Background Paper

Full Evidence Report on the RTS,S/AS01 Malaria Vaccine

Prepared by the Malaria Vaccine Implementation Programme (MVIP) Programme Advisory Group (PAG) in its capacity as the RTS,S SAGE/MPAG Working Group to support the joint review of the RTS,S/AS01 malaria vaccine by the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG).

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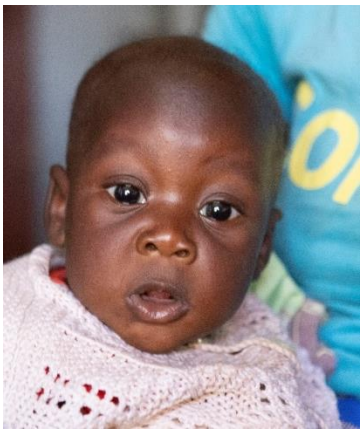
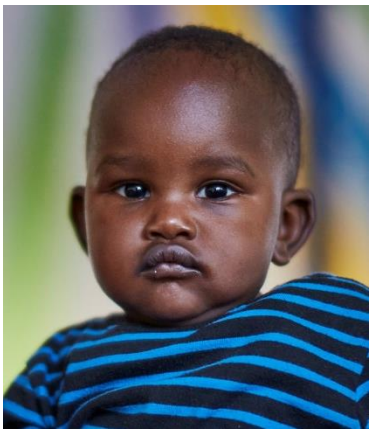




The first children to be vaccinated with the malaria vaccine as part of the MVIP in Malawi, Ghana and Kenya (Photo credit: ©WHO/M.Nieuwenhof; ©WHO/F.Combrink; ©WHO/Neil Thomas)

Content

List of abbreviations

AACVS	African Advisory Committee on Vaccine Safety
Anti-CS	Anti circumsporozoite antibody
ACTs	Artemisinin-combination therapies
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
ATP	According to Protocol
AVPU	Alert, Voice, Pain, Unresponsive
CDC	Centers for Disease Control and Prevention
CHMI	Controlled Human Malaria Infection
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CSP	Circumsporozoite protein
DALY	Disability-adjusted life year
DHS	Demographic and Health Survey
DSMB	Data and Safety Monitoring Board
DSS	Demographic Surveillance System
DTP	Diphtheria, Tetanus, Pertussis
DTP3	Third Dose of DTP vaccine
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
FIC	Fully immunized child
GACVS	Global Advisory Committee on Vaccine Safety
GCS	Glasgow Coma Scale
GDP	Gross domestic product
GMT	Geometric mean titres
GSK	GlaxoSmithKline
GTS	Global Technical Strategy
HBHI	High burden to high impact
HepB	Hepatitis B
HHS	Household survey
Hib	Haemophilus influenzae type b
HIV	Human Immunodeficiency Virus
HUS	Health utilization study
ICER	Incremental cost-effectiveness ratio
IEC	Information, Education and Communication
IPTi	Intermittent preventive treatment of malaria in infants
IPTp	Intermittent preventive treatment of malaria in pregnancy
IRS	Indoor Residual Spraying
ITN	Insecticide-Treated Net
JTEG	Joint Technical Expert Group
KEMRI	Kenya Medical Research Institute
LLIN	Long-Lasting Insecticidal Net
LSHTM	London School of Hygiene and Tropical Medicine
LP	Lumbar Puncture
MCV1	First Dose of Measles-Containing Vaccine

MICS	Multi-Indicator Cluster Survey
MIS	Malaria Indicator Survey
MoH	Ministry of Health
MPAC	Malaria Policy Advisory Committee
MPAG	Malaria Policy Advisory Group
MRC	Medical Research Council
MVIP	Malaria Vaccine Implementation Programme
MVPE	Malaria Vaccine Pilot Evaluation
NICD	National Institute for Communicable Diseases
NRA	National Regulatory Agency
NVIP	Kenya National Vaccines and Immunization Programme
PAG	Programme Advisory Group
PCGs	Primary child caregivers
PCR	Polymerase Chain Reaction
PCV	Pneumococcal conjugate vaccine
PfPR	*Plasmodium falciparum* parasite rate
PIE	Post-Introduction Evaluation
PSU	Primary sampling units
PV	Pharmacovigilance
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
RR	Risk Ratio
RTS,S-1	First dose of RTS,S/AS01 vaccine
RTS,S-2	Second dose of RTS,S/AS01 vaccine
RTS,S-3	Third dose of RTS,S/AS01 vaccine
RTS,S-4	Fourth dose of RTS,S/AS01 vaccine
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunization
SAP	Statistical Analysis Plan
SE	Study End
SMC	Seasonal malaria chemoprevention
SP	Sulfadoxine-pyrimethamine
SV	Seasonally delivered RTS,S vaccination in seasonal settings
TOR	Terms of Reference
UNC	University of North Carolina at Chapel Hill
VR	Village Reporters
WHO	World Health Organization

1 Executive Summary of RTS,S SAGE/MPAG Working Group's assessment and proposed recommendations

Information available preceding the Malaria Vaccine Implementation Programme

In July 2015, based on the results from the Phase 3 trial of the malaria vaccine RTS,S/AS01, the European Medicines Agency (EMA) issued a positive scientific opinion on the vaccine under Article 58, concluding that the vaccine had an acceptable safety profile and that the benefits of the vaccine outweighed the risks. The Phase 3 trial of the RTS,S/AS01 malaria vaccine was conducted in two age-groups, with the first vaccine dose given either between the ages of 6 and 12 weeks or between 5 and 17 months. WHO issued a position paper summarizing the assessment and recommendations for this vaccine. The vaccine was efficacious, with the potential to provide important impact when added to current malaria control interventions. It was well-tolerated with a known association with febrile seizures.

Three potential safety signals were noted in the Phase 3 trial. First, in children in the older age category, a higher number of meningitis cases occurred in the malaria vaccine group compared to the control group. However, excess meningitis cases were not temporally related to the timing of vaccine doses, were clustered at 2 of 11 trial sites, and there were a range of etiologies in the cases identified. In addition, an excess of meningitis was not seen in children vaccinated in the younger age group. Whether the increase in meningitis was due to chance or represented a true adverse effect of the vaccine was unknown. Second, in children in the older age group, in the context of a statistically significant decrease in all forms of severe malaria combined, there was an increased number of cerebral malaria cases (a subset of severe malaria) in the malaria vaccine groups compared with the control group. This finding was from an unplanned *post-hoc* analysis and its significance in relation to vaccination was unclear. An excess of cerebral malaria was not seen in children vaccinated in the younger age group. Third, and also in an unplanned *post hoc* analysis, there was an imbalance in mortality among girls, with about 2-fold higher deaths among girls who received RTS,S/AS01 than among girls who received comparator vaccines (p=0.001); the ratio of deaths among boys was slightly lower in the RTS,S/AS01 arms versus the control arm. A relationship between the RTS,S/AS01 vaccine and these findings has not been established. The EMA and WHO advisory bodies concluded that all these described safety signals may have arisen by chance.

The vaccine had a larger impact on malaria when given at 5-17 months of age and WHO, on advice from SAGE and MPAC, agreed that the vaccine, given as a 4-dose schedule to children from 5 months of age, could have high impact, but recognized there were outstanding questions to be addressed before a recommendation for broader use could be made. Recognizing that in children who received 3 doses, there was an initial reduction in severe malaria, but this was balanced by an increase in severe malaria from around 18 months after the initial vaccine course, an important question was whether it was operationally feasible to reach children at high coverage with a 4-dose schedule (with the 4th dose provided around 2 years of age); and consequently, the extent to which the protection demonstrated in children aged 5 - 17 months in the Phase 3 trial could be replicated in the context of use of the vaccine in routine health systems. Other questions to be addressed were impact of the vaccine on mortality (including gender-specific mortality) when it was in routine use and whether the excess cases of

meningitis and cerebral malaria identified during the Phase 3 trial were causally related to the RTS,S/AS01 vaccination.

To respond to these outstanding questions, WHO recommended that pilot implementations using the 4-dose schedule, with rigorous evaluation be conducted, and that the pilot should include sufficiently large populations of children 5-17 months of age in 3-5 distinct epidemiological settings in sub-Saharan Africa in moderate to high transmission settings. The Malaria Vaccine Implementation Program (MVIP) was therefore conceived, designed and initiated to support delivery of RTS,S/AS01 through routine immunization programmes, and the collection of evidence on safety, impact, and operational feasibility in routine use.

MVIP and Malaria Vaccine Pilot Evaluation (MVPE)

The MVIP has three objectives:

1. To further characterize vaccine safety in the context of a routine immunization programme, with special attention to the safety signals observed in the Phase 3 trial (meningitis, cerebral malaria, excess mortality in girls compared to boys).
2. To evaluate the vaccine's impact on severe malaria and all-cause mortality; and
3. To assess the programmatic feasibility of delivering the recommended four-dose schedule, including new immunization contacts, in the context of routine health service delivery.

A Framework for WHO recommendation on RTS,S/AS01 malaria vaccine (Framework), endorsed by SAGE and MPAG in 2019, lays out how data from the MVIP will inform WHO guidance. The Framework endorses a step-wise approach to anticipate how and when data collected through the MVIP can inform WHO recommendations on use of RTS,S/AS01 beyond the pilots. The aim of the step-wise approach is to ensure a recommendation is made as soon as the risk-benefit of the vaccine can be established with the necessary level of confidence, such that the vaccine would not be unnecessarily withheld from countries in need, if it is found to be safe and beneficial. Thus, a WHO recommendation can be made if and when concerns regarding the safety signals are satisfactorily resolved, and severe malaria or mortality are assessed as consistent with a beneficial impact of the vaccine. Noting that data from studies conducted since 2015 show that children living in areas of perennial moderate to high malaria transmission benefit from 3 or 4 doses of the vaccine, and that attaining high coverage of new vaccines, particularly in the second year of life takes time, the Framework clarified that a recommendation was not predicated on attaining high coverage, including high coverage with the 4th vaccine dose.

An evaluation protocol and statistical analysis plan were developed and reviewed by external experts and are publicly available. The MVIP is coordinated by WHO in close collaboration with ministries of health (MoH) in the three participating countries - Ghana, Kenya, Malawi - and a range of in-country and international partners. The MoH of the pilot countries have introduced the RTS,S/AS01 vaccine through their childhood immunization services using routine vaccine introduction strategies and methods. In-country research partners are leading the evaluation of the RTS,S/AS01 vaccine pilot implementation, planned over 4 years. Within the pilot region in each country, districts or similar areas were randomized to introduce the vaccine in 2019, or to delay introduction until a decision is reached about safety and effectiveness. The areas where introduction was delayed serve as comparison areas for the purpose of

the evaluation. The scale of the introduction and duration of the evaluation was chosen in order to be able to measure the impact of vaccine introduction on child survival. Delivery of RTS,S/AS01 in each country is being monitored by the EPI programme, and uptake of the vaccine is being assessed independently through household surveys, conducted about 18 months and 30 months after introduction of the malaria vaccine. Surveillance for severe malaria and other conditions is being conducted through sentinel hospitals where diagnostic procedures have been strengthened, and surveillance for mortality has been established in the community throughout the implementation and comparison areas. Mortality surveillance aimed to build on, and substantially expand, existing vital registration systems. Hospital and mortality surveillance started in each country when the malaria vaccine was introduced or shortly afterwards.

Safety: Through April 2021, 24 months of data after the MVIP started, sufficient data had accrued to evaluate safety concerns in a primary analysis. Based on the analyses of these data, the MVIP Data Safety and Monitoring Board (DSMB) concluded that the safety signals seen in the Phase 3 clinical trial (2009 – 2014) were not seen in the pilot implementation. The MVPE results showed no evidence of an excess of meningitis, cerebral malaria, or gender-specific mortality comparing age-eligible children living in implementation areas with those in the comparison areas. Additionally, based on data reviewed from the national pharmacovigilance (PV) programmes and ongoing GSK Phase 4 studies, the DSMB did not find evidence of new conditions that warrant closer safety tracking. Notably, the safety signals seen in the Phase 3 trial have also not been observed in the pooled safety data from Phase 2 trials of RTS,S/AS[1] in the trial of seasonal use of RTS,S/AS01 with or without seasonal malaria chemoprevention[2],nor in a soon to be published trial on fractional dose of RTS,S/AS01 (Personal communication, Christian Ockenhouse, MD, PATH). The African Advisory Committee on Vaccine Safety (AACVS), the Global Advisory Committee on Vaccine Safety (GACVS), and the RTS,S SAGE/MPAG Working Group (referred to hereafter as Working Group) agreed with the DSMB conclusions.

Impact: The DSMB concluded that the MVPE findings demonstrated effectiveness of RTS,S/AS01 vaccine against severe malaria, with a 30% reduction in severe malaria, and a 21% reduction in hospitalization with malaria parasitemia, both of which were statistically significant.

As anticipated, the results from the pilot evaluation through April 2021 were insufficiently powered to detect an effect on mortality. Nonetheless, a non-statistically significant reduction in all-cause mortality (excluding accidents/trauma) was also seen with a size of effect consistent with expected impact. The Working Group agreed with the DSMB conclusions.

Feasibility: The primary decisions regarding a broader recommendation for RTS,S/AS01 are to be based primarily on safety and impact considerations, however, the available feasibility data are encouraging. This assessment was based on the following observations:

Despite RTS,S/AS01 being a new vaccine delivered through EPI and requiring an expanded schedule, reasonably high coverage of the first three doses was achieved in all three pilot countries. This was achieved in a relatively short time period and in the context of substantial challenges to the health system due to the COVID-19 pandemic. While it is too early to assess fourth dose coverage, preliminary information suggests drop-out rates between dose 3 and dose 4 have been around 19-30% in Malawi

and Ghana (after 9-10 months of implementation). Insufficient time has passed since 4th dose introduction to assess drop-out rates in Kenya.

Malaria vaccine introduction did not have an impact on the uptake of routine vaccinations, nor did it have an impact on health care seeking behaviours for febrile illness, use of insecticide-treated nets (ITNs), or other child health activities such as deworming.

In the midline household surveys, malaria vaccine uptake was 69-75% among children who had not used an ITN in the previous night, indicating the vaccine reaches children who may have lower access to, and lower use of, other malaria prevention measures. Introduction of the vaccine ensured that access to at least one malaria prevention tool (ITNs or vaccine) was expanded substantially.

Based on qualitative studies conducted as part of the MVIP, care givers and health care providers generally had positive attitudes towards the vaccine. Further work is required to improve community sensitization and engagement; to work with health care providers on guidance around provision of missed or off-schedule doses and to reduce missed opportunities for vaccination (including other EPI vaccines); and to assure proper data recording tools are available.

Estimates on cost of RTS,S/AS01 delivery during the pilot were comparable to costs of HPV vaccine pilot implementation, and interim cost estimates show that the resources needed to delivery RTS,S/AS01 may be generally comparable with those for other new vaccines.

Additional data that have become available on RTS,S/AS01 since Phase 3 trial completion and the SAGE/MPAG recommendation for pilot implementation studies

Long-term follow-up of Phase 3 trial: 6-7 years follow-up of a subset of Phase 3 trial study participants showed that during the period following RTS,S/AS01 vaccination, the incidence of severe malaria declined with age in children in both vaccinated and unvaccinated groups. Although there was no evidence of continued vaccine efficacy against severe malaria during the additional three years of follow-up, neither was there evidence of increased susceptibility (age shift to older children). Over the entire 6-7 year period, vaccine efficacy against severe malaria was significantly positive for children receiving 4 doses in both age categories, and for those receiving 3 doses in the 6-12 week age group. Thus, children in areas with moderate to high perennial malaria transmission who received 3 or 4 doses of RTS,S/AS01 benefitted for at least 7 years after vaccination, and did not have an excess risk of clinical or severe malaria. Noting these results, MPAG assessed that these data provided further reassurance on the potential impact of an age shift effect in immunized children and reinforced the safety profile of the vaccine.

Seasonal use of RTS,S/AS01: The high initial efficacy over 4-6 months, after the primary RTS,S/AS01 regimen, as observed in the Phase 3 trial has stimulated interest in consideration of use of RTS,S/AS01 in areas of highly seasonal malaria transmission. The proposed strategy would be to deliver a primary 3 dose regimen in young children (5-17 months) immediately prior to the onset of the 4-6 month transmission season. Subsequent booster doses could then be delivered to these children annually, again just prior to the transmission season, to provide additional protection during this period of greatest risk.

To evaluate a seasonal vaccination strategy, an individually-randomized, controlled trial was conducted in young children (5-17 months) in Burkina Faso and Mali to assess whether vaccination with the malaria vaccine RTS,S/AS01 was non-inferior to seasonal malaria chemoprevention (SMC) with monthly amodiaquine plus sulfadoxine-pyrimethamine in preventing uncomplicated malaria and/or whether the interventions combined were superior to either alone in preventing uncomplicated malaria and severe malaria-related outcomes. Over 6000 children were enrolled starting in early 2017. The incidence of uncomplicated clinical malaria in the SMC and RTS,S/AS01 groups were similar – The hazard ratio (HR) comparing RTS,S/AS01 to SMC was 0.92, (95% confidence interval (CI): 0.84, 1.01), which excluded the pre-specified non-inferiority margin of 1.20, indicating that administration of RTS,S/AS01E was non-inferior to chemoprevention in preventing uncomplicated malaria. However, the combination of the vaccine and SMC was significantly better than either SMV alone or RTS/AS01 alone – the protective efficacy of the combination as compared with chemoprevention alone was 63% (95% CI, 58 to 67) against clinical malaria, 70% (95% CI, 42 to 85) against hospital admission with severe malaria, and 73% (95% CI, 3 to 93) against death from malaria.

The safety signals observed in the Phase 3 trial between 2009 and 2014 were not seen in this trial. Additionally, no other serious adverse events were assessed by the investigator to be related to vaccination. Eight cases of clinically suspected meningitis occurred: four in the chemoprevention alone, three in the RTS,S/AS01 alone, and one in the combined group. These were investigated by lumbar puncture, but none had proven meningitis. There was no evidence of differential mortality or hospital admissions in girls compared to boys who received RTS,S/AS01. In this large study, seasonally targeted RTS,S/AS01 was safe and non-inferior to SMC in preventing uncomplicated malaria. In addition, the combination of these interventions was associated with substantially lower incidence of uncomplicated malaria, severe malaria, and death from malaria.

Modelled public health impact and cost-effectiveness estimates

Both the Swiss TPH and Imperial College models predict a positive public health impact of the introduction of RTS,S/AS01 in settings with *Pf*$Pr_{2\text{-}10}$ between 10% and 50% over a 15-year time horizon, which is consistent with previously published estimates. Compared with the previous 2015 analysis, the cost per case and DALY averted have slightly increased due to the inclusion of more comprehensive information on cost of delivery, but estimates remain consistent with the cost per DALY averted for other vaccines in a broad range of LMICs and predict the vaccine to be cost-effective compared with standard norms and thresholds (e.g. well below the annual gross domestic product).

Analyses indicate that delivery of RTS,S/AS01 is cost-effective in areas of moderate or high malaria transmission where delivery is through routine EPI programmes or through seasonal delivery where malaria is highly seasonal, at an assumed cost per vaccine dose of US$ 5. Both trial and modelling results indicate RTS,S vaccination would be a cost-effective addition to existing SMC programmes.

Conclusions and recommendations for SAGE/MPAG consideration

The RTS,S SAGE/MPAG Working Group recommends that RTS,S/AS01 should be provided at a minimum of 4 doses to reduce malaria disease and burden in children from 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission. The RTS,S/AS01 vaccine

has an acceptable safety profile, and its introduction results in a significant reduction in severe malaria, an acceptable surrogate indicator for the likely impact on mortality. The Working Group notes that the vaccine provides substantial added protection against malaria illness and death even when provided in addition to a package of existing interventions which are known to reduce the malaria burden. The introduction of a vaccine at this time would come when progress in recent years has stalled in malaria control in Africa, when our current tools are threatened by drug and insecticide resistance, and when malaria remains a primary cause of illness and death in African children, with more than 260 000 child deaths from malaria annually.

In areas of moderate to high, perennial malaria transmission, the vaccine should be provided as a 3-dose primary series, starting from around 5 months of age and with a minimal interval between doses of 4 weeks. For children who are delayed in receiving their first dose, vaccination should be started before 18 months of age. A fourth dose should be given between about 12 and 18 months after the 3rd dose (i.e., at around 18 months to 2 years of age), however there can be flexibility to optimize delivery. The minimal interval between the 3rd and the 4th dose should be 4 weeks.

In areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks, the RTS,S SAGE/MPAG Working Group recommends that consideration should be given to the option of providing the RTS,S/AS01 vaccine seasonally, with potential 5-dose strategies including:

1. For all children under 5 years of age who have already completed the 3-dose primary series through routine administration, provide annual dose(s) just prior to the peak transmission season, or
2. For all children 5-17 months of age, give the 3-dose primary series monthly as a “campaign” just prior to the peak transmission season and then in subsequent years provide an annual dose just prior to peak seasons.

The RTS,S SAGE/MPAG Working Group makes this recommendation for possible 5-dose seasonal malaria vaccination strategies based on available data. The Working Group understands that this trial is continuing with additional doses provided to children up until the age of 5 years, and final results will contribute evidence on vaccine efficacy beyond 5 doses. The Working Group also notes that providing the first dose from 5 months of age may limit opportunities for integration with the delivery of other vaccines and/or for protection of children slightly younger (i.e., 4 months).

The Working Group notes that the careful and intentional monitoring for the safety signals seen in the Phase 3 trial, through quality data collection at sentinel hospitals and through community-based mortality surveillance, has revealed no evidence that the safety signals observed in the Phase 3 trial were causally related to the RTS,S/AS01 vaccine. Thus, the Working Group does not recommend special mechanisms be put in place to look for these signals during expansion of vaccine use or adoption by other countries.

WHO should lead the development of a Framework to guide where the initial limited doses of a malaria vaccine should be allocated, through a transparent process that incorporates input by key parties, with appropriate representation and consultation. This Framework should include dimensions of market

dynamics, learning from experience, scientific evidence for high impact, implementation considerations, and social values, including fairness, and equity.

The MVIP should continue as previously planned for an additional two years to 1) measure the impact of the introduction of RTS,S/AS01 on mortality; and 2) measure the added benefit of the fourth dose (the Working Group noted that in the Phase 3 clinical trial, the impact on severe malaria was only seen among children who had received 4 doses of the vaccine but there was impact on clinical malaria among children who received only 3 doses, though lower than that observed on children who had received 4 doses). Data collection on severe malaria and safety endpoints should continue. Any revisions or modifications concerning the recommendation for the fourth dose can be made at the end of the pilots.

2 Introduction

In September 2015, the Strategic Advisory Group of Experts (SAGE) and the Malaria Policy Advisory Committee (MPAC, now termed MPAG for Malaria Program Advisory Group) convened to consider the evidence available for a WHO recommendation on the use of the RTS,S/AS01 malaria vaccine. At that time, the available evidence was summarized in a background paper prepared by the Joint Technical Expert Group (JTEG) on malaria vaccines [3].

Based on this evidence review, WHO published its position on the RTS,S/AS01 vaccine in January 2016 [4]. Data tables reporting details on immunogenicity, efficacy, and safety are in the JTEG background paper. The key summary points from the WHO position paper were:

- Malaria remains a major cause of morbidity and mortality, particularly in sub-Saharan Africa, and despite considerable scale-up of life-saving interventions, malaria transmission, morbidity and mortality remain high in many endemic settings.
- Prevention needs to be strengthened still further and new tools are needed, including a malaria vaccine.
- Based on the Phase 3 trial results over 4 years of follow-up, among children 5-17 months of age at the time of first vaccination who were given a fourth dose 18 months after the primary series, RTS,S/AS01 was noted to be immunogenic, and to have moderate protective efficacy against clinical malaria (39%), severe malaria (31.5%), and malaria-related hospitalizations (37.2%).
- Vaccine efficacy was reasonably high over the first 6 months following completion of the initial 3 monthly doses (67.6%) but waned over time to essentially zero in the last six-month interval at trial's end, which occurred a median of 48 months after the 3rd dose. At six months following the 4th dose, vaccine efficacy was 42.9%; thus, the 4th dose did extend the period of protective efficacy but did not restore efficacy to the same level seen after the initial vaccine series, likely due to the acquisition of partial immunity from natural infection in the comparison group.
- The vaccine was generally well tolerated. Fever was the most frequently reported symptom; febrile convulsions were significantly more frequent after any of the initial vaccinations or after the fourth dose compared to the control group.
- Safety signals were noted without established causal relationship with vaccination (noting that these findings could be due to chance) including:
    - an excess of meningitis in the RTS,S/AS01 group compared to the control group among the 5-17 month age-group only, although these were not associated with any specific etiology or temporal pattern related to vaccination, lacked consistency across sites (64% of cases were from 2 study sites of 11 – both outside of the meningitis belt); the imbalance was not seen in infants first vaccinated at 6-12 weeks of age; and the outlier seemed to be an exceptionally low number of cases in the control group, where a single case of meningitis was captured during a median of 48 months of follow-up.

- a higher number of cerebral malaria cases (identified *post-hoc*) compared to the control group among the 5-17 month age-group only.
- In a *post-hoc* analysis, an excess of deaths from all causes among vaccinated girls compared to unvaccinated girls, but not in vaccinated boys compared to unvaccinated boys.

Mathematical models suggested implementation of RTS,S/AS01 at high coverage in moderate to high endemicity settings would be associated with substantial public health impact, averting 200-700 deaths per 100 000 vaccinees in a 4-dose schedule, and preventing 10-28% of all malaria deaths in children aged < 5 years.

In cost-effectiveness models, a 4-dose schedule was estimated to cost US$ 87 per DALY averted (assuming US$ 5 vaccine cost per dose in moderate to high endemic settings), consistent with cost per DALY averted for other vaccines in a broad range of developing countries.

In summarizing the balance between benefits and harms[3], WHO noted that RTS,S AS01 had been shown to protect against clinical and severe malaria, with unknown benefits against malaria-related or all-cause mortality, which the Phase 3 trial was not designed to measure. Identified risks included febrile convulsions following vaccination. A significant risk difference was also observed for meningitis following vaccination, but the causal relationship remained uncertain, with no clear causality model -the excess in meningitis cases in vaccinated children was seen only in the older age category (5-17 months at first vaccination), and not the younger age-category; there was no temporal relationship with vaccination, with cases occurring more than 1000 days after first vaccine dose; clustering of meningitis cases occurred by site, with 64% of cases from only 2 of the 11 sites; and, there was inconsistency in etiology, with cases of bacterial, mycobacterial, viral, and those with no pathogen isolated. It was also unclear if the imbalance of cerebral malaria cases (in the setting of reduced severe malaria, of which cerebral malaria is a subset), or the excess mortality in vaccinated girls seen in the trial were due to the vaccine, or were more likely chance findings. None of the safety signals were seen in the pooled safety analysis from Phase 2 trials[1] (N ~ 2000, Vekemans et al). Overall, the benefits of the vaccine administered to 5–17-month-old children were assumed to outweigh the risks for a 4-dose schedule; however, in children who received 3 doses, there was an initial reduction in severe malaria, but this was balanced by an increase in severe malaria around 18 months after the initial vaccine course. Therefore, an important outstanding question was whether it was operationally feasible to reach children at high coverage with a 4-dose schedule, (with the 4th dose provided around 2 years of age); and consequently, the extent to which the protection demonstrated in children aged 5 - 17 months in the Phase 3 trial could be replicated in the context of routine health systems.

To evaluate these outstanding questions, in January 2016 WHO recommended that pilot implementations with rigorous evaluation be conducted using the 4-dose schedule, and that this pilot should include sufficiently large populations of children 5-17 months of age in 3-5 distinct epidemiological settings in sub-Saharan Africa in moderate to high transmission settings. It was also recommended that the pilot implementations should be phased designs conducted in the context of ongoing high coverage of other proven malaria control measures, including long-lasting insecticide treated nets, access to quality diagnosis and treatment, and seasonal malaria chemoprevention where

appropriate, and be of sufficient duration. The Malaria Vaccine Implementation Program (MVIP) was therefore conceived, designed and initiated to support delivery of RTS,S/AS01 through routine immunization programs by the MoH in the participating countries, and the collection of evidence on operational feasibility, impact, and safety in routine use.

In October 2017, the MVIP Programme Advisory Group (PAG) was formed to oversee technical aspects of the MVIP. Specifically, the PAG's role is two-fold: to provide technical advice and recommendations to WHO on issues concerning the design and implementation of the MVIP; and, in its role as the RTS,S SAGE/MPAG Working Group (hereafter referred to as Working Group), to review the evidence, as it becomes available, including but not limited to the MVIP, on the balance of benefits and risks of RTS,S/AS01 and to consolidate the feedback into a report to SAGE and MPAG with recommendations on potential wider scale use of the vaccine in sub-Saharan Africa.

Beginning in July 2018 , WHO convened a working group to develop a Framework for WHO Recommendation on RTS,S/AS01 vaccine (hereafter referred to as the Framework) that was subsequently endorsed by SAGE and MPAG[5]. The Framework describes the stepwise approach for how and when data collected through the MVIP can inform WHO recommendations on use of the vaccine beyond the pilot countries. The Framework aims to ensure a recommendation is made as soon as the risk-benefit of the vaccine can be established with the necessary level of confidence, such that provision of the vaccine would not be unnecessarily delayed from countries in need, if it is found to be beneficial.

Accordingly, a WHO recommendation could be made if and when: i) concerns regarding the safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria, and gender-specific mortality) have been satisfactorily resolved, and by demonstrating either the absence of a risk of an important size of adverse effects during the RTS,S/AS01 pilot implementation or assessment of a positive risk-benefit profile despite adverse events; and ii) severe malaria or mortality data trends have been assessed as being consistent with a beneficial impact of the vaccine. Furthermore, the Framework clarifies that a recommendation for broader use would not be predicated on attaining high coverage, including high coverage of the fourth dose (Annex 1). Based on assumptions across the MVIP countries with respect to the expected rate of accumulating events and vaccine introduction timings, such data on safety and impact trends were expected to be available approximately 24 months after RTS,S/AS01 vaccine introduction in the MVIP.

This report summarizes information available from the MVIP after 24 months of vaccine introduction, including the primary outcome measures from the Malaria Vaccine Pilot Evaluation (MVPE) on safety and impact on severe malaria. In addition, this report also summarizes information on RTS,S/AS01 from sources other than the MVIP that have become available since the 2015 JTEG report , including a study of 7-year follow-up of a subset of children from the Phase 3 trial, the impact of seasonal use of RTS,S/AS01 with and without seasonal malaria chemoprevention (SMC) and efficacy and safety data from RTS,S/AS01 fractional dose regimens. The report concludes with the Working Group's assessment and summary of key recommendations on RTS,S/AS01 vaccine use for consideration by SAGE/MPAG.

3 Background

3.1 Epidemiology and disease burden of malaria

Based on 2019 data, WHO estimated that approximately 229 million cases and 409 000 deaths per year were attributable to malaria, with 94% of these deaths occurring in sub-Saharan Africa, and nearly all of the remaining occurring in South-East Asia, the Indian subcontinent and South America[6]. Most malaria deaths in Africa occur in children younger than 5 years. Adults who grew up in malaria endemic areas since childhood and remain resident in such areas acquire a degree of protective immunity are thus generally not at risk of death or severe malaria. Infants and young children in malaria-endemic countries in Africa typically experience several clinical episodes of malaria before they acquire partial immunity, which in older childhood protects against severe and fatal malaria. The immunity to uncomplicated clinical malaria is acquired more gradually during childhood. Malaria exerts an enormous toll on endemic country economies; data on malaria and gross domestic product (GDP) from 180 countries between 2000 and 2017 shows that each 10% reduction in malaria incidence is associated with an average rise of 0.3% in GDP per capita and faster GDP growth[7].

In most African countries substantial malaria-control efforts have been implemented, including the widespread deployment of long-lasting insecticide-treated bed-nets (LLIN), the use of indoor residual spraying of insecticide in some settings, chemoprevention strategies for certain high-risk groups such as pregnant women or young children living in areas of highly seasonal malaria transmission, and prompt diagnosis and treatment using quality assured rapid diagnostic tests (RDTs) and artemisinin-combination therapies (ACTs). In many settings, these measures have substantially reduced the annual incidence rates of new malaria cases; between 2000 and 2015, global malaria case incidence declined by 27%. Globally, an estimated 1.5 billion malaria cases and 7.6 million malaria deaths have been averted in the period 2000–2019. Most of the cases (82%) and deaths (94%) averted were in the WHO African Region, followed by the WHO South-East Asia Region (cases 10% and deaths 3%). While economic development and other factors may also have played a role in reducing the malaria burden, much of the decrease is likely attributable to large scale deployment of highly cost-effective interventions supported by an over 10-fold increase in financing for malaria control over the last 10-15 years.

However, between 2015 and 2019 the annual case incidence decreased by less than 2%, indicating a slowing of the rate of decline since 2015[5]. This levelling off of incidence (in some countries an increase occurred) has been attributed mainly to the stalling of progress in several countries with moderate or high transmission. As a result, 2020 milestones for reductions in malaria morbidity and mortality as laid out per the Global Technical Strategy were not achieved[8]. WHO and RBM subsequently launched the high burden to high impact (HBHI) country-led approach[9], as a mechanism to support the 11 highest burden countries to get back on track to achieve the GTS 2025 milestones.

Malaria parasite transmission in Africa may occur throughout the year or be strongly seasonal, determined largely by rainfall patterns. Transmission intensity generally is related to the vector man biting rate and vector survival, which is strongly influenced by temperature and humidity, as well as coverage with vector control measures. Because of variations in climatic factors, the availability of vector breeding sites, and differences in access to prevention and control measures, malaria parasite

transmission may be quite heterogeneous within a country. For example, in areas of western Kenya malaria transmission is very high, and malaria contributes substantially to childhood mortality, whereas in some other parts of Kenya there is currently little or no malaria parasite transmission. Over the last decade the number of areas with such intense transmission has decreased considerably, mainly due to scaled up malaria control measures.

Malaria remains a primary cause of childhood morbidity and mortality in sub-Saharan Africa. The clinical presentation, course, and frequency of episodes of clinical malaria may vary, depending on the age of the individual (Figure 1), and the intensity and seasonality of malaria parasite transmission. Morbidity due to *Plasmodium falciparum* infection can range from a non-specific mild febrile illness, to fulminant and life-threatening disease characterized by obtundation and coma, or respiratory distress, or severe anaemia or a shock syndrome requiring immediate parenteral treatment, blood transfusions, fluid therapy and supportive measures, often in combination.

The distribution of clinical manifestations varies by age as a function of transmission intensity (Figure 2). Repeated exposure results in acquired protection, developing first against severe malaria, then against illness with malaria, and, much more slowly, against parasitaemia without apparent symptoms. In settings when transmission is seasonal or perennial, some clinical manifestations of malaria, such as cerebral malaria, occur more frequently in older children. In contrast, severe life-threatening anaemia tends to occur in younger age-groups and is more prevalent in settings where malaria parasite transmission is intense and year-round[10]. In children and non-immune adults, the clinical picture can change rapidly over 1-2 days, from an illness that appears to be relatively mild to a life-threatening disease. Obstacles to access to quality care can result in delayed treatment and death, underscoring the importance of prevention.

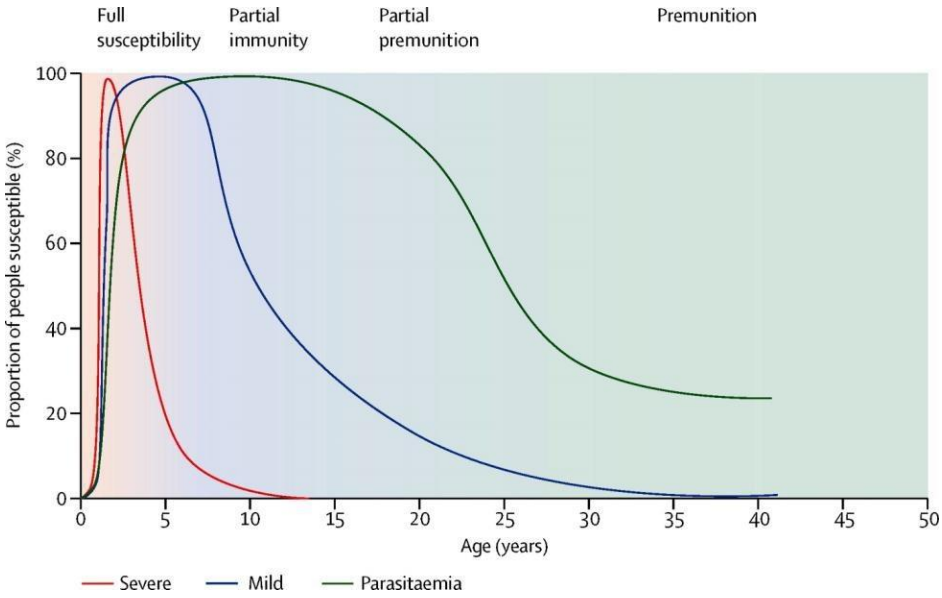


Figure 1: Relation between age and malaria severity in an area of moderate transmission intensity. From White *et al.* 2014[11].

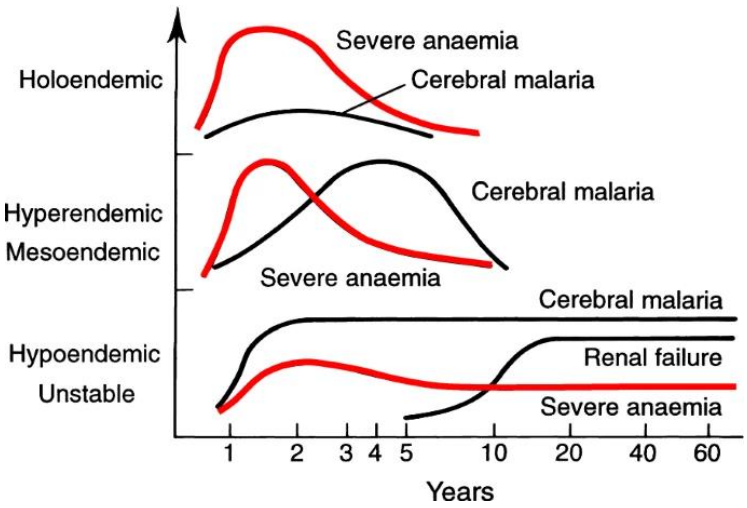


Figure 2: Relationship of severe falciparum malaria manifestations to age at different levels of malaria transmission From White *et al.* 2018[11].

3.2 Malaria parasites and pathogenesis

Four species of the *Plasmodium* protozoan parasite have been identified which account for most human infections (*P. falciparum, P. vivax, P. ovale, P. malariae*) and which do not have an animal reservoir. A fifth, *P. knowlesi,* infects long tailed macaques and zoonotic transmission to humans occurs in some parts of South-east Asia. *P. falciparum* accounts for more than 90% of all malaria-attributable cases and deaths. *P. vivax* accounts for much of the remaining disease burden and is the dominant *Plasmodium* species in many areas outside of sub-Saharan Africa. Human infection with the malaria parasite is established following the injection of the sporozoite form of the parasite by female anopheline mosquitoes. The parasite develops in the liver over 5-10 days and then emerges and enters the bloodstream and infects red blood cells. Subsequent cycles of replication, emergence, destruction of red blood cells and re-infection of more red blood cells causes symptoms, including fever. Morbidity and mortality from malaria may arise from a variety of causes including sequestration of infected red blood cells, severe anaemia due to red blood cell dysregulation and lysis, inflammation-related brain pathology, lactic acidosis, and a general shock- like syndrome with hypotension, hypoglycaemia and poor tissue perfusion. Vaccine development efforts have focused on *P. falciparum* and, to a lesser extent, on *P. vivax* (an overview of malaria vaccine targets and the malaria vaccine pipeline is provided in Annex 2).[12]

3.3 Immune response to malaria infection

After repeated exposure to *P. falciparum* malaria infections, individuals acquire a significantly reduced risk of developing serious illness or dying from subsequent infections. This acquisition of immunity through natural exposure occurs first to severe malaria and death, and then more slowly to milder clinical features of malaria such as fever. Although immunity to patent parasitaemia (detectable by microscopy) does occur by adulthood after many exposures, sub-patent infections of very low parasite density may still occur which can be detected by molecular techniques such as PCR. It is remains unclear whether or not complete (sterile) immunity is acquired by some individuals after repeated infections.

