social mobilization or other interventions. If round-three coverage of SMC is low, it makes little sense to attempt to introduce a fourth or fifth round.

Innovations should be piloted in a limited area where the safety and impact of the modified approach can be evaluated before deciding to expand it more widely. Issues of context and the transferability of learning from the pilot to an expanded programme should be considered in the planning stage. WHO was encouraged to provide guidance for countries on the design of evaluations to maximize the utility of pilot activities.

Meeting participants were comfortable endorsing an increase in the number of rounds of SMC in settings where this can be justified on epidemiological grounds and would prioritize this over expansion to new geographic areas.

The group encouraged the implementation and evaluation of IPTi in settings where the baseline *pfdhps*540 mutation frequency is >50%. This should contribute to the evidence base and help to inform a review of the reference to this mutation frequency in the existing guidance.

The group also encouraged evaluation of the safety and impact of increasing the number of IPTi SP doses alongside other routine contacts with the EPI/child health services beyond the first year of life.

Recommendations to develop or review

The following recommendations were identified as priorities for review or development:

- A generic, overarching recommendation on the use of chemoprevention should be developed. This should be formulated to maximize impact and support flexibility in implementation. For example:
    - Specify the need to target the highest risk groups, whoever these may be in a specific setting.
    - Encourage the use of local epidemiological data, including quality-assured hospital data, to inform key decisions about the number of treatments, target age and timing.
    - De-link the intervention (e.g., IPTi) from the delivery strategy (e.g., the EPI) and encourage identification and use of the most appropriate delivery channel or delivery across a range of platforms.

  Such generic chemoprevention guidance should encourage strong monitoring and evaluation of safety and impact. It may also enable marginalized communities with poor access to routine services (e.g., nomadic pastoralists) or other specific risk groups to benefit from the potential of chemoprevention.
- IPTp: Support national malaria control programmes in deciding where and how this strategy will be implemented. Ensure adequate evaluation (e.g., using quality-assured hospital data) when there is a change in national policy.

- Develop a generic guideline on the emergency use of chemoprevention, with a view to more flexible invocation of chemoprevention interventions in emergencies.
- Develop guidance on learning from evaluations.

Research needs

The group recognized the value of implementation and operational research early in the development of an innovative strategy. Such research was deliberately included early in the development of SMC, perhaps because the strategy was not easily added to existing platforms, and uptake and implementation has been relatively swift. The importance of implementation research on IPTp has been highlighted, recognizing the problems faced in maximizing its coverage.

Several research needs were identified in addition to those identified in the plenary discussions:

- Appropriate formulations of malaria medicines for chemoprevention, e.g., child-friendly, dispersible, long-acting, should be developed.
- Medicines for chemoprevention in pregnancy: This will always be challenging, especially for preventive rather than curative indications. Evaluation of existing drugs will be much more rapid than the development of new drugs specifically for use in pregnancy.
- Drug resistance: There is a need to understand the relationship between chemoprevention and drug resistance, measured using molecular markers and/or in vivo efficacy studies, e.g., in asymptomatic infections or post-treatment reinfection studies in target groups exposed to malaria transmission.
- When should chemoprevention (e.g., IPTp) be stopped?
- Alternative delivery channels should be explored for delivering chemoprevention to target groups.
- It is important to understand risk groups within risk groups, and how best to reach those at highest risk. For example, among pregnant women, *primigravidas*, HIV-infected pregnant women, adolescents and those living in high-intensity transmission settings are at greatest risk. Specific approaches may be needed to deliver chemoprevention to them. It will be important to ensure that inequities and potential barriers are understood and dealt with.

The MESA-TRACK tool summarizes information about relevant ongoing research projects on IPTp,[2] IPTi,[3] SMC[4] and MDA.[5]

Synthesis of key issues in malaria chemoprevention

Terminology

Provide clear definitions of what is meant by the various terms: chemoprevention, preventive therapy, chemoprotection, chemoprophylaxis, etc., and IPT, IPTp, IPTi, IPTpd, IPTsc, SMC, MDA, etc. This is important, as the currently recommended monthly dosing of IPTp and the stated intention of SMC to provide continuously protective blood concentrations of antimalarial drugs means they could both be considered chemoprophylaxis. Likewise, SMC could be considered a form of age-targeted MDA.

[2] https://mesamalaria.org/index.php/mesa-track/deep-dives/intermittent-preventive-treatment-pregnancy-iptp
[3] https://mesamalaria.org/index.php/mesa-track/deep-dives/intermittent-preventive-treatment-infants-ipti
[4] https://mesamalaria.org/index.php/mesa-track/deep-dives/seasonal-malaria-chemoprevention-smc
[5] https://mesamalaria.org/index.php/mesa-track/deep-dives/mass-drug-administration-mda

Transferability

Provide guidance on transferability, i.e., the extent to which evidence generated in one situation may be applicable to another, and encourage the use of the following "lenses":

- Safety: Is there any reason that the safety profile of an adaptation may differ from that of the strategy upon which it is based?
- Biology (e.g., drugs and parasites): Does the adaptation make biological sense?
- Epidemiology: Does the adaptation target the highest risk group(s) in the highest risk places at the highest risk times?
- Delivery platforms: What is the best option to deliver the intervention to the target group? Delivery could be through some sort of facility (e.g., antenatal clinics, immunization clinics, hospitals, schools) or through a community-based approach (e.g., community-based IPTp is being explored as a complement to facility-based delivery).
- Programme evaluation/learning: What is the best design and approach to data capture in order to ensure strong learning from the adaptation?