The development of protection against severe disease following repeated natural malaria infections, along with an increased understanding of immune mechanisms of protection, both contributed to the development of an effective malaria vaccine.

3.4 Other malaria prevention and control measures

As noted earlier, major gains in morbidity and mortality reduction have been achieved over the last 20 years with the improvements in malaria control and enhanced coverage with and access to prevention and treatment services. Vector control tools are critical components of prevention – principally use of long-lasting insecticide treated nets (LLINs) or deployment of indoor residual spraying (IRS) of houses with insecticide. LLINs have been shown to cause a reduction in childhood mortality in randomized controlled trials, and a Cochrane Review estimated 50% efficacy of ITNs against uncomplicated malaria episodes and 17% efficacy of ITNs against all-cause under five mortality (compared to no nets) in areas of high transmission[13]. IRS can be associated with marked reductions in malaria parasite transmission. In some countries IRS and ITNs are deployed together, while in others IRS is largely reserved for response to epidemics. Globally, the percentage of the populations at risk protected by IRS in malaria endemic countries declined from 5% in 2010 to 2% in 2019[6]. reflecting some of the challenges of effectively deploying and maintaining IRS. The WHO African Region has the highest proportion of the population at risk protected by IRS: in 2019, this proportion was 5.7%.

Antimalarial drugs to prevent malaria - chemoprevention – is also used in high-risk groups such as pregnant women, infants, and young children. For endemic countries in Africa, WHO recommends intermittent preventive treatment of malaria in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), delivered at each scheduled ANC visit after the first trimester. In 2019, among 33 reporting countries, 62% of pregnant women received at least one dose of SP; only 34% received the target of three or more doses.

Seasonal malaria chemoprevention (SMC), recommended for children living in areas of highly seasonal transmission, is defined as the intermittent administration of full treatment courses of an antimalarial medicine to children aged 3-59 months during the malaria season (typically monthly during the transmission season) to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk. In clinical trials, conducted in areas of highly seasonal transmission (where the majority of malaria cases occurred over a 4 month period), SMC reduced incidence of malaria (including severe malaria) by 75%[14]. In 2019, 13 countries in the Sahel region were implementing SMC and reached nearly 22 million children[6]. A programmatic evaluation in seven west African countries showed that during the high transmission period, implementation of SMC was associated with reductions 42-57% in the number of malaria deaths in hospital, and 26-41% in confirmed outpatient malaria cases[15].

Intermittent preventive treatment in infants (IPTi) with SP is also recommended by WHO but has not been widely implemented. IPTi is defined as the administration of a full course of an effective antimalarial treatment at specified time points to infants at risk of malaria, regardless of whether they are parasitaemic. In clinical trials, IPTi with SP delivered through EPI provided an overall protection

during the first year of life of 30% against clinical malaria, 21% against anaemia, 38% against hospital admissions associated with malaria parasitaemia, and 23% against all cause hospital admissions[16].

Diagnosis with a rapid diagnostic test (RDT) or microscopy and treatment of laboratory confirmed malaria with artemisinin-based combination therapy (ACTs) are mainstays of malaria case management. In 2019, based on recent household surveys, the rate of diagnosis (by finger or heel prick) among children aged under 5 years with fever for whom care was sought 38%; among children who sought care, the proportion who were treated with an ACT was 81%, suggesting that many children received ACTs without parasitological diagnosis. An equity analysis of fever prevalence and treatment seeking at subnational level showed that, although in most countries children in poorer households had a higher prevalence of fever in the 2 weeks before the survey, treatment seeking was higher in febrile children from wealthier households[6].

Although current malaria prevention and control tools remain generally effective, there are limitations, particularly with respect to prevention. Many well documented situations exist where intense transmission of malaria parasites persists at unacceptably high levels even with good coverage with ITNs or IRS[17]. IPTi has not been widely adopted. SMC is limited to deployment in highly seasonal areas in west Africa. Moreover, in most areas where SMC is now deployed, malaria remains the main cause of death and hospitalization in young children[6].

There are also significant biological threats on the horizon. Increasing physiological resistance of *Anopheles* mosquitoes to insecticides is recognized as a major threat that requires an urgent and coordinated response[18]. Antimalarial drug resistance has been and continues to be an ongoing global challenge for all malaria programs[19]. The emergence of malaria parasites that do not express the HRP-2 marker that is detected by the most widely used diagnostic testing platforms threatens the viability of inexpensive rapid diagnostic tools[20].

Malaria is associated with considerable heterogeneity geographically and over time. Within any malaria endemic country, it is not unusual that the intensity of transmission and the associated burden of disease vary considerably due to climate, socioeconomic development, urbanization, health system as well other factors. Over time, parts of a country could also change from one level of endemicity to another due to changes in the determinants, especially as coverage and use of interventions impact on transmission and burden of disease. This heterogeneity requires a targeted response and a choice of interventions based on data and local (subnational) information. This is essential for the development and monitoring of prioritized malaria control and elimination programmes, based on (i) stratification, of malaria risk and approaches to service provision , (ii) development of an optimal national strategic plan which that defines the packages of interventions needed to optimize malaria control and elimination in a country; (iii) informing rational prioritization to maximize impact when the resources are insufficient to provide the optimal packages; (iv) monitoring the impact of the deployed intervention packages[21].

As noted previously, after steady reductions in malaria morbidity and mortality between 2000 and 2015, recent progress has stalled, and the 2020 malaria morbidity and mortality GTS targets were not achieved. A revitalization effort, called “High burden to high impact”, was launched in 2018 by WHO, the RBM partnership and countries with a high malaria burden[9]. 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. In this context of stalled progress along with both limited efficacy and biological threats to current prevention approaches, a malaria vaccine would be a valuable complementary tool.

4 Malaria Vaccine Implementation Programme - Overview

4.1 Rationale

The Malaria Vaccine Implementation Programme (MVIP) was conceived, designed and initiated to act on the 2016 WHO recommendation to pilot the RTS,S/AS01 malaria vaccine in routine immunization programmes. The MVIP has three objectives:

1. To further characterize vaccine safety in the context of a routine immunization programme, with special attention to the safety signals observed in the Phase 3 trial.
2. To evaluate the vaccine's impact on severe malaria and all-cause mortality; and
3. To assess the programmatic feasibility of delivering the recommended four-dose schedule, including new immunization contacts, in the context of routine health service delivery.

The evidence generated on these outstanding questions is expected to inform a WHO recommendation on broader use of the vaccine in sub-Saharan Africa.

An evaluation protocol and statistical analysis plan were developed and reviewed by external experts, and are publicly available. They both provide additional detail to the material presented in this section.

The MVIP is coordinated by WHO in close collaboration with ministries of health in participating countries and a range of in-country and international partners. WHO is working with PATH and GSK on the MVIP through a collaboration agreement. PATH provides technical and project management support and is leading studies on health care utilization and the economics of vaccine implementation. GSK is donating up to 10 million doses of RTS,S/AS01 vaccine for use in the pilot and is leading additional studies to continue monitoring the vaccine's safety and effectiveness in routine use. UNICEF is supporting the forecasting and deployment of the donated vaccines to pilot countries. The MoH of the pilot countries have introduced the RTS,S/AS01 vaccine using routine vaccine introduction strategies and programmes. In-country research partners are leading the evaluation of the RTS,S/AS01 vaccine pilot implementation.

4.2 Country selection

WHO launched a public call for expressions of interest for participation in the MVIP from the ministries of health (MoHs) in sub-Saharan Africa in December 2015. Ten countries, all classified as low or lower-middle income per World Bank definition, submitted written expressions of interest. A country selection process from January to April 2016 included criteria such as demonstrated engagement and interest from MoHs; presence of functional immunization and malaria control programmes as evidenced by DTP3 and MCV1 coverage, and LLIN usage; high all-cause mortality in the planned regions of the pilots, with high malaria transmission, consistent with a large proportion of malaria related childhood deaths in such settings; presence of at least one highly capable sentinel hospital per region to facilitate the collection of high quality data on meningitis and cerebral malaria; and national pharmacovigilance (PV) readiness. Prior participation in the RTS,S/AS01 Phase 3 trial was also considered favourably. Based on these criteria, Kenya, Ghana and Malawi were invited to participate in the MVIP; following this, the MoH of each country then selected the subnational pilot areas. Each country has a track record of

strengthening malaria and immunization programmes, as well as experience introducing new vaccines, and links with immunization and malaria research infrastructures for the evaluation components.

4.3 Regulatory review

The European Medicine Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) issued a positive scientific opinion for RTS,S/AS01 in July 2015 under the Article 58 procedure for an indication of active immunization of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* and against hepatitis B, concluding that the benefits of the vaccine outweigh its risk[22]. The Article 58 procedure allows the EMA to assess the quality, safety and efficacy of a product intended exclusively for use outside the European Union (EU), but which is manufactured in an EU member state, to address a disease recognized by the World Health Organization (WHO) as of major public health interest. This assessment requires medicinal products to meet the same standards as those intended for use in the EU[22]. Formal annual reviews have been conducted by EMA based on GSK submission of Periodic Safety Update Reports, and the positive scientific opinion has been maintained since 2015[22]. Regulators from Ghana, Kenya and Malawi agreed during a February 2017 African Vaccines Regulatory Forum (AVAREF) meeting on a pathway and strategy for joint regulatory review with support from the EMA. By May 2017, the national regulatory authorities (NRAs) from the three pilot countries authorized RTS,S/AS01 for use in pilot areas.

4.4 Key questions on safety, impact, and feasibility

The following key questions are being evaluated in groups of children, eligible to receive RTS,S/AS01 vaccine, residing in the RTS,S/AS01 implementation and comparison areas.

Safety:

- Does the introduction of routine RTS,S/AS01 vaccination result in an increased rate of meningitis and/or cerebral malaria in communities where the vaccine is introduced?
- Does the introduction of RTS,S/AS01 have a different effect on all-cause mortality for boys and girls? Does RTS,S/AS01 increase mortality in girls?
- What is the frequency and profile of RTS,S/AS01 reported AEFI?

Impact:

- Is there any reduction in all-cause mortality following the introduction of the routine delivery of RTS,S/AS01?
- By how much does the routine delivery of RTS,S/AS01 vaccine reduce the incidence of hospital admission with severe malaria?

Feasibility:

- What coverage is achieved with RTS,S/AS01 (including the fourth dose in the second or third year of life) and how timely are the doses?
- What is the coverage and timeliness of recommended EPI vaccines and does it change with RTS,S/AS01 introduction?

- What is the coverage and utilization of other recommended malaria prevention and control measures, including ITN and IRS, and does it change with RTS,S/AS01 introduction?
- Do treatment seeking behaviours for febrile children, use of malaria prevention measures, and EPI vaccination coverage change with the introduction of RTS,S/AS01?
- What strategies help to achieve optimal coverage of the fourth dose?
- Does the introduction of additional contacts between 5-9 months of age influence vaccine programme drop-out rates and the number of fully vaccinated children?
- Does the introduction of RTS,S/AS01 alter the coverage of other key childhood interventions, including Vitamin A supplementation?

5 Malaria Vaccine Implementation Programme (MVIP) - Design, Implementation, and Evaluation Methods

5.1 Overview of design

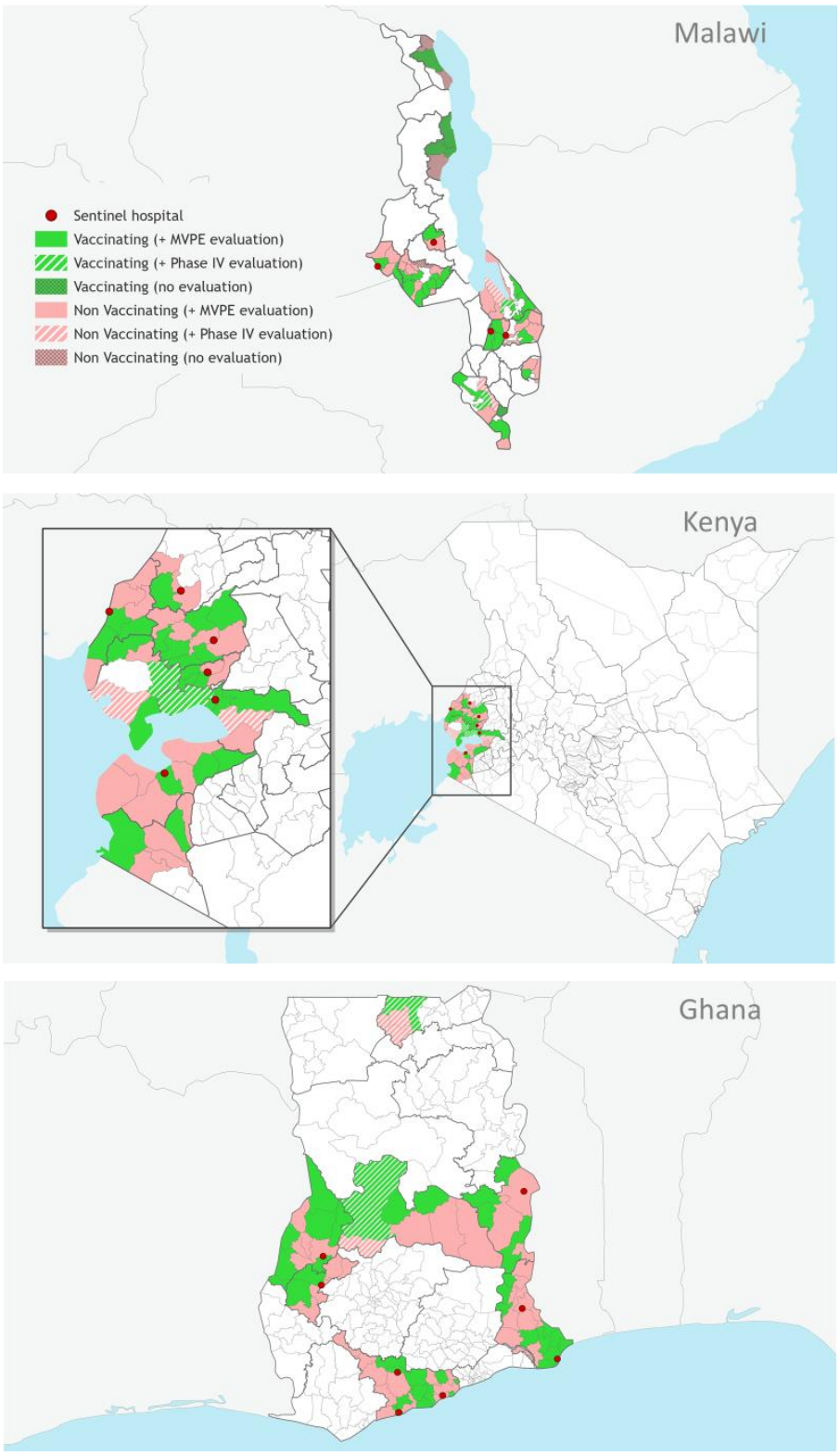
The MVIP evaluation is being conducted in the context of the early, limited deployment of the RTS,S/AS01 vaccine through the routine health systems. Vaccine implementation is expected to continue beyond the evaluation period, with the progressive roll out beyond the pilot areas if there are no significant safety signals or concerns about the feasibility of deploying the vaccine.

A master protocol was developed by WHO for revision and adaptation to local country contexts, and was the basis of country-specific protocols. The protocols received ethical approval by the WHO Ethical Review Board and the Institutional Review Boards of the pilot countries. The protocols describe the MVIP evaluation, which has been designed on the basis of approximately 60 clusters per country, evenly split between implementation and comparison areas, with each cluster contributing approximately 4,000 children per year to the pilot evaluation. The detailed master protocol is publicly available at clinicaltrials.gov[23]. clusters per country, evenly split between implementation and comparison areas, with each cluster contributing approximately 4,000 children per year to the pilot evaluation. This detailed protocol is publicly available[23].

The MVPE uses a cluster-randomized design, with some areas (e.g., Districts, Sub-counties), referred to as “areas”, introducing RTS,S/AS01 at the beginning of the programme and other areas, without RTS,S/AS01, acting as comparison. The division of areas into implementation or comparison areas was randomized to enable the MVPE pilot implementation programme to generate the strongest possible evidence on the impact and safety of the vaccine by limiting potential biases and providing a contemporaneous comparison group allowing for statistical inferences to be made. Randomized introduction was also seen as a fair way to select areas to receive the RTS,S/AS01 vaccine during the initial period of implementation in which delivery of the new vaccine is being piloted. Areas were randomly assigned as implementation or comparator, taking into account the capacity of hospitals and health facilities within the areas; malaria transmission (as reflected by the *P falciparum* prevalence in children aged 2-10 years modelled to the cluster level, divided into terciles); and geographic location (such as county/region) and population size (divided in terciles). A constrained randomization procedure was used to ensure that the vaccination and comparison areas were balanced for these characteristics, which could be associated with the incidence of the outcome measures.

Areas were defined according to the size of the birth cohort, aiming for an annual birth cohort of 4,000 children. Identical monitoring systems were established in both implementation and comparison areas to record impact and safety outcomes.

Figure 3 illustrates the MVIP areas and location of sentinel hospitals in each of the three pilot countries.



The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: MoH Kenya; MoH Malawi; MoH Ghana

Map Production: WHO GIS Centre for Health, DNA/DDI

Figure 3: Maps indicating the Malaria Vaccine Implementation Programme areas in Malawi, Kenya, and Ghana.

Figure 3 presents an illustrative overview of study timing and activities to generate data to evaluate safety, impact, and feasibility. Surveillance will be maintained in children aged 1-59 months throughout the pilot. This allows for an assessment of the effects of vaccine introduction in the age groups of children eligible to receive RTS,S/AS01, while the data for children too young or old to be eligible for the vaccine provide information about background rates of outcomes in the same cluster.

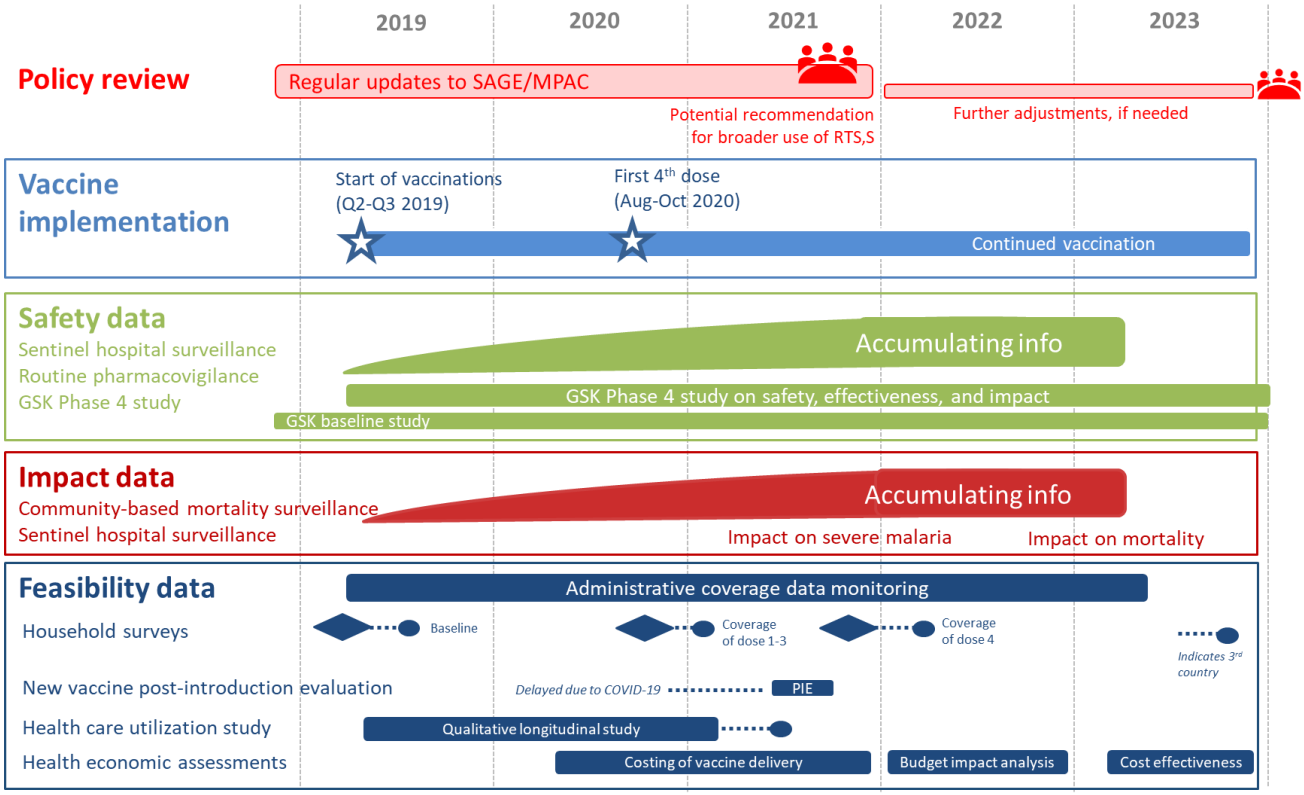


Figure 3: Timeline for evidence generation and review

5.2 Routine implementation of the RTS,S/AS01 vaccine

Ministries of health in each country are delivering the malaria vaccine through their national immunization programmes in the selected areas. National malaria control programmes are ensuring that existing WHO-recommended prevention tools, such as long-lasting insecticidal nets (LLINs) and artemisinin-based combination therapies (ACTs), continue to be deployed on a wide scale. There is a compilation of key milestones in the development of the Malaria Vaccine Implementation Programme that include country-specific stakeholder engagement and preparations for vaccine introduction[24].

The administration of the four doses of RTS,S/AS01 are integrated within the EPI schedules. Based on the WHO recommendations, the respective EPI Programmes identified the best target age for children to receive each dose of RTS,S/AS01, given the existing routine immunization schedule. Ghana and Kenya provide the four doses at 6, 7, 9, and 24 months of age. Malawi opted for a different schedule with the four doses given at 5, 6, 7, and 22 months of age, in an effort to administer the primary vaccination series- and additional protection against malaria- as early as possible (Figure 4).

Child Age / Vaccine/1	Birth	6 wks	10 wks	14 wks	5 mo	6 mo	7 mo	9 mo	12 mo	18 mo	22 mo	24 mo
BCG	1											
Oral polio	0	1	2	3								
DTP-HepB-Hib (penta)		1	2	3								
Pneumococcal conj.		1	2	3								
Rotavirus		1	2									
Inactivated Polio				1								
Meningococcal A conj.										1		
Measles-Rubella								1		2		
Yellow Fever								1				
RTS,S in Ghana						1	2	3				4
RTS,S in Kenya						1	2	3				4
RTS,S in Malawi					1	2	3				4	
Vitamin A						1			2	3		4
Growth Monitoring	●	●	●	●	●	●	●	●	●	●	●	●
Deworming												●

1/ The upper part of the figure reflects Ghana's vaccination schedule, the lower part other child health interventions

Figure 4: Integration of RTS,S/AS01 malaria vaccine into the childhood immunization schedule

Ahead of the vaccine launches, all three countries implemented the typical preparatory activities for a new vaccine introduction, in line with the respective RTS,S/AS01 New Vaccine Introduction Plan developed by MOH. Key activities included development of training materials for health workers and of information, education and communication (IEC) materials; adaptation, printing and distribution of revised routine monitoring and reporting tools for use in facilities; distribution of vaccines and injection supplies; cascade-manner trainings for health officials and health care workers; and information, communication and social mobilization activities.

Among the key messages reinforced during trainings of health workers and engagements with caregivers and communities are the reasons for pilot introductions; the vaccination schedule; that the RTS,S/AS01 malaria vaccine does not prevent all malaria episodes and that it is therefore important to continue to use other methods to protect children from getting malaria. Other prevention methods include sleeping under an insecticide treated net every night and throughout the night and, in some areas, allowing homes to be sprayed with insecticide during spraying periods. Also, a child with fever should be taken to a health facility immediately for malaria testing and appropriate treatment if necessary. Examples of how this message is being conveyed through the countries' communication materials are shown in Figure 6.

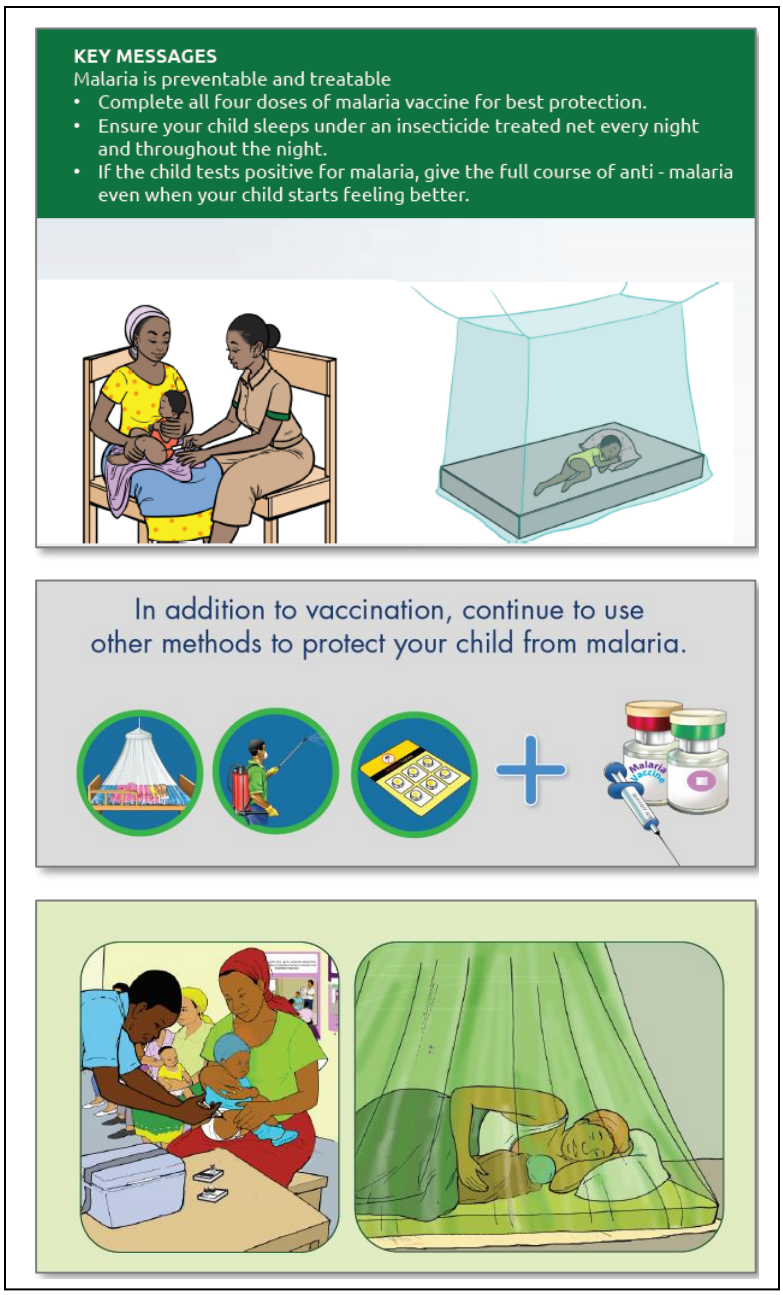


Figure 5: Extracts from countries' communication materials, developed under the leadership of the MOH, highlighting the complementarity of RTS,S/AS01 with other malaria control interventions.
From top to bottom: Ghana Flip Chart; Kenya Flyer; Malawi Flyer and Key Facts Booklet

5.3 Evaluation methods

5.3.1 Case definitions

The case definitions used for the MVPE are provided in the Statistical Analysis Plan[25].They include detailed definitions for meningitis (probable, and confirmed); malaria (severe, and cerebral, a subset of severe); malaria associated anaemia (any, severe), hospital admissions (all cause, malaria related, non-malaria related); deaths (all cause, all cause excluding injuries, malaria associated in hospital), transfusions, and febrile convulsions.

5.3.2 Safety

The MVIP was designed to address the 3 safety signals, meningitis, cerebral malaria, and an excess in female mortality compared with male mortality, observed during the Phase 3 trial, following on SAGE/MPAG recommendations from 2015.

Data for the safety evaluation in the MVPE was captured through four complementary systems: 1) sentinel hospital surveillance, established specifically to address the safety signals of meningitis and cerebral malaria, 2) community morality surveillance, established to measure impact on mortality, including gender- specific mortality; 3) the GSK Phase 4 studies, which follows a cohort of 45000 children as part of a post-authorization safety study; and 4) routine pharmacovigilance by the respective MoH, to detect rare adverse events following immunization (AEFI). A detailed description of methods used to capture safety data are found in Section 10 of the MVPE protocol[23]. A Data Safety Monitoring Board (DSMB) meets quarterly and has been monitoring data from the MVPE, the GSK Phase 4 study, and the routine pharmacovigilance systems of the 3 pilot countries.

5.3.2.1 MVPE sentinel hospital surveillance

A detailed description of sentinel hospital surveillance is provided in the MVPE protocol, Section 10. In brief, 18 sentinel hospitals were identified across the three countries, serving RTS,S/AS01 introduction and comparison areas. Each hospital had a catchment area with an annual birth cohort of approximately 4,000 children in each cluster in its catchment areas. Hence, a total of at least 48 000 children in implementation areas and the same number in comparison areas contributed to the hospital-based evaluation of safety across the programme. These data were complemented by data generated by the GSK Phase 4 study (up to 6 hospitals in areas implementing and 6 in areas not implementing RTS,S/AS01, serving an area with a total annual birth cohort of approximately 24 000 children).

Children admitted to hospital aged 1 to 59 months were included in the evaluation. This enabled the documentation of critical events in children who are vaccinated near the beginning of the programme. Additionally, events in children too young or old to receive RTS,S/AS01 provide information about underlying rates in the same cluster which is used in the statistical analysis (see 5.3.2.2).

Sentinel hospitals in the MVPE were selected that: a) had a catchment area comprising areas which implemented RTS,S/AS01 or that was a comparator area; or b) served catchment areas some of which implemented RTS,S/AS01 and others which served comparator areas; or c) had available a vaccine registry which could be linked to inpatient data. Selection criteria also included: a catchment area which includes approximately 4,000 infants from the MVPE area; a functional system of case note recording for patients on the paediatric ward; a track record of regular reporting of routine data (inpatient and vaccination clinic data) to the district health team; and demonstrable experience of lumbar punctures on children with signs of neurological illness. A restricted randomization procedure was used to balance apportionment between implementation and comparison areas of the limited number of hospitals (1-3) with considerable experience in meningitis surveillance, or diagnosing meningitis or cerebral malaria in a research setting.

Sentinel hospitals included different types of admitting facilities, offering a range of levels of investigation and care to different numbers of children. The number of each type of hospital was balanced in implementation and comparison areas such that a similar number of children were admitted in each area to each type of facility. A list of characteristics and types of investigation performed at each level hospital is provided in Section 10 of the protocol. Hospitalization was defined as spending at least one night at a sentinel health facility or having been admitted and dying within the first 24 hours of admission.

Hospital-based surveillance systematically documented admissions to the paediatric ward in order to capture information on impact (malaria-specific mortality, severe malaria) and safety (changes in the hospital-based incidence rates of meningitis, cerebral malaria, febrile convulsions, other illnesses, all-cause and malaria-specific mortality. Relevant demographic, vaccination and clinical data were captured in a CRF on all children under 5 years of age admitted to the paediatric wards of sentinel hospitals. Consolidated, quality assured, inpatient surveillance systems were supported by evaluation partners in each country with minimum standards assured to enable systematic, standardized clinical and laboratory assessment and management of all admissions. Additional detail on demographic and clinical data collected; biological sampling and processing; and laboratory analyses conducted are described in Section 10 of the MVPE protocol.

5.3.2.2 MVPE sentinel hospital surveillance: Statistical methods

The statistical methods used for analysis of the sentinel hospital data are presented in detail in the MVPE statistical analysis plan (SAP)[25] and the MVPE statistical report (Annex 2: Malaria vaccine targets and pipeline Annex 3). The analysis followed a pre-defined analysis plan that has been published, and is available at https://clinicaltrials.gov/ct2/show/NCT03806465[25]. The original statistical analysis plan had only minor amendments. Of note, the analyses were powered only for pooled analysis across the three countries.).

In brief, for each outcome of interest, the incidence rate ratio was estimated comparing the incidence rate among children eligible to have received the malaria vaccine in regions where the vaccine was introduced, with that in the corresponding age groups in comparison areas. The method took advantage of the fact that surveillance was maintained for all children between 1 and 59 months of age, including both eligible children, and children who were not eligible for vaccination because they were too young or were too old when the vaccine was introduced. If the vaccine had no effect, the ratio of the number of events in eligible versus non-eligible children would have been the same for implementation and comparator areas.

The ratio of these ratios was an estimate of the incidence rate ratio associated with vaccine introduction in the vaccine-eligible age group. Confidence intervals were estimated using standard methods. Events were classified as belonging to vaccine-eligible children, or non-eligible children. To avoid contamination, children who were too old to be eligible, by up to two months, were excluded from

analysis, as the vaccine uptake in this group was unknown. For this reason, the total events in eligible and non-eligible categories was slightly less than the total number of events for that outcome.

By using the data for the non-eligible children in each region there was an adjustment for underlying differences in disease burden or access to hospital between implementation and comparison regions, in so far as these factors would have tended to be highly correlated between different age groups. A second advantage was that reliance on population denominators, which are challenging to estimate reliably, was avoided when estimating incidence rate ratios.

The safety outcomes explored whether the unexplained excess cases of meningitis and cerebral malaria, and the excess mortality in girls were causally related to the vaccine. The number of events required for 90% power to detect rate ratios for these safety signals was estimated, if they were of the magnitude observed in vaccinated children the Phase 3 trial, after allowing for dilution due to vaccine coverage being less than 100%, and allowing for effects of confounding and contamination.

In the case of meningitis, confounding was possible if RTS,S/AS01 recipients had also received Hib and pneumococcal vaccine, which protect against meningitis. To some extent, this could have masked a safety signal; however, in practice this was a small effect due to the fact that vaccine-preventable serotypes were relatively uncommon causes of meningitis.

5.3.2.3 MVPE study size and expected number of events

The meningitis signal in the Phase 3 trial was calculated to equate to a rate ratio 4 to 5 if vaccine coverage was 60% to 70% in implementation areas and 5% in comparison areas. The cerebral malaria signal would equate to a rate ratio of 1.7 to 2, and the mortality signal in girls to a mortality ratio of 1.4 to 1.6. (These values were used in the power calculations. More accurate estimates were made subsequently, when data on RTS,S/AS01 coverage from the household surveys became available).

For safety outcomes, it was estimated that 90 cases of meningitis and 400 cases of cerebral malaria, in eligible and non-eligible age groups combined, would be required for 90% power, and that 2000 deaths in vaccine-eligible ages would allow 90% power to detect a gender interaction. Based on event rates observed in the first year of the evaluation, it was anticipated that the required number of events for each outcome would have accrued by approximately the same time, at about 24 months after the first introduction of the vaccine (April 2021), if data for all three countries were combined. By April 30, 2021, there were 134 cases of meningitis, and 572 cases of cerebral malaria.

5.3.2.4 GSK Phase 4 Study

A Phase 4 study (EPI-MAL-003) is led by GSK (the RTS,S/AS01 vaccine manufacturer), as part of the risk management plan that was developed with the EMA. The Phase 4 studies will continue after the pilots are completed and after a potential recommendation for use, with the interim analysis planned for late 2023 and final analysis planned for late 2025. The Phase 4 studies are designed to: a) assess a potential association between vaccination with RTS,S/AS01 and the safety signals observed in the Phase 3 trial; and b) assess any potential association between vaccination and other adverse events of special interest (Phase 4 AESIs); which include rare potential immune-mediated disorders, and other AEFI leading to hospitalization or death (these outcomes were selected as part of a general safety evaluation, and are not related to specific prior safety signals); and c) assess vaccine effectiveness.

The GSK-led Phase 4 study is conducted in areas that are physically separate from the MVPE but located within the MVIP pilot area (Figure 3). It includes an observational cohort study designed to evaluate the safety, effectiveness and impact of the RTS,S/AS01 vaccine in routine use, and includes both temporal and concurrent comparisons of the occurrence of adverse events
(including meningitis, AESIs, deaths (overall and by gender) and other AEs leading to hospitalization or death) and malaria (including cerebral malaria cases) between vaccinated and unvaccinated subjects living in areas with or without the RTS,S/AS01 vaccine. This cohort longitudinal study, or so-called Active Surveillance (AS), component of the GSK-sponsored study enrolled approximately 20 000 children at the time of routine DTP vaccination before RTS,S/AS01 vaccine introduction as part of the baseline study, and enrolled approximately 45 000 children (half living in areas where the RTS,S/AS01 vaccine was introduced and half in areas where the vaccine was initially not introduced after RTS,S/AS01 vaccine introduction), at the time of routine DTP vaccination, after the introduction of the RTS,S/AS01 vaccine. Longitudinal follow-up of enrolled subjects is being conducted by monitoring at both primary and secondary health care facilities, and at the community level (10 home visits and continuous monitoring of outpatient visits and hospitalizations at all health care facilities).

5.3.2.5 Detection of Adverse Events Following Immunization (AEFIs)

Routine pharmacovigilance (PV) is led by the respective Ministries of Health in the pilot countries. This is the routine passive surveillance system used to capture and describe AEFI (including pre-specified AESI) reported from health practitioners and the general public. Causality is assessed during the investigation of individual cases. Routine PV systems have an important role in identifying signals for rare and severe adverse events, such as anaphylaxis, when their occurrence follows closely after the time of product administration. Such events are generally too uncommon to be captured or accurately quantified during product development. PV systems may be subject to under- or over-reporting and reporting biases, especially if the events of concern are not temporarily related to vaccination. The routine PV systems in the pilot countries were not well-suited to generate sufficiently reliable data to measure the association between vaccination and the 3 safety signals identified in the Phase 3 clinical trial -none of which were temporally related to vaccination. Furthermore, in resource limited hospitals, meningitis and cerebral malaria are often diagnosed based only on clinical signs, without laboratory confirmation, and cases can easily be misclassified if systems are not established to support accurate diagnoses. For these reasons, the MVIP includes sentinel hospital and community mortality surveillance systems to address the safety concerns related to meningitis, cerebral malaria and gender-specific mortality.

Through the MVIP, routine national PV systems were strengthened in the 3 pilot countries through a standardized set of activities. The PV strengthening was the responsibility of the respective ministries of health, with support from WHO, as was routine reporting on AEFI and AESI. The strengthened PV system was designed to capture any spontaneously reported vaccine-related adverse events, including febrile convulsions and rare and unexpected AEFI. AESI were captured through country-specific protocols, as agreed with national authorities, as a complement to the detailed information generated by GSK's Phase 4 study. In Ghana, Malawi, and Kenya, AEFI data are regularly reviewed by the MoH and those from MVIP areas are presented to the MVIP DSMB at each of their meetings by representatives from the NRAs in each MVIP country.

5.3.2.6 Limitations

Sentinel hospitals are a minority of the available hospitals and are usually better performing than other health facilities. They may tend to serve more urban-dwelling, and possibly less-poor patients than may be typical of the entire population living in the pilot areas. Thus, children presenting to these hospitals may under-represent those with poor access, who may also be at greater risk of adverse outcomes. The sentinel hospital surveillance may therefore tend to under-estimate rates of severe disease. Such rates also depend on distance or ease of access to facility, as well as the availability of alternative health facilities for those seeking care. Estimates of rates and rate differences are therefore inevitably context specific.

The primary analyses depend on area of residence (implementation or comparator) of the child, rather than individual vaccination status. Nonetheless, identification of vaccination status in admitted children is important for secondary or exploratory analyses. In most sentinel hospitals it is likely that vaccination data were available only on the child's health and vaccination card. These cards were modified by the EPI programmes in implementation areas to document doses of RTS,S/AS01. Per usual practice, child caregivers are encouraged to carry the card to all contacts with the health services. When not available at the time of admission, caregivers were encouraged to make the card available before discharge. In the absence of the health card, immunization information was collected through verbal recall. However, the validity of recall for the new malaria vaccine under different circumstances (household survey, hospitalization, verbal autopsy) is unknown.

5.3.3 Impact

The primary impact outcomes are hospitalized severe malaria and all-cause mortality in children excluding accidents and injuries.

5.3.3.1 Community based surveillance for mortality

The population contributing to the impact evaluation surveillance systems includes vaccinated and unvaccinated children living in areas of moderate to intense malaria transmission and aged from 1 month to 59 months. The surveillance period is 46 months, to provide 12 months of surveillance activities after children vaccinated during the first year of the programme receive their fourth vaccine dose, assuming that the fourth dose is given by age 27 months. A 12 month surveillance period after dose 4 brings children to 39 months of age. Data were collected in children aged up to 59 months to enable documentation of delayed critical events in children vaccinated at the beginning of the programme. Collecting information on children reported to have died between the ages of 1 and 59 months facilitated operational activities and minimised the risk of excluding relevant events due to inaccuracies in initial reporting of age. In addition, the data for those too young or old for RTS,S/AS01 provides important information about underlying rates of outcomes in the same cluster.

Because the majority of deaths in many sub-Saharan countries occur in the community, rather than in hospitals or health facilities, the evaluation of the impact of RTS,S/AS01 on survival requires the development and consolidation of community-based systems to document and report deaths. A cadre of village-based reporters (VRs) was trained to identify and document deaths occurring in their village and any surrounding area assigned to the VR. Deaths were identified either through (i) door-to-door

visits of each household in the VR's assigned area, or through notification of VRs of any key events by a specially developed local network of informants. The MVPE built on relevant existing and developing capacities for this vital event monitoring.

Where possible, existing cadres VRs were trained to document deaths in the target age group. The VRs were trained to ensure an understanding of the importance of mortality monitoring and causes of death, inquiring about deaths in locally appropriate ways, use of local events calendars to help capture critical dates, and where appropriate, vaccine safety principles and AEFI surveillance to contribute to the strengthening of routine PV. Verbal autopsies (VA) were conducted after a locally acceptable period of time to capture key variables and to identify deaths due to accidents or injury for exclusion from the primary analysis on mortality impact. Information was obtained either using the full VA questionnaire, or alternatively using a minimal set of questions that included age at death, sex, vaccine status, location of normal residence, and whether the death was due to illness or accident/ trauma.

5.3.3.2 Sentinel hospital surveillance (severe malaria)

Sentinel hospital surveillance is described the Safety section above (5.3.2.1) and Section 10 of the MVPE protocol.

5.3.3.3 Study size and expected number of events (mortality and severe malaria)

Details on sample size and power calculations for impact on mortality and severe malaria are presented in detail in the Statistical Analysis Plan.

The final evaluation of vaccine introduction impact on mortality will be available in 2023, after a sufficient number of deaths have accrued. To detect a 10% reduction in mortality with 90% power, approximately 24000 deaths would be required; currently just over 13,500 deaths have accrued. However, the evaluation by 24 months was well powered to detect a gender imbalance in all-cause mortality of the magnitude observed in the Phase 3 trial, if it occurred in the pilot implementations, in children up to about 2 years of age.

For severe malaria, a total of about 3000 severe malaria cases (age eligible and non-eligible groups combined) were required for 80% power to detect a reduction of 24%, and 4000 cases for 90% power. At the time of analysis, 4091 cases of severe malaria had accrued (1406 and 2685 in the age eligible and non-age eligible groups respectively).

5.3.3.4 Limitations

The lack of routine vital event registration systems poses a challenge to the evaluation of impact on survival. Especially in more remote areas, deaths of children may not be reliably notified to either the authorities or the village-based reporting system. To address this challenge, supervisory strategies were developed and instituted in each of the pilot countries, as were quality assurance measures. Monthly performance data review meetings were held with the statistical team, which included a designated statistician or data manager from each of the pilot countries, to review the frequency of key variables (e.g., number of households visited, number of deaths reported, etc.) and outlying values were identified and in-depth discussions held to identify any corrective actions. Attempts were made to triangulate data collected through the community-based mortality surveillance systems, including

through cross-referencing hospital-based deaths from the surveillance hospitals and through comparison with estimates from DHS surveys and from DSS data.

It is possible that children living in comparison areas might be brought for vaccination in areas allocated to RTS,S/AS01 implementation (resulting in "contamination"). This could potentially lead to an under-estimate the impact of the vaccine on all-cause mortality detected at the community level. The level of contamination in the pilots was reduced by selecting areas which are as geographically large as possible, making it more difficult for people to seek vaccinations outside their own area. Contamination rates were able to be estimated through survey data, and analyses were adjusted accordingly (Annex 3).

5.3.4 Feasibility

5.3.4.1 Overview

A variety of approaches were used to assess the feasibility of delivering RTS,S/AS01 according to the recommended schedule. Malaria vaccine coverage is the primary quantitative outcome measure representing both programmatic feasibility as well as community and health worker acceptance. The coverage, acceptability, and cost of introduction of RTS,S/AS01 was estimated using complementary approaches:

1. Routine, facility-based administrative coverage data, reported monthly.
2. Household surveys (HHS): EPI representative cluster -sample household surveys, conducted three times during the programme (baseline, midline, and end line)
3. New vaccine post-introduction evaluation (PIE)
4. Health utilization survey (HUS)
5. Cost of delivery study

The two complementary approaches to estimating vaccine coverage, facility based administrative coverage and representative cluster- sample household survey, have pros and cons which are discussed in more detail in Section 11.1 of the MVPE protocol.

In addition to coverage estimates, programmatic assessments through WHO's Post Introduction Evaluation (PIE) tool seek to examine programme operations with a view to improving the delivery of RTS,S/AS01. The PIE tool has been adapted for the malaria vaccine pilot implementation.

A longitudinal, qualitative assessment (health utilization survey), included exploration of any behaviour change, providing a contextual background for the quantitative estimates. The qualitative assessments provided insights as to whether and how behaviours, such as treatment seeking for febrile children, use of malaria prevention measures, EPI vaccination, etc., changed with the introduction of RTS,S/AS01. The qualitative evaluation complemented the quantitative data gathered during representative household cluster surveys.

Finally, a cost of delivery study was conducted to evaluate the cost of introducing and delivering the malaria vaccine in each of the pilot countries from the provider perspective. The costing study did not include costs to household in seeking vaccination.

5.3.4.2 Routine administrative coverage

The EPI programmes in the three implementing countries routinely collect administrative vaccination data on vaccines they administer. The programmes, together with national statistics offices, compute and determine target vaccination populations. The vaccination data and the target population are used in the calculation of coverage rates. Vaccination facilities receive vaccine eligible children, vaccinate them and collect data about vaccination and the vaccinees. The data about vaccine coverage are then sent to an intermediate level (sub-district/sub-county/district/county) in the reporting pathway for consolidation. The intermediate level sends consolidated coverage data to the national level. The national level shares relevant data with the MVIP. The MVIP receives monthly coverage data on RTS,S/AS01 by dose number. In addition, the MVIP receives monthly coverage data for the 3rd dose of pentavalent (DTP-HepB-Hib) vaccine, and for the 1st and 2nd dose of measles-rubella vaccine, from the same areas for comparison.

5.3.4.3 EPI cluster-sample household surveys

A baseline representative sample household survey was conducted in each country to provide data on the prevalence of malaria infection and coverage of EPI vaccines, in both implementation and comparator areas before RTS,S/AS01 introduction. Follow-up surveys were conducted at approximately 18 – 24 (midline) and are planned for 30-36 months (endline) after the start of RTS,S/AS01 vaccination in implementation and comparator areas. These surveys estimate the coverage of the standard EPI vaccines and, in implementation areas, the coverage of the primary series of RTS,S/AS01 (in the midline survey) and of the primary series and the fourth dose of RTS,S/AS01 (in the endline survey). Results from the baseline and midline surveys are presented in Section 6.3 of this report.

The survey methodology is described in detail in Section 11 of the MVPE protocol. In brief, surveys were carried out in a sample of households from implementation and comparison areas. Four groups of ~25 households (survey “clusters” or primary sampling units, PSUs) were selected from each implementation and comparison cluster, such that each household in a PSU had an equal probability of being sampled. New samples of households were drawn for each survey. Sampling methods were the same as used in standardized national surveys (DHS, MIS, MICS) to enhance comparability of the findings. Typically, a two-stage cluster design was used but could have been varied or adapted as long as a probability sampling approach was used.

All consenting primary caretakers/mothers of children aged 5-48 months were interviewed, with data collected on contextual factors (e.g., use of insecticide-treated nets, socio-economic status, access to health facilities) as well as receipt of EPI vaccines and vitamin A. An interview was conducted for each eligible child. The second household survey was restricted to children aged 12-23 months, the target group for the assessment of coverage of RTS,S/AS01 doses 1-3. The variables included in the feasibility analysis were taken from standard household survey questionnaires, and are summarized in Section 11 of the MVPE protocol.

Vaccination status was assessed from the child health card. When no health card was available the information was solicited from the caregiver and documented as such. Vaccination information collected through maternal recall included asking about each vaccine (per country-specific EPI

guidelines) and the number of doses, with detailed prompts characterizing the vaccines to enhance the quality of the recall. For the midline survey, a sample of children with the health card available was selected for an assessment of the reliability of verbal recall to enable the comparison between the written record and the verbal recall by the caregiver.

A sample size of 100 houses per cluster allowed for an estimate of the cluster-specific coverage of RTS,S/AS01 to within 10% (i.e., 95% CI from 40 to 60%) using a conservative estimate of 50% coverage and a high response rate above 95% in each cluster. Assuming a design effect of 1.5 between clusters, the overall precision in RTS,S/AS01 and coverage estimates of other vaccines over the MVIP implementation and comparison areas was 2% (i.e., 95%CI 48% to 52%) in each country. The second household survey was powered to generate coverage estimates in the RTS,S/AS01 implementation vs. comparator areas, rather than in each cluster, to within ±2% of the true value.

5.3.4.4 Post-Introduction Evaluation (PIE)

A PIE was anticipated in each pilot country to systematically assess the overall impact of malaria vaccine introduction on the existing immunization system, with a focus on identifying positives and challenges for implementation, documenting best practices and lessons learned, and developing recommendations for improvement. Evaluations are typically conducted across all levels of the health system (national, sub-national, health facility), and involve a variety of data collection efforts, including desk reviews of relevant reports and plans, observation at vaccination sessions at facilities, and interviews with key informants at national, sub-national, and health facility, including clients (mothers/caregivers). Specific areas explored are pre-implementation planning and vaccine introduction, training, vaccine coverage, cold-chain management, vaccine management, transport and logistics, vaccine wastage, waste management and injection safety, monitoring and supervision, adverse events following immunization, and advocacy, communication and acceptance.

Typically, the PIE seeks to capture the status of vaccine implementation 6 to 12 months after the start of vaccinations, and to document best practices of its introduction. Due to COVID-19, the PIE for the malaria vaccine were postponed in all countries from early 2020 due to travel restrictions and other priorities by the MoH. By the time of this report, the PIE had been completed in Malawi in May 2021, Kenya in August 2021, and plans are underway to complete in Ghana later in 2021.

5.3.4.5 Health Utilization Survey (HUS)

The detailed methods for the HUS are provided in Annex 5. In brief, the HUS generates qualitative evidence to provide insight into three broad areas. First, RTS,S/AS01 uptake, mainly through interviews with primary child caregivers (PCGs) of children eligible to receive the vaccine, specifically exploring how PCGs learn and hear about RTS,S; identify factors that facilitate or obstruct the adoption of RTS,S/AS01 and adherence to recommended doses; changes in PCGs perceptions, behaviours, and experiences related to RTS,S/AS01 over time; how the adoption of RTS,S/AS01 affects malaria prevention and treatment-seeking behaviours; and how PCGs' interactions with the health system and the child's receipt of the vaccine shape RTS,S/AS01 uptake and adherence to recommended doses.

Second, issues around delivery and integration are explored through interviews with health workers administering vaccines, focusing on understanding: provider perceptions about and understanding of

RTS,S, including adverse events; how the vaccine is being promoted in communities and in child health services; how providers communicate partial protection of RTS,S/AS01 and messages about the four-dose schedule; challenges and facilitators in the provision of RTS,S/AS01 and integrating its delivery with existing EPI services; and how and why providers' perceptions, attitudes, and experiences related to RTS,S/AS01 change over time. Service provider interviews are supplemented with interviews with health programme managers and policymakers, focusing on similar areas as well as policy-level and planning issues.

Third, Community reception of RTS,S/AS01 is explored through individual and group interviews with various other community groups. Areas explored include: different communication channels through which communities learn about RTS,S; what community leaders/members take away from their exposure to RTS,S/AS01 messaging and how they, in turn, talk about RTS,S/AS01 and promote or discourage uptake; and how and why community leaders'/members' perceptions and attitudes about RTS,S/AS01 change over time

The HUS uses a longitudinal study design, involving both cohort and cross-sectional samples, to understand RTS,S/AS01 introduction and uptake as a process shaped by changing contexts over time. There are three data collection rounds planned for the HUS: Round 1 data collection commenced shortly following introduction of RTS,S/AS01 dose 1 in targeted communities in 2019; Round 2 data collection was completed after initial delivery of dose 3 but prior to delivery of dose 4 and; Round 3 data collection follows the delivery of dose 4 and is ongoing as of this report.

5.3.4.6 Cost of introduction and delivery study

The cost of introduction and delivery study generated incremental cost estimates of RTS,S/AS01 introduction and delivery using data on actual activities (for example, planning and coordination, procurement and distribution, training, sensitization, social mobilization, service delivery, supervision and monitoring) and costs incurred from 2018 through the end of 2020. The study included operational cost data collected from representative health facilities (between 24 to 32 facilities) within MVIP areas as well as at regional/national levels, in each country. At the time of this report, limited data were available to estimate the cost of dose 4 vaccination and cost per fully immunized child (FIC), as the vaccine's schedule and age-eligibility meant that children only began receiving dose 4 at the very end of the study period. Under this constraint, dose 4 and FIC unit cost estimates were generated under assumed coverage levels. For RTS,S/AS01 doses 1-3, observed coverage during MVIP up until the end of 2020 were used. Drop-out rates for measles-containing vaccines (MCV) dose 1 to dose 2 for 2019 were used to proxy drop-out rates for RTS,S/AS01 dose 3 to dose 4 to derive an estimate for dose 4 coverage and provide an indication of the potential cost of delivery by dose. These interim cost estimates will be updated in 2022 using more comprehensive data on dose 4 coverage and costs, in order to generate cost of delivery by dose and cost per FIC.

6 Malaria Vaccine Implementation Programme (MVIP) - Evaluation Results

6.1 Safety results

Three safety signals were identified in the Phase 3 trial, which were unexplained: an excess of meningitis cases in vaccine recipients (rate ratio of 10.5:1), an excess of cerebral malaria cases (rate ratio 2.15:1) and, among girls, excess all-cause mortality (rate ratio 2.0), with a mortality ratio (RTS,S/AS01: control) that was 2.6 fold greater among girls than for boys.

In the MVPE, high coverage of the primary three doses of RTS,S/AS01 was achieved in each country (see Section 6.3) in Malawi, Ghana and Kenya respectively) and sufficient events observed, from the three countries combined, to allow effects of the magnitude observed in the Phase 3 trial to be detected, if they occurred, with 90% power in pooled analysis.

The results below are taken from the MVPE statistical report, which is provided as Annex 3. The population contributing to the evaluation of vaccine safety comprises children eligible to have received at least one RTS,S/AS01 vaccine dose.

6.1.1 Sentinel hospital surveillance

6.1.1.1 Meningitis

A total of 4,311 suspected cases of meningitis were investigated. Lumbar punctures were performed in 2,652 (62%) of these patients, and polymerase chain reaction (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 (identified based on examination of CSF, or a positive PCR result) 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, 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, 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, and there were sufficient cases, and high coverage of the vaccine, to detect an excess of the magnitude observed in the Phase 3 trial.

Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received 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) 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*).

6.1.1.2 Cerebral malaria

There were 1,405 cases of severe malaria (*P. falciparum* infection with severe anaemia, or respiratory distress, or with impaired consciousness or convulsions but not meeting criteria for meningitis) among children who were eligible to have received at least one dose of the malaria vaccine, 558 from implementation areas and 847 from comparison areas (Figure 3). Among these, there were 55 cases of cerebral malaria (positive for *Plasmodium falciparum* by rapid diagnostic test or microscopy, with impaired consciousness (i.e. a Glasgow coma score <11 or Blantyre coma score <3 or assessed as P or U on the AVPU ("Alert, Voice, Pain, Unresponsive") score, in whom lumbar puncture had been performed to exclude cases with probable meningitis), 25 from implementation areas and 30 from comparison areas. Among age groups of children not eligible to have received 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% 0.44, 1.35). The incidence rate ratio for admission with other forms of severe malaria (excluding cerebral malaria) was 0.70 (0.54, 0.89), but there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (0.57, 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 had not been 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, and 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, 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" on the AVPU score.[1]. Among children eligible to have 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, 1.43).

Therefore, there was no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria, and there were sufficient cases to detect an excess of the magnitude observed in the Phase 3 trial, if it was present.

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

[1] The AVPU scale (an acronym from "alert, verbal, pain, unresponsive") is a system by which a health care professional can measure and record a patient's level of consciousness and is a simplification of the Glasgow Coma Scale, used in the two case definitions above

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 an LP, was 1.58, 95%CI 0.66,3.80).

6.1.1.3 *Gender-specific mortality*

Excluding deaths due to injury, among children eligible to have received three doses of RTS,S/AS01, there were 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 between implementing and comparison regions, was 0.93 (95%CI 0.84,1.03), a 7% reduction (95%CI -3%,16%). There was no evidence that the mortality ratio differed between girls and boys (p 0.343). The mortality ratio in girls was 0.98 and in boys 0.90, yielding a relative mortality ratio (girls:boys) of 1.08 (95%CI 0.92,1.28).

When analysis was extended to children eligible to have received at least one dose of vaccine, similar results were obtained (ratio of mortality ratios: 1.08 (95%CI 0.93, 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, 1.29, and in eligible children aged 18 months and above, 0.95, 95%CI 0.70, 1.31).

Therefore, 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, and there were sufficient deaths to detect an excess of the magnitude observed in the phase 3 trial, if it was present.

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 RTS,S/AS01 was 77.6% in girls and 73.0% in boys in Ghana and 75.1% and 70.1% in Malawi.

6.1.2 Adverse events following immunization

Based on data reviewed from the national PV programs, the DSMB did not find evidence of new conditions that warrant closer safety tracking (Annex 6). In Ghana, Malawi, and Kenya, AEFI data are regularly received from the MVIP areas and have been presented to the MVIP DSMB at each of their meetings by representatives from the NRAs in each MVIP country.

Representatives from the Ghana Food and Drugs Authority (GFDA), the Malawi Pharmacy and Medicine Regulatory Authority (PMRA) and the Kenya Pharmacy and Poisons Board (PPB) provided updates on cumulative AEFI and AESI cases for their representative countries. None of the assessed serious AEFIs reported through May 2021 in Kenya and through June 2021 in Ghana were identified as causally related to RTS,S/AS01 by the NRAs. In Malawi, the causality assessment has not yet been completed; financial support has been made available and the NRA was requested to prioritize this activity.

At the 27-28 July 2021 MVIP DSMB meeting, the DSMB Chair asked the NRA representatives to indicate if, based on the experience to date, they have any safety concerns or adverse events they are monitoring for the routine implementation of the RTS,S/AS01 malaria vaccine. Each indicated there are no specific concerns and the observations from the safety monitoring thus far have been comparable to other vaccines in the EPI schedule for this age range.

The DSMB did note that collecting and investigating adverse events following vaccination remains a challenge for national PV programs. Most of the reports were generated in the context of the Phase 4 study or the MVPE, and very few serious events or deaths were investigated. Regarding the target minimal reporting threshold of 10 AEFI per 100 000 surviving infants per year (a proxy measure for an established national AEFI reporting system), Ghana and Malawi exceeded this threshold, whereas in Kenya the reporting ratio has been below this target.

6.1.3 GSK Phase 4 Study

At the time of the preparation of this summary, the GSK Phase 4 study data were still in the process of data entry and cleaning, so no conclusions can be drawn from those data. An interim analysis of the phase 4 studies will be available in 2023, with final analysis in 2025, after a potential WHO recommendation for broader RTS,S/AS01. Although not a formal analysis, event monitoring through the GSK Phase 4 study, presented to the DSMB on a quarterly basis, has not exposed an apparent excess of the safety signals seen in the Phase 3 trial and has not revealed any new safety signals to date.

Formal annual reviews have been conducted by EMA based on GSK submission of Periodic Safety Update Reports, and the positive scientific opinion has been maintained since 2015[22].

6.1.4 Interpretation of safety findings

The DSMB reviewed the MVPE 24-month results (DSMB 24 months review report, Annex 6). They concluded that the safety signals seen among 10,306 infants and children who received RTS,S/AS01 in the Phase 3 clinical trial of RTS,S/AS01 (2009-2014) were not detected through pharmacovigilance in the pilot implementation after 652,673 children received their first dose (and 494,745 their third dose) in implementation areas where the vaccine was provided, or among the 9,994 age-eligible children admitted to the pilot evaluation sentinel hospitals (4,853 from implementation areas), during the period from start of vaccination in 2019 until 30 April 2021 .

The DSMB concluded that the safety signals seen in the Phase 3 clinical trial (2009 – 2014) were not seen in the pilot implementation. The MVPE results showed comparable burden for meningitis, cerebral malaria, and gender-specific mortality among age-eligible children living in implementation areas and those in the comparison areas. Key data to support this included:

- Power calculations for the three safety endpoints indicated that the number of endpoints accrued was adequate to exclude associations of a similar magnitude to those observed in the Phase 3 trial, after accounting for observed levels of vaccine coverage and contamination on population-level effects.
- The results consistently show risk ratios near 1 (i.e., no association) for probable meningitis, cerebral malaria, and the vaccine-gender interaction with mortality. In addition, pooled estimates were inconsistent with the corresponding risk ratio point estimates (adjusted for vaccine exposure) observed in the Phase 3 trial. In other words, the hypotheses were rejected that the vaccine was associated with increased risk levels for those three specific safety endpoints of a magnitude seen in the Phase 3 trial.
- The proportion of patients with meningitis, or cerebral malaria, from implementation areas, who had received RTS,SA01 was not greater than that for patients with other conditions, and

among the children who died, the proportion of girls who had received RTS,S/AS01 was similar to that for boys, reflecting the similar coverage in girls and boys in the household surveys, indicating vaccine uptake was not higher in children who presented with the safety signals seen in the Phase 3 trial.

- The real-world setting of the MVIP and generation of an imperfect dataset was acknowledged, which is unlike a Phase 3 clinical trial. However, it was noted that the MVIP team and partners sought to ensure that as much complete and quality-assured data as possible were available for the analyses. The MVIP had continuously responded to feedback from the DSMB and PAG to identify and act upon areas for improvement since the beginning of the programme. Any deficiencies or missing data are expected to be equally distributed between the RTS,S/AS01 vaccine-implementation areas and non-implementation areas so as not to bias the analysis.
- Some limitations were noted, but those did not alter the conclusions regarding safety:
  - Unlike the analyses of the other safety endpoints (deaths among girls and meningitis), the cerebral malaria analysis, when a broader definition was used, had an upper confidence limit (1.52) closer to the (coverage-adjusted) point estimate of the Phase 3 trial (1.60). The results were less certain about the cerebral malaria endpoint because of these numbers, the difficulty of diagnosing cerebral malaria given the lack of resources to exclude other causes of encephalopathy in the MVPE sentinel hospitals, and the rarity of the outcome. The DSMB support plans to strengthen the safety assessment for cerebral malaria through further data collection in the MVPE that includes tracking of this endpoint.
  - The challenges with meningitis surveillance were noted, specifically the potential for many missed probable and confirmed cases because of variable performance of lumbar punctures among suspected cases. However, there is no reason to suspect that the use of lumbar puncture in age-eligible children vs age-ineligible children differed between implementation and comparison areas, so it is unlikely that under-detection biased the analysis.

The recently established African Advisory Committee for Vaccine Safety and the well-established Global Advisory Group for Vaccine Safety agreed with the DSMB conclusions following their review of the DSMB recommendations and MVPE results (Annex 7).

Following the review of the MVPE results, the MVIP Programme Advisory Group agreed with the DSMB conclusions presented to the Programme Advisory Group by the DSMB Chair.

6.2 Impact results

6.2.1 Community based mortality surveillance

Overall, a total of 13682 deaths 1-59 months of age were reported to March 31, 2021 (deaths in April 2021 were excluded because verbal autopsies have not all been completed). Of these deaths, 4729 were in vaccine-eligible age groups, and 95.5% of these had verbal autopsies completed (or, in the case of facility deaths in Malawi, hospital records obtained), and a cause of death (categorized as due to injury, or other causes) established for 4280/4729 (90.5%). As noted above, the evaluation was not powered at this time point to assess impact of vaccine introduction on overall mortality. Gender-specific mortality findings are discussed in Section 6.1.1.3.

6.2.2 Sentinel hospital surveillance – severe malaria

Among children eligible to have received all three primary doses of RTS,S/AS01, there were a total of 1107 admissions with severe malaria (*P. falciparum* infection with severe anaemia, or respiratory distress, or with impaired consciousness or convulsions but not meeting criteria for meningitis), 418 from implementation areas and 689 from comparison areas. Among children who were not eligible to have received any doses of RTS,S/AS01 there were 1313 patients admitted from implementation areas and 1390 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementation and comparison areas was 0.70 (95%CI 0.54, 0.92), a reduction of 30% (95%CI 8%, 46%) in the context of overall vaccine coverage during the first two years of vaccine introduction of approximately 60-70%. As per Section 6.1.1.2, there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria.

Of the severe malaria cases in children eligible for three doses of RTS,S/AS01, a total of 284/1107 patients had severe malaria anaemia (26%). The incidence rate ratio for this subgroup of severe malaria was 0.78 (95%CI 0.55, 1.09), with no evidence that effectiveness differed when compared to that for other forms of severe malaria (interaction test p-value 0.529).

6.2.3 Sentinel hospital surveillance, secondary outcomes measures for impact

6.2.3.1 Hospital admissions with a positive malaria test

Patients admitted to sentinel hospitals were routinely tested for malaria infection by 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, 0.93), a reduction of 21% (95%CI 7,32%).

6.2.3.2 All cause hospital admissions

Severe malaria represented 19% of all admissions to sentinel hospitals (with at least one overnight stay) in comparison areas, among children who would have been eligible to have received 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, 1.03), a reduction of 8% (95%CI -3%, 17%).

6.2.4 Interpretation of impact findings

The DSMB concluded that the MVPE findings demonstrated effectiveness of RTS,S/AS01 vaccine against severe malaria. These conclusions were based on:

- The number of events accrued were adequate to demonstrate significant benefit for preventing severe malaria. For mortality, the number of accrued events had not yet reached the target sample size, so the analysis was not yet adequately powered.
- The pooled analysis indicated that RTS,S/AS01 vaccine significantly reduced the incidence of severe malaria in the implementation areas, and hospital admissions with a positive malaria test; a non-statistically significant reduction in all-cause mortality (excluding accidents/trauma) was also seen.

As expected, the results were not yet powered to detect an effect on mortality, but the size of effect is consistent with expected impact.

The MVIP Programme Advisory Group agreed with the DSMB conclusions presented by the Chair, following their review of the MVPE results.

6.3 Feasibility results

6.3.1 Routine administrative coverage

As of the end of June 2021, 2 million doses of the RTS,S/AS01 malaria vaccine have been administered across Ghana, Kenya and Malawi (see Figure 7). Over 710 000 children have received at least one dose of the malaria vaccine, and over 110 000 children have received their fourth and final dose.

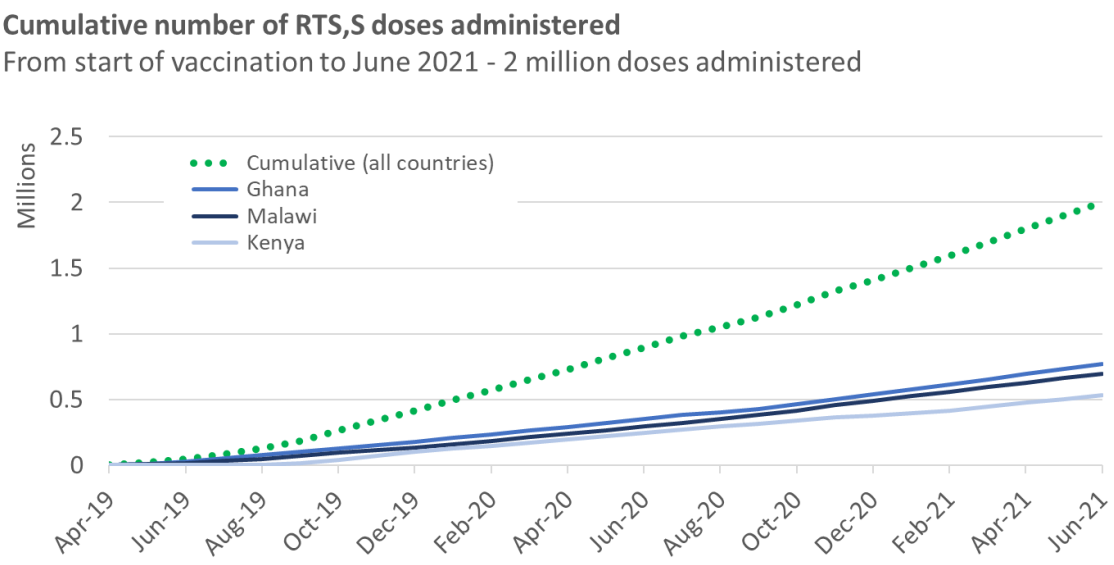


Figure 6*: Cumulative number of RTS,S administered since start of the programme*

Table 1: Vaccine coverage estimates for different time periods according to routine administrative data

Country	Time period	RTS,S-1	RTS,S-2	RTS,S-3	RTS,S-4	Penta-3	MR-1	MR-2
Malawi	Since start (Apr 2019 – Jun 2021)	77%	67%	63%	39%	89%	85%	n/a
	2020 annual (Jan – Dec)	88%	79%	73%	28%	95%	90%	n/a
	2021 first half (Jan – June)	**93%**	**84%**	**82%**	**46%**	**96%**	**94%**	**78%**
Ghana	Since start (May 2019 – Jun 2021)	70%	67%	65%	38%	91%	85%	n/a
	2020 annual (Jan – Dec)	71%	67%	66%	30%	92%	85%	n/a
	2021 first half (Jan – June)	**74%**	**72%**	**74%**	**42%**	**88%**	**87%**	**77%**
Kenya	Since start (Sept 2019 – Jun 2021)	80%	71%	62%	41%	75%	76%	40%
	2020 annual (Jan – Dec)	69%	64%	60%	*	72%	73%	39%
	2021 first half (Jan – June)	**80%**	**72%**	**63%**	*****	**83%**	**86%**	**53%**

*Notes: * Considered too early for calculation of meaningful coverage estimate for the 4th dose.*
Penta-3 = 3rd dose of pentavalent (DTP-HepB-Hib) vaccine; MR 1 = 1st dose of measles-rubella vaccine; MR 2 = 2nd dose of MR vaccine

Demand and uptake of the malaria vaccine has been strong across all three countries despite the challenges brought about by the COVID-19 pandemic. While there was variation in performance observed, according to administrative data, since start of vaccination, all three countries reached at least 70% of their target populations with the first RTS,S/AS01 dose and at least 62% with the third RTS,S/AS01 dose (see Table 1). This level of uptake is considered satisfactory and within expectations for a new vaccine with a novel schedule, i.e., targeting children as of 5 months (in Malawi) and 6 months (Ghana and Kenya) for the first dose.

Administration of the malaria vaccine as part of the routine immunization system has continued despite the challenges and effects of the COVID-19 pandemic. It is notable that Ghana experienced malaria vaccine stock-outs at certain health facilities in August 2020 due to delayed shipment of the vaccine, which was in part related to COVID-19 and Kenya experienced health worker strikes related to COVID-19 working conditions in August 2020 and between December 2020 and February 2021, but vaccine uptake swiftly recovered once these disruptions were resolved. The ability of the EPI Programmes to maintain or improve upon performance, and to quickly recover from COVID-19 related disruptions, is a testament to their resilience. It also demonstrates the demand for the vaccine by parents and the acceptance by health workers who provide the vaccine.

MVIP partners have supported MoHs and country-level partners to develop vaccine implementation strategies that support timely uptake of the four-dose schedule. The approaches build on efforts to clarify age eligibility to reduce drop-out rates between vaccine doses and to encourage catch-up of missed vaccinations.

The following section reviews each country's performance in more detail and in comparison with the third dose of the Pentavalent vaccine protecting against diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae type b (Penta-3, given at 14 weeks) and first and second dose of the Measles-Rubella vaccine (MR1, given at 9 months and MR2 given at 15 or 18 months) for the same target population in the same MVIP areas.

6.3.1.1 RTS,S/AS01 uptake in Malawi

Malawi introduced the malaria vaccine into its routine immunization programme in select areas of 11 districts on 23 April 2019. Over 695 000 doses of RTS,S/AS01 have been administered to eligible children between start of vaccination and 30 June 2021. Approximately 247,000 children have received the first vaccine dose and 44 700 children have completed the 4-dose course. The National Task Force advised there be no formal launch event when RTS,S/AS01 vaccination started. Minimal community engagement and social mobilization activities began around the time the vaccine was introduced. This 'silent' launch has likely contributed to low initial uptake. The EPI and partners have conducted further social mobilization and community engagement, which has been associated with steadily increasing coverage.

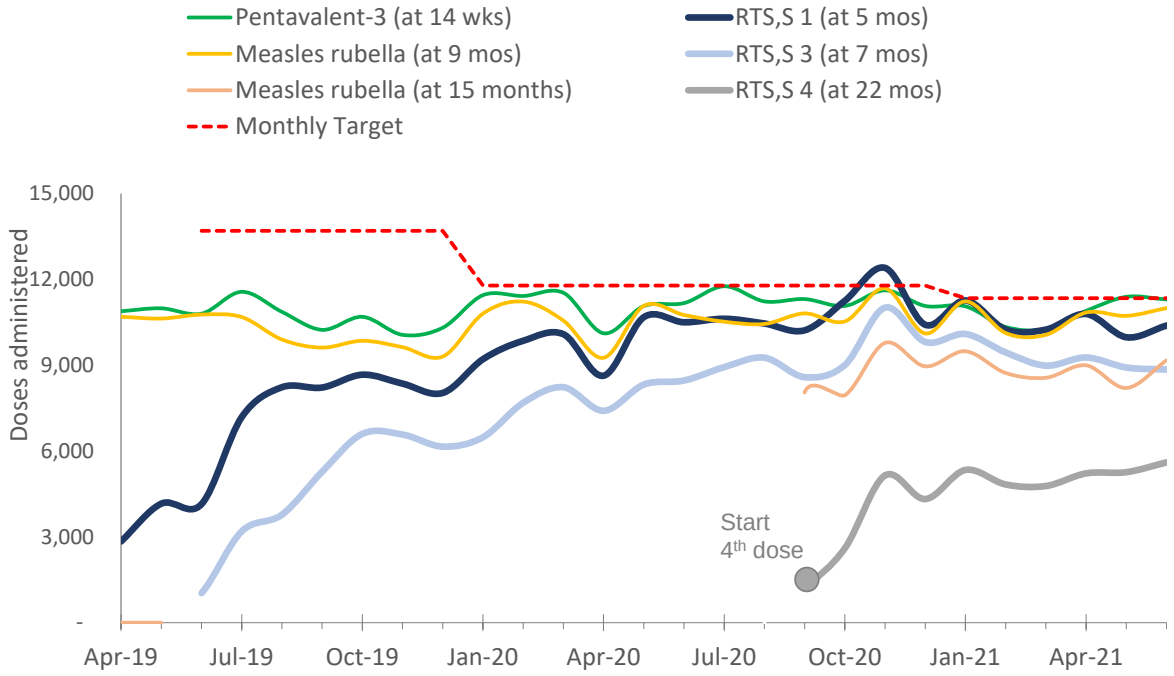


Figure 7*:* Number of doses administered for selected antigens including RTS,S from April 2019 to June 2021 among MVIP target population, Malawi, administrative data

By July 2020, just over a year after vaccine introduction, uptake of the first dose of RTS,S reached the level of MCV1, and by October 2020 the level of Penta-3 (Figure 8). Coverage reported in the first half of 2021 remained relatively stable at high levels: 93% coverage of RTS,S/AS01 dose 1, 84% of dose 2, and 82% of dose 3 based on monthly targets (Table 1). This is improvement compared to already strong performance in 2020 when annualized coverage of the first dose was 88%. Measured over the first half of 2021, the coverage of RTS,S-1 reached a similar level as MR-1 at 94% and reported slightly below Penta-3 at 96% and significantly above MR-2 at 78%. In the same period, the overall drop-out rate from first to second dose of RTS,S/AS01 was 10%; the drop-out rate from first to third dose was 12%, indicating an improvement compared to the previous year when drop-out rates were over 20%.

The first children who were 5 months of age at the start of the programme in Malawi in April 2019 were age eligible (22 months) for the fourth dose in September 2020. Therefore, as of June 2021, there has been approximately ten months of fourth dose administration. During this period, approximately 81% of all age-eligible children who received dose 3 have returned for dose 4 (i.e., a drop-out rate of approximately 19%). Relatively high drop-out rates continue to be a main area for improvement, particularly for the fourth dose.

6.3.1.2 RTS,S/AS01 uptake in Ghana

Ghana introduced the malaria vaccine into routine childhood immunization in 42 districts (7 regions) on 1 May 2019 preceded by a themed community launch event –"Malaria vaccine for additional protection." Over 772 000 doses have been administered to eligible children between start of

vaccination and 30 June 2021. Almost 261 000 children have received the first vaccine dose and over 49 000 children have completed the 4-dose course.

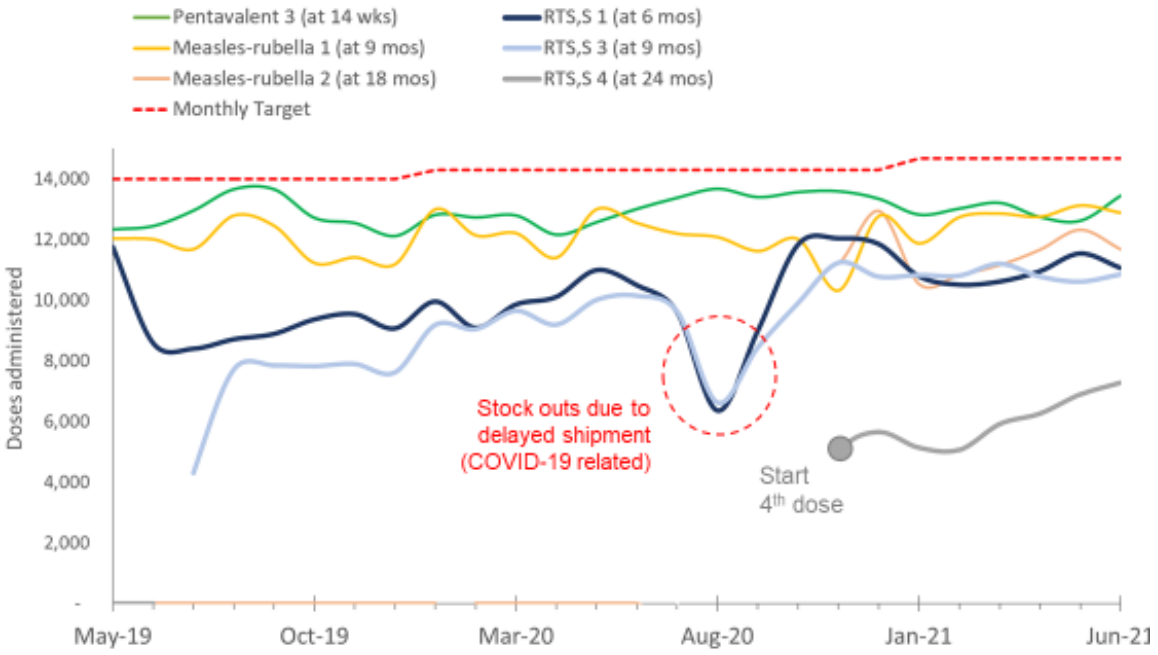


Figure 8: Number of doses administered for selected antigens including RTS,S from May 2019 to June 2021 among MVIP target population, Ghana, administrative data

Uptake was high in the first month of introduction, likely driven by the MOH guidance to target children 6 and 7 months of age for the first dose of RTS,S/AS01. There has been a slow but steady increase in the number of doses administered per month, with the majority of MVIP regions reaching 60% to 85% of the monthly target population with the first dose by mid-2020 (Figure 9). The significant drop in malaria vaccine coverage in August 2020—when only around 45% of the monthly target population was reach – was due to a delayed international RTS,S vaccine shipment that led to stock-outs in some facilities. Stocks were replenished over the course of August and missed children identified for catch up immunization activities. Mop-up activities enabled a strong recovery exceeding pre-stock out coverage levels by October 2020.

Coverage in the first half of 2021 across all implementing districts was 74% for the first dose, 72% for the second dose and 74% for the third dose (Table 1). Compared to the annualized coverage for 2020, this represents a 3% increase in first dose coverage and an 8% increase in third dose coverage. This remains below the reported coverage for Penta-3 (88%), MR-1 (87%) and slightly below MR-2 (77%) in the same areas during the same time period. During the first half of 2021, the drop-out rate from first to second dose of RTS,S/AS01 was 3%; the drop-out rate from first to third dose was 1%, suggesting a high return rate of children who were initiated with the malaria vaccine. The first children who were 7 months of age at the start of the programme in Ghana in May 2019 were age eligible (24 months) for the fourth dose in October 2020. Therefore, as of June 2021, there have been approximately 9 months of fourth dose administration. During this period, approximately 70% of all age-eligible children who received

dose 3 have returned for dose 4 (i.e., a drop-out rate of approximately 30%). Relatively high drop-out rates for the fourth dose continue to be a main area for improvement.

6.3.1.3 RTS,S/AS01 uptake in Kenya

Kenya introduced the RTS,S/AS01 malaria vaccine into routine childhood immunization in 26 Sub-Counties with high malaria burden in 8 counties on the 13 September 2019. There was a major launch event and subsequent county-level launch events for other participating sub-counties. Over 530 000 doses have been administered to eligible children in the selected areas between the start of vaccination and 30 June 2021. More than 204 000 children have received the first vaccine dose and over 17,300 children have completed the 4-dose course.

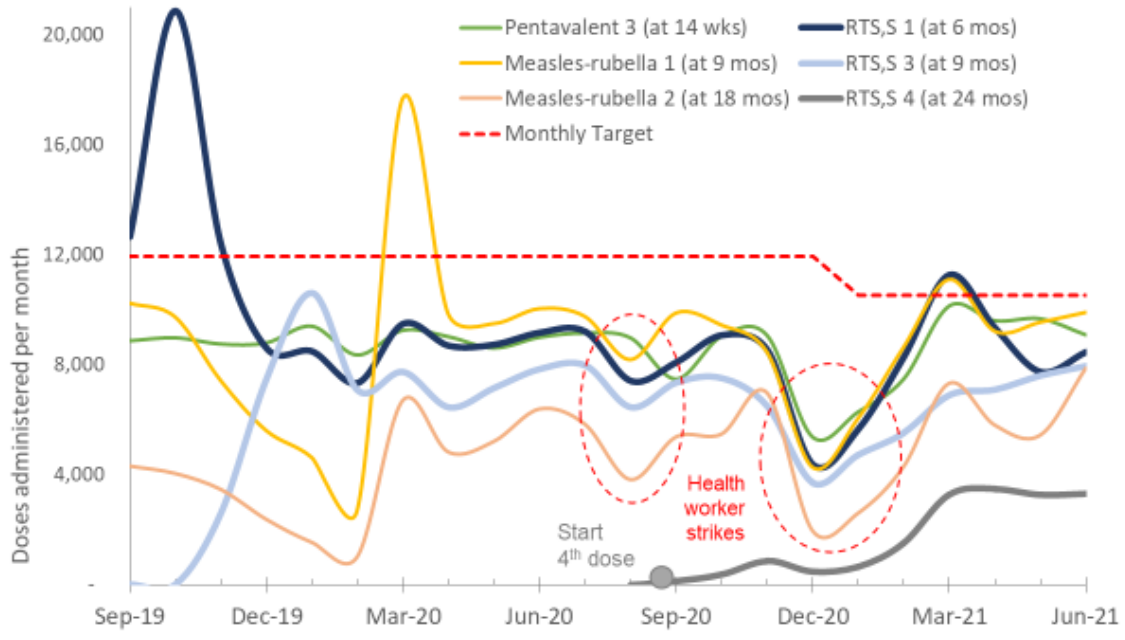


Figure 9*:* Number of doses administered for selected antigens including RTS,S from September 2019 to June 2021 among MVIP target population, Kenya, administrative data

The MOH guidance was to offer the first dose of RTS,S/AS01 to children aged 6 to 12 months at the time of the launch. This policy explains the high uptake of the vaccine in the initial months. Within a few months following introduction, the coverage of RTS,S-1 reached similar levels as Penta-3, indicating a high capacity by the Kenya National Vaccines and Immunization Programme (NVIP) to mobilize caregivers to return for a new vaccination visit when the child is 6 months old (Figure 10). Health worker strikes in mid-2020 and between December 2020 to February 2021 have led to a considerable drop in vaccination rates for all antigens. Full recovery to pre-strike levels and some evidence of catch-up of missed children was seen starting in March 2021.

Coverage in the first half of 2021 across all implementing sub-counties was 80% for the first dose, 72% for the second dose and 63% for the third dose (Table 1). Compared to the preceding 6-month period (July-December 2020), this represents a 15% increase in first dose coverage and an 8% increase in third

dose coverage. Coverage of RTS,S-1 has maintained similar levels as Penta-3 since the first few months of introduction. In the first half of 2021, the drop-out rate from first to second dose of RTS,S/AS01 was 10%; the drop-out rate from first to third dose was 22%. Due to the expanded age group (6 to 12 months old) at the time of vaccine introduction in Kenya, there is a small proportion of children that reached the age of 2 years and have returned for the 4th dose of RTS,S, starting in September 2020. The first children who were 6 months of age at the start of the programme in September 2019 were age-eligible for dose 4 when celebrating their 2nd birthday in March 2021. During either observation period (September 2020 to June 2021 for older children or March to June 2021 for younger children), the estimated drop out during this period was 59%; i.e., approximately 41% of age-eligible children who received the third dose of RTS,S/AS01 have returned for their fourth dose.

6.3.2 Household survey (HHS)

Highlights of findings of the midline HHS for Ghana, Malawi and Kenya are summarized here.

Key findings were as follows:

- Enrolment: In Ghana, Malawi, and Kenya, the number of children 12-23 months enrolled was 2311, 2568, and 3074 respectively. Of these, 91.1% in Ghana, 88.1% in Malawi and 88.0% in Kenya had vaccination cards available and this did not differ significantly between vaccine and comparator areas or from baseline.
- In Malawi, in the survey conducted in March-April 2021 in children 12-23 months of age, who were due for their first dose between Sep 2019 and Aug 2020, 72.5% had received their first dose of RTS,S/AS01 according to the home-based record (HBR) or caregiver recall, and 62.3% had received three doses. The median age at dose 3 was 8.5 months, with 90% of third doses received by 13 months of age.
- In Ghana, the survey in November 2020, assessing uptake in children due for dose 1 between June 2019 and May 2020, found 75% of children 12-23 months of age had received the first dose and 67% three doses. Among those who received three doses the median age at the time of the third dose was 9.7 months and 90% of third doses were received by 13.4 months of age.
- In Kenya, in the survey conducted in May - July 2021 in children 12-23 months of age, who were due for their first dose between October 2019 and November 2020, 78.6% had received their first dose of RTS,S/AS01 according to the home-based record (HBR) or caregiver recall, and 62.3% had received three doses. The median age at dose 3 was 9.7 months, with 90% of third doses received by 11 months of age.
- In Ghana, coverage of the first dose of RTS,S/AS01 (75%) was less than for the first dose of measles-containing vaccine (88.3%), indicating that there are missed opportunities for RTS,S/AS01 vaccination when children attend for measles vaccine. In Malawi, coverage of the first dose of measles-containing vaccine was 79.7%, compared to 72.5% for the first dose of RTS,S/AS01 and in Kenya coverage of the first dose of measles-containing vaccine was 90.1%, compared to 78.6% for the first dose of RTS,S/AS01.
- In comparison areas, the survey in Ghana found that 6% of children 12-23 months with an HBR had documented receipt of RTS,S/AS01, in Malawi 1.9%, and in Kenya 10.2%. RTS,S/AS01 was not provided in comparison areas but children may have visited a facility in a neighbouring area

where the vaccine was available, or could have moved to live in a comparator area having previously lived and received vaccines in an implementation area.

- EPI impact: In all countries, there was no impact of RTS,S/AS01 introduction on the uptake of other routine childhood vaccines.
- Use of malaria prevention and control: In all countries, there was no impact on the use of ITNs in children following the introduction of the malaria vaccine when comparing the implementation versus the comparison areas, and no impact on health seeking behaviour. Seeking treatment for fever, getting a diagnostic test, or receiving antimalarials for treatment was comparable between baseline and midline survey in Ghana, Malawi, and Kenya, and between implementation and comparison areas.
- Equity: Vaccine coverage was equitable by gender, socioeconomic status, or ITN use.
- Improved access to malaria control interventions: data from the household surveys (reflecting the first 18-20 months of vaccine introduction) show that the availability of the malaria vaccine expanded the reach of malaria preventive interventions to vulnerable children. In Ghana 69% of children reportedly slept under an ITN the night prior to the survey and 77% had received a first dose of RTS,S/AS01. Among children who did not sleep under an ITN, 72% received a first dose of the malaria vaccine. The introduction of the malaria vaccine expanded the percentage of children accessing at least one malaria prevention measure – an ITN or the malaria vaccine - with coverage increasing from 69% to 91%, while 55% of children benefitted from both an ITN and the vaccine. Similar results were observed in Malawi, where ITN use was 67%, vaccine coverage was 79%, and among the children who did not sleep under an ITN, 75% were vaccinated with the malaria vaccine. The introduction of the malaria vaccine expanded the uptake of at least one malaria preventive intervention from 67% of children to 92%, with 54% benefiting from both interventions. In Kenya, reported ITN use was very high, at 92%, malaria vaccine coverage was 79% and among children who did not sleep under an ITN the prior night, 69% received the first malaria vaccine dose. The addition of the malaria vaccine resulted in 97% of children accessing at least one malaria preventive intervention, with 73% of children benefiting from both interventions.
- Impact of RTS,S/AS01 on other child health activities or indices: Overall, there was no impact on the uptake of Vitamin A or anthelminthics (deworming).

6.3.3 New Vaccine Post-Introduction Evaluation

At the time of this report, only the PIE results from Malawi were available for inclusion. In general, positive findings following the malaria vaccine introduction included improvements in the quality, consistency and frequency of supervision. Also noted was an increase in knowledge, detection and reporting of adverse events following immunization. Another observation was that the malaria vaccine introduction increased the opportunity for health care workers to screen children for any missed vaccine doses and provide catch up.

In Malawi, challenges noted included the need for more involvement of Districts in formulating the introduction and implementation plans. In addition, the evaluation found that comprehensive social mobilization and community and community engagement was not achieved prior to vaccine

introduction. Activities such as orientation of local leaders and engagement of peer-to-peer educators were done after the vaccine was already introduced. The delayed social mobilization in Malawi likely contributed to poor malaria vaccine uptake in the first few months following introduction. Additionally, there was a delay in provision of revised data recording and reporting tools, resulting in the need for improvised documents to track malaria vaccine indicators. Overall, the introduction was considered successful despite the observed challenges, most of which were addressed during the implementation period.

The Kenya PIE was completed in mid-August 2021, and the Ghana PIE preparations are underway.

6.3.4 Health Utilization Study

The Health Utilization Study received human subjects ethics approval from Institutional Review Boards within each of the implementing countries and from PATH's Research Ethics Committee. At the time of this report, two data collection rounds for the Health Utilization Study (HUS) – a qualitative longitudinal study-- have been completed and the final round is underway. A report of preliminary findings from round 1 (R1) was completed in June 2020. In addition to a cross-country report on findings from the Primary Child Caregiver cohort sample (Annex 5), available HUS data include: R1 results, a background document summarizing HUS methods and study status, R1 results, and three country-specific reports. In this report the focus is on R2 results including:

- Provider perceptions on RTS,S/AS01 uptake through dose 3, including factors that facilitate or threaten receipt of all three doses.
- Primary care giver (PCG) perceptions about RTS,S, sources of RTS,S/AS01 information, and new/or persistent questions and concerns about RTS,S/AS01.
- Impact of RTS,S/AS01 uptake on malaria treatment seeking and other prevention behaviours.
- Health provider perceptions of the acceptability and feasibility of providing RTS,S/AS01.

Primary care givers. The uptake of the RTS,S/AS01 vaccine through the third dose was generally strong, with coverage rates among the study cohort comparable to coverage from the household surveys and administrative data. Instances of children who had not received any RTS,S/AS01 doses were thought typically to be due to early barriers, including initial PCG concerns about the vaccine's safety or confusion about eligibility, resulting in PCGs refusing or delaying initial doses until their children were no longer eligible. Instances of children who had received fewer than the expected three doses of RTS,S were thought typically to be due to service access barriers or to the PCGs' personal circumstances. Most caregivers expressed their intent to take their children to receive dose 4, and many did so enthusiastically.

Positive attitudes and trust in RTS,S/AS01 among PCG increased substantially between R1 and R2 interviews, driven mainly by their perception of the health benefits of the vaccine in their own children and in the broader community. Early concerns about safety have been replaced by widespread perception that adverse events following RTS,S/AS01 immunization (AEFI) are "normal" and similar to other vaccines. Fewer threats to RTS,S/AS01 uptake - such as rumours or fears about safety - were evident in R2 compared to R1. In the absence of perceived threats around the vaccine, access and programmatic barriers (e.g., service access) were more frequently reported in R2. This pattern of access

barriers becoming more important in R2 is consistent with the responses given by PCGs as to why their children have not received all recommended doses of RTS,S.

Malaria treatment seeking and other prevention in the context of RTS,S/AS01. PCGs perceived malaria to be less frequent or severe because of the vaccine. These impressions were expressed with equal frequency by PCGs for RTS,S/AS01-eligible children having had episodes of malaria since receiving RTS,S/AS01 vaccinations. RTS,S/AS01 uptake did not seem to interfere with or change existing malaria treatment or prevention behaviours at the time of R2 interviews.

Although caregivers have demonstrated growing knowledge of RTS,S/AS01 and understanding of the 4-dose schedule across the first two rounds of data collection, some confusion and questions persisted around the level and duration of protection conferred by the vaccine.

At a high-level, these patterns were observed consistently across all three countries. However, cross-country findings require country-specific contextualization to better call out and understand variations across the three countries. For instance, although the data revealed common issues and events that could undermine trust in all three countries, there was country-specific contextualization in how these issues or events appeared or were interpreted. For example, in Ghana there were issues with disinformation (e.g., early rumours); in Malawi, the silent launch resulted in some perceptions of inadequate information; and in Kenya, there were service access barriers (e.g., health worker strikes and stockouts). Additional detail is provided in country-specific reports.

Health care providers. In provider feedback on the acceptability and feasibility of providing RTS,S/AS01, the vaccine itself was not the subject of questions or challenges, suggesting the antigen itself is acceptable to providers. Providers also expressed an increasing perception of the effectiveness of the vaccine as they experience a perceived reduction in the number of children reporting to their facilities with malaria since the inception of the RTS,S vaccine within the routine immunization system. Providers also reported improvements in the community perceptions surrounding the vaccine, which they attributed to an increase in health promotion efforts.

The chief concerns from health providers were around operational challenges faced in introducing and delivering RTS,S/AS01. Operational challenges noted included: 1) increased health provider workloads, primarily due to additional documentation; 2) lack of adequate training and supportive supervision; 3) lack of clarity about eligibility, and how to handle children who had missed doses or presented off-schedule; 4) lack of community sensitization on key messages through local leaders and influencers; this was noted as a limitation during the RTS,S/AS01 launch, and is still seen as a need.

6.3.5 Cost of introduction and delivery

The costing analysis estimated both the financial cost, representing the actual financial outlays, and the economic costs, including the opportunity cost of existing resources. The incremental non-vaccine cost of introducing and delivering a dose of RTS,S/AS01 ranged between US$ 1.20 and $2.50 (financial) and $ 2.07 and $4.77 (economic) across MVIP countries. The cost of delivery was slightly lower for the first 3 doses, (range: $0.94 to $1.97 (financial) and $1.71 to $3.86 (economic)). The cost of delivery of the fourth dose based on assumed coverage levels ranged between US$ 1.64 and $3.12 (financial), and

$2.48 and $5.82 (economic). Considering only the recurring costs, the non-vaccine cost of delivery per dose of RTS,S/AS01 ranged between US$ 0.40 and $1.10 (financial) and $0.96 and $2.67 (economic) across MVIP countries. The cost per FIC, based on assumed coverage levels, were estimated to be US$ 8.92 to $10.8 (financial) and $33.71 to $41.65 (economic).

These interim unit cost estimates are reported under assumed coverage levels for dose 4 and may be indicative of the potential costs of delivery by dose and the cost per FIC. Estimates of costs of RTS,S/AS01 delivery during the pilot were higher than the cost per dose for other newly introduced vaccines such as PCV or Rotavirus at US$ 0.84 (range: $0.48 to $1.38, economic)[26]. However, RTS,S/AS01 estimates are comparable to the costs of HPV vaccine pilot implementation[26]. The interim cost estimates show that the resources needed to deliver RTS,S/AS01 may be generally comparable with other new vaccines. However, comparisons of the current results to findings from the literature should be made cautiously, acknowledging that the methods and the delivery strategies are different, and these estimates are drawn from ongoing pilot studies rather than a full national introduction.

6.3.6 Interpretation of feasibility findings

Although at this time the primary decisions regarding a broader recommendation for RTS,S/AS01 are to be based primarily on safety and impact considerations, the available feasibility data are encouraging. This assessment is based on the following observations:

- Despite RTS,S/AS01 being a new vaccine delivered through EPI and requiring an expanded schedule, reasonably high coverage of the first three doses was achieved in all three pilot countries. This was achieved in a relatively short time period and in the context of substantial challenges to the health system due to the COVID-19 pandemic. It is too early to assess fourth dose coverage, although preliminary information suggests drop-out rates between dose 3 and dose four have been around 19-30%.
- Malaria vaccine introduction did not have an impact on the uptake of routine vaccinations, nor did it have an impact on health care seeking behaviours for febrile illness, use of ITNs, or other child health activities such as deworming.
- Malaria vaccine uptake was 69-75% among children who had not used an ITN in the previous night before the survey, suggesting the vaccine was reaching children who may have lower access and have lower use of other malaria prevention measures.
- In general, care givers and health care providers had positive attitudes towards the vaccine. Further work is required to improve community sensitization and engagement; work with health care providers on guidance around provision of missed or off-schedule doses and reduction of missed opportunities for vaccination (including other EPI vaccines); and assure proper data recording tools are available.
- Estimates on cost of RTS,S/AS01 delivery during the pilot were comparable to costs of HPV vaccine pilot implementation.

7 Review of RTS,S/AS01 Phase 3 trial results (2009 - 2014)

7.1 History, technical specifications, and previous clinical trial results

The development history, technical specifications, and information on clinical trials with RTS,S/AS01 trials preceding the Phase 3 trial are described in detail in the JTEG report "Background paper on the RTS,S/AS01 malaria vaccine."

7.2 Phase 3 trial - summary of results

The RTS,S/AS01 trial methods and results have been summarized and published both in peer reviewed literature[27] and as summary reports for WHO meetings to consider recommendations (JTEG report). The following sections summarize this information briefly; for additional details the original references should be consulted.

RTS,S/AS01 is the first and, to date, only vaccine to show a protective effect against malaria among young children in a Phase 3 trial. This multisite trial was conducted over 5 years at 11 sites in seven sub-Saharan African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and the United Republic of Tanzania). The trial was conducted in settings with improved access to quality care, high coverage and use of LLINs, and there was very low mortality among children enrolled in the trial.
Vaccine efficacy: When four doses of RTS,S/AS01 were given to children aged 5–17 months at first vaccination the vaccine efficacy was 39% (95% CI, 34–43) against clinical malaria and 29% (95% CI, 6–46) against severe malaria during a median of 48 months follow-up(according to protocol analysis) (MAL 055 Phase 3 trial results, Lancet 2015). The vaccine reduced severe malaria anaemia, the most common manifestation of severe malaria in moderate to high transmission areas, by 61% (95%CI 27–81) and the need for blood transfusions by 29% (95% CI 4–47). Among 5–17-month children who received four doses, vaccine efficacy against malaria-related hospitalization was 37% (95%CI 24, 49) during the full observation period. The Phase 3 data summarized in the JTEG report and WHO position paper indicate that a fourth RTS,S/AS01 dose given 18 months after the third dose provided sustained vaccine efficacy against clinical and severe malaria in children aged 5–17 months. This result suggested that three doses alone had no effect on the overall incidence of severe malaria, the apparent protective effect in the first 18 months being balanced by a relative increase in cases in the period from 18 months to the end of the trial[3].

Impact: Among participants in the 5–17 month age category who received a 3-dose schedule or a 4-dose schedule, the estimated numbers of cases of clinical malaria averted by study end (M2.5-SE) were 1363 (95% CI, 995–1797) and 1774 (95% CI, 1387–2186) per 1000 vaccinated children, respectively. Because of the high frequency of malaria in endemic countries, with children suffering many bouts of malaria each year, the absolute impact was considerable despite the modest vaccine efficacy[27]. The largest numbers of cases averted per 1000 vaccinees were at sites with the greatest disease burden, reaching more than 6500 cases averted per 1000 children vaccinated with 4 doses.

Modelled public health impact and cost-effectiveness: A comparison of four mathematical models enabled the assessment of RTS,S/AS01's potential public health impact and cost-effectiveness[28].This was carried out using Phase 3 clinical trial clinical malaria outcome data for the 5–17 month age group

with follow-up time of 32 months or longer to generate estimates of cases, deaths, and disability-adjusted life-years (DALYs) averted over a 15-year period[28]. The models assumed that vaccine implementation was added to existing levels of malaria control interventions and treatment. With an assumed coverage of 90% for the first 3 doses, with 80% of these individuals receiving the fourth dose (72% coverage overall), all models predict a substantial additional public health impact of RTS,S/AS01 in settings with PfPR2-10 between 10% and 65%[28]. In these settings, median modelled estimates range from 200 to 700 deaths averted per 100 000 children vaccinated with a four-dose schedule, and 10% to 28% of all malaria deaths averted in vaccinated children aged <5 years. Public health impact and cost-effectiveness tended to be greater at higher levels of transmission.

At an assumed vaccine price of US$ 5 per dose and a PfPR2–10 of 10–65%, the models predicted a median incremental cost-effectiveness ratio compared with no vaccine of $30 (range 18–211) per clinical case averted and $80 (44–279) per DALY averted for the three-dose schedule, and of $25 (16–222) and $87 (48–244), respectively, for the four-dose schedule. Higher incremental cost-effectiveness ratio (ICERs) were estimated at low PfPR2–10 levels. These predictions of RTS,S/AS01 cost-effectiveness per DALY averted are positive and comparable with other new vaccines based on mathematical models. Estimates for ICERs for clinical cases and DALY's averted were also calculated for vaccine prices at US$ 2 and $10 per dose[28].

Safety: No fatal adverse events were assessed as causally related to RTS,S/AS01 vaccination. In the 5–17 month age category, from the first dose to the trial end, serious adverse events (SAEs) were slightly less frequent in the RTS,S/AS01 groups than in the control group. In this age group, febrile convulsions were an identified risk in RTS,S/AS01 recipients in the 7 days following vaccination, but overall seizures were balanced among children who received RTS,S/AS01 and those who received the comparator vaccine (possibly due to a reduction in malaria-related seizures). Febrile seizures resolved without long-term consequence and are not unique to this vaccine[3].

Two safety signals were identified during the trial for which causality has not been established: meningitis (any cause) and cerebral malaria. Among 5–17 month olds in the 20 months following the first RTS,S/AS01 dose, meningitis was reported in 16 of the 5948 participants in the RTS,S/AS01 group, and in 1 of the 2974 participants in the control group, a relative risk of 8.0 (95%CI, 1.1–60.3). From study month 21 until trial end, 2 cases of meningitis were reported in the RTS,S/AS01 4-dose group (n=2681), 3 cases in the 3-dose group (n=2719), and 0 cases in the control group (n=2702). Cases were clustered at 2 of 11 the study sites, located outside of the meningitis belt (Kombewa, Kenya and Lilongwe, Malawi), from which 64% of the meningitis cases in the 5-17 month age group were reported. Of note, there was no clustering of cases relative to time of vaccination, and no increase in risk was seen in the younger age category. A variety of pathogens, including bacterial and viral, were responsible for the meningitis. In addition, there was a remarkably low number of meningitis cases in the comparator group of the older age category (1 case over 4 years). In the same age group, in an unplanned subgroup analysis from study months 0 to 20, 13 cases of possible cerebral malaria (by expert review) occurred in the combined 3- and 4-dose RTS,S/AS01 group compared to 7 in the control group. 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[3].

A *post hoc* analysis showed an imbalance in mortality among girls, with about 2-fold higher deaths among girls who received RTS,S/AS01 than among girls who received comparator vaccines (p=0.001); the ratio of deaths among boys was slightly lower in the RTS,S/AS01 arms versus the control arm. A relationship between the RTS,S/AS01 vaccine and these findings has not been established.

The WHO advisory bodies and EMA concluded that all of these described safety signals may have arisen by chance. The signals were not seen in a pooled analysis of 2981 children who received RTS,S/AS01 during Phase 2 trials[3] nor have the potential meningitis, cerebral malaria or mortality signals been seen in the more than 4000 children who received RTS,S/AS01 in two recently completed trial, one to evaluate alternative dosing regimens and a second to measure efficacy with annual boosters in highly seasonal areas. The signals were not seen in a pooled analysis of 2981 children who received RTS,S/AS01 during Phase 2 trials[3] nor have the potential meningitis, cerebral malaria or mortality signals been seen in the more than 4000 children who received RTS,S/AS01 in two recently completed trial, one to evaluate alternative dosing regimens and a second to measure efficacy with annual boosters in highly seasonal areas. The pilot evaluations and a Phase 4 study (further explained below) have been designed to provide further information.

7.3 RTS,S/AS01 immunogenicity

Background information on RTS,S/AS01 immunogenicity is provided in the JTEG report. In the Phase 3 trial there were very few non-responders to RTS,S/AS01. Anti-CS antibody geometric mean titres (GMTs) were highest at one-month post-vaccination, but did not return to the original level with a fourth dose (Figure 11).

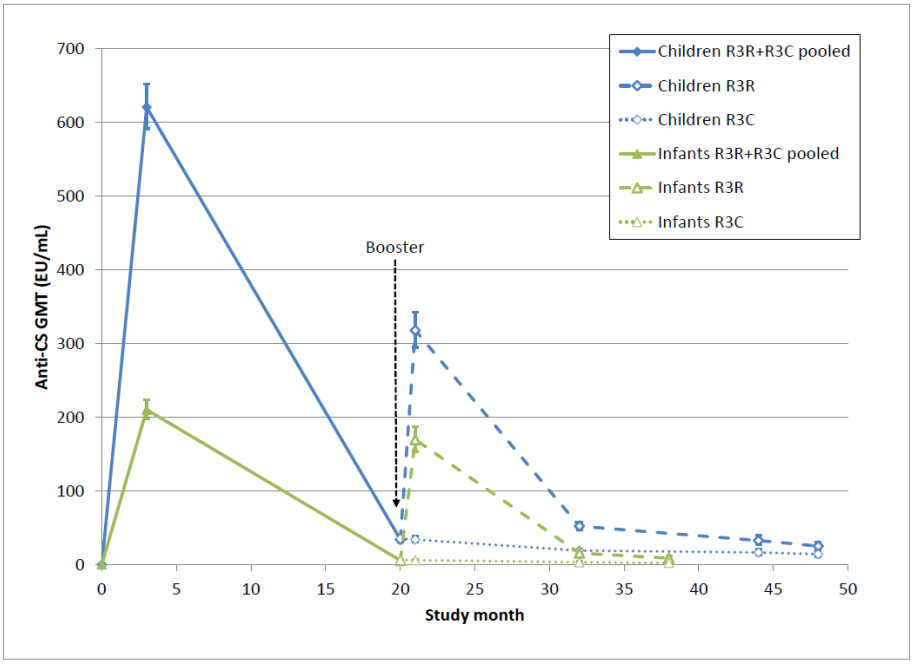


Figure 11: Anti-CS geometric mean titres in 5–17-month age category (labelled as “children”) and 6–12-week-old age category (“infants”) in pivotal Phase 3 trial (per-protocol population for immunogenicity). Provided by GSK

The absolute GMT value was higher in the 5–17-month age group compared to the 6-12 week age group at each time point following vaccination, as previously noted in Phase 2 studies. There was site-to-site variation in GMTs. In the 5–17-month age category there was no clear correlation between anti-CS IgG and protection against disease (Figure 12).

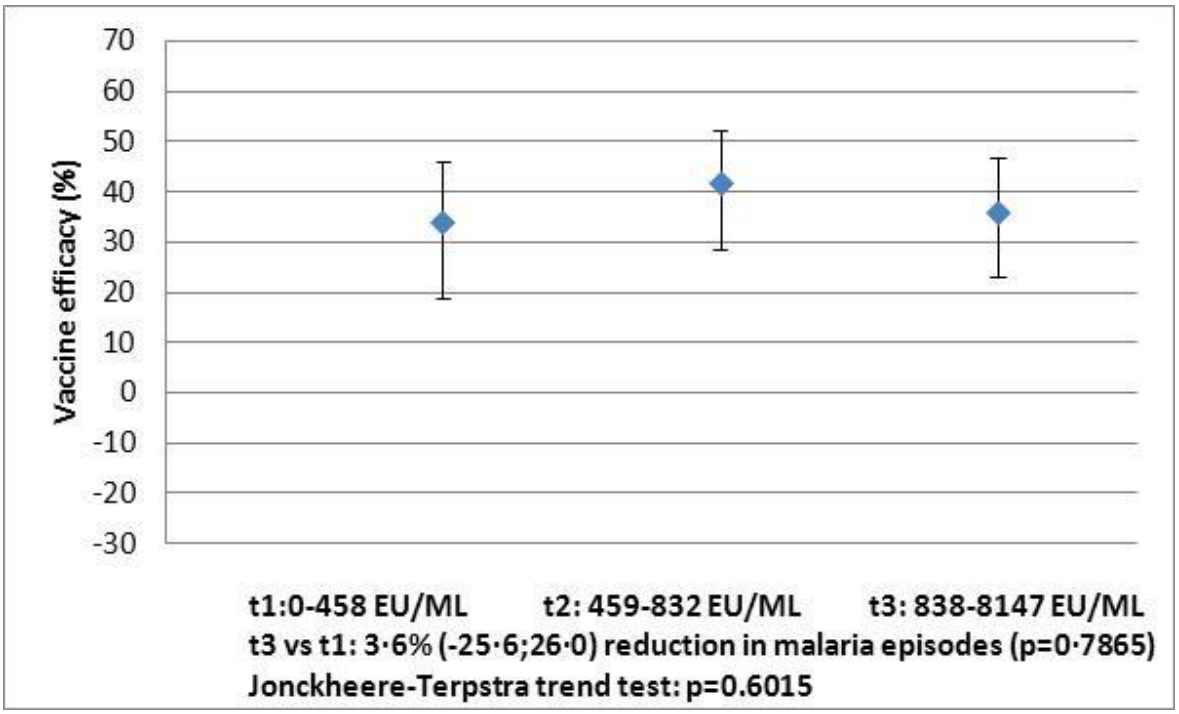


Figure 12: Vaccine efficacy by tertile of anti-CS antibody concentration (ATP population) in 5-17 month age category (R3C, 3-dose schedule). Error bars represent 95% confidence interval. t1-3: tertile 1-3 of anti-cs titre post vaccination. Provided by GSK on request

In a modelling analysis of the Phase 3 trial data examining the association of the titres of anti-CS antibody with the incidence of clinical malaria, analysis showed: 1) anti CS antibody titres were higher in 5-17 month olds than in 6-12 weeks olds; 2) immunogenicity of the fourth dose was strongly associated with immunogenicity after primary vaccination; 3) anti-CS antibody titres waned according to a biphasic exponential distribution , with 5-17 month olds showing a short half-life component (45 days [95% credible interval 42-48 days) and a long lived component, 591 days (557-632); 4) after primary vaccination, 12% of the response was estimated to be long-lived, rising to 30% after a booster dose; and 5) an anti-CS titre of 121 EU/ml (98-153) was estimated to prevent 50% of infections[11]. In addition to anti-CS antibody titres, immunogenicity data from both challenge studies[29] and the Phase 3 study[29] suggest that the avidity of anti-CS IgG, particularly to the C-terminus domain of CSP, is also associated with vaccine efficacy. Although most data on immunogenicity of RTS,S/AS01 derive from subjects in Africa, Europe and North America, it has also been shown be immunogenic in healthy Thai adult volunteers[30].

As noted, antibody titres after the fourth dose did not reach levels seen after the first three doses consistent with efficacy also not being as high. The reasons for this are not fully understood. One hypothesis is that high titre hepatitis B antibodies induced by first three doses would interfere with

subsequent induction of anti-CS immunogenicity. Perhaps a more likely hypothesis, supported by the lower anti-CS titres elicited in malaria- immune than naïve adults[31] is that increasing exposure to CS – whether through repeated malaria infection or vaccination - leads to hypo-responsiveness of B cell lymphocytes. First described for meningococcal and pneumococcal polysaccharide vaccines[32], this phenomenon reflects the recruitment and differentiation of fewer antigen-specific B cells into successive responses, with the B cell reservoir being exhausted by repeat and/or high-dose antigen exposure. This has two implications: 1) the booster dose is a fourth dose; 2) the capacity of subsequent doses to "reactivate" immunity and protection is unknown and difficult to predict.

Prior to the pivotal Phase 3 study, there was a consistently reported association between IgG that binds CS and protection from infection, but not from disease. This is consistent with the pre- erythrocytic biological target of the vaccine. It is possible that complete protection occurs in some volunteers, but in high transmission settings most vaccinees do eventually develop malaria, suggesting that the proportion completely protected is probably small. This needs to be taken into account in interpreting associations of immune responses and efficacy, as partial protection from infection might be expected in most individuals. This also implies that vaccinated individuals, during the initial period when protected against malaria, also experience less exposure to blood-stage parasites and therefore may have a deferred development of naturally acquired blood stage immunity[31] which may later render them more susceptible to adverse effects of malaria infection as vaccine efficacy wanes compared to those who have not been vaccinated.

8 Additional data since Phase 3 trial completion and recommendation for pilots in 2015

8.1 Long-term follow-up Phase 3 trial

Participants in the Phase 3 trial from 3 sites (Korogwe, Tanzania; Kombewa, Kenya; Nanoro, Burkina Faso) were followed for an additional three years following the main study, for a total of 6 years (for those age 6-12 weeks at initial study enrolment) or 7 years (5-17 month age group). The primary outcome of interest was the incidence of severe malaria[33].

Among the 1739 older children (aged 5-7 years during the follow-up) and 1345 younger children (aged 3-5 years during follow-up), there were a total of 66 cases of severe malaria during the three-year follow-up period. In the older age category, the overall incidences of severe malaria per person year at risk were 0.004 (95% CI 0 to 0.33) in the 4-dose group, 0.007 (0.001 to 0.052) in the 3-dose group, and 0.009 (0.001 to 0.066) in the control group (Figure 13). In older children, vaccine efficacies against severe malaria over the entire follow-up period of 6-7 years in older children were 36.7% (14.6 to 53.1) for the 4-dose group and 10.1% (-18.1 to 31.6) for the 3- dose group; in younger children these were 31.0% (4.7 to 50.0) for the 4-dose group and 34.2% (8.7 to 52.6) for the 3-dose group.

Participants were also followed for incidence of clinical malaria during the three years, and no additional benefit of vaccination was seen during the extended three-year follow-up period. In the older children, the overall vaccine efficacy against clinical malaria during the entire 6–7-year period remained positive; 23.7% (15.9-30.7) for the 4-dose group and 19.1% (10.8-26.7) for the 3-dose group. In one site with intense seasonal transmission (Nanoro), there were more episodes of clinical malaria among vaccine recipients during the extended follow-up than in the control group; in the 4-dose group the vaccine efficacy against clinical malaria was –30.3% (-59.5 to –6.4), and in the 3-dose group it was –26.0% (-56.0 to –6.4). Nonetheless, in Nanoro there was still overall (6–7-year period) benefit of vaccination, with a vaccine efficacy against clinical malaria of 13.8% (3.3 to 23.1) for the 4-dose group and 7.2% (-4.2 to 17.5) for the 3-dose group. Among younger children, there were no significant differences among groups in terms of clinical malaria incidence during the three-year follow-up.

In both age categories, no vaccine related severe adverse events or potential immune related disorders were reported during the three years of additional follow-up. Meningitis cases were reported infrequently and there was no imbalance observed among groups.

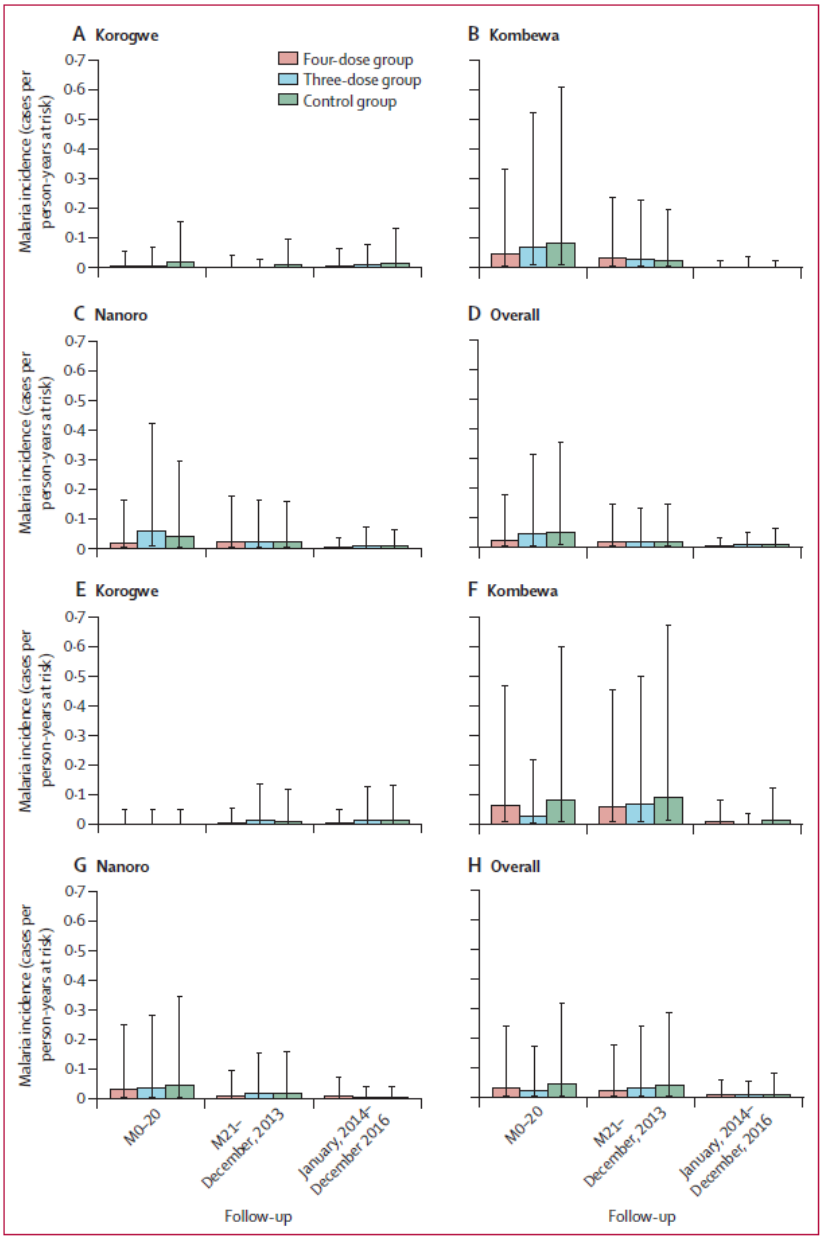


Figure 13: Incidence of severe malaria in children from the older age category (A–D) and the younger age category (E–H) in the intention-to-treat population (A, E) Korogwe. (B, F) Kombewa. (C, G) Nanoro. (D, H) Overall. Older