Use cases

Be clear about:

- the intention – to reduce morbidity and mortality, or to reduce transmission
- the populations to be targeted, considering:
    - age: <1yr, <2yr, <5yr, 5–15yr, adults
    - pregnancy
    - hospitalized children with severe anaemia
    - emergencies
    - schoolchildren
    - special at-risk groups
    - everyone
- the implications of seasonal variation in transmission intensity
- potential delivery platforms:
    - facilities, e.g., clinics, hospitals, schools
    - communities, e.g.,
        - case management moving from the clinic to communities
        - IPTp moving from ANC to community
        - SMC moving from community to EPI clinics (IPTi)
        - MDA in communities.

Evaluation and learning

- What are the best approaches to document impact and inform future guidance?
- Ensure that costs are tracked and evaluate cost-effectiveness to inform rational, prioritized resource allocation for the control of malaria.

Choice of drug

- What are the properties of the drugs needed for the different use cases?
- Avoid using the same drug for case management and prevention.

Annex 2. Meeting agenda

Wednesday, 16 October 2019		
09:00 – 09:15	Welcome and opening remarks	Dr Pedro Alonso
09:15 – 09:30	Meeting objectives	Dr David Schellenberg
09:30 – 10:00	The age pattern of clinical malaria, severe disease and malaria death	Professor Robert Snow
10:00 – 10:30	Chemoprevention: a history and overview	Professor Brian Greenwood
Session 2 – Seasonal Malaria Chemoprevention		
11:00 – 12:00	A summary of the WHO/TDR technical consultation on seasonal malaria prevention: evidence review and data requirements for policy update	Dr Peter Olumese
12:00 – 12:30	Discussion	Chair
Session 3 – Intermittent Preventive Treatment in pregnancy (IPTp)		
13:30 – 14:00	IPTp: the evolving evidence base and WHO policies	Dr Larry Slutsker
14.00 – 14.20	IPTp implementation: an overview of barriers and facilitators	Dr Paula Ruiz-Castillo
14:20 – 14:40	Changes in WHO antenatal guidelines since 2010	Dr Özge Tuncalp
14:40 – 15:00	Exploring community-based delivery of IPTp	Dr Franco Pagnoni
Session 4 – Intermittent Preventive Treatment in infants (IPTi)		
15:30 – 15:50	From evidence to WHO policy	Dr Peter Olumese
15:50 – 16:10	Early experience of IPTi implementation	Dr V. Buj De Lauwerier
16:10 – 16:20	Experience with IPTi – Sierra Leone	Dr Samuel Smith
16:20 – 16:30	Experience with IPTi – DRC	Dr Martin de Smet
16:30 – 16:45	Why has IPTi not been implemented?	Dr Celine Audibert
16:45 – 17:00	Routine immunization services: an evolving platform	Dr Laura Nic Lochlainn
17:00 – 17:30	Discussion: Changes in epidemiology, biomedical understanding and child health programmes: implications for IPTi policy?	Chair

Thursday, 17 October 2019		
Session 5 – Mass Drug Administration (MDA) and malaria chemoprevention strategies being evaluated		
09:00 – 09:30	The evolution of WHO policies on MDA and evidence-base: transmission reduction and mortality reduction use cases	Dr Andrea Bosman
09:30 – 09:45	Experience of implementing MDA for disease reduction: Age-targeted MDA in fragile situations: northern Nigeria	Dr Lynda Ozor
09:45 – 10:00	MDA in emergency settings: Sierra Leone	Dr Sam Smith
10:00 – 10:15	IPT in school children	Dr J. Nankanbirwa
10:15 – 10:30	IPT post discharge	Professor Kamija Phiri
Session 6 – Chemoprevention – the tools		
11:00 – 11:20	Drug resistance and implications for the choice of drug	Professor Miriam Laufer

11:20 – 11:40	MMV candidate Product profiles for IPTp, SMC, IPTi and MDA – a need for updates?	Dr André-Marie Tchouatieu
Session 7 – Perspectives from endemic countries		
11:40 – 12:30	Perspectives from endemic countries and general discussion	All
Session 8 – Group Work		
13:30 – 15:00	Group work: 1. A framework to enhance impact of malaria chemoprevention in the short (5yr), medium (5-10yr) & longer term 2. Improving WHO guidance on chemoprevention: which policies & principles to consider	Working groups
15:30 – 16:15	Presentation & discussion of working groups' outputs	Working groups
16:15 – 16:40	Consensus building	Chair
16:40 – 16:45	Summary of points of agreement	Rapporteur
16:45 – 16:55	Proposed next steps	Chair
16:55 – 17:00	Closing remarks	Dr Pedro Alonso

Annex 3. List of participants

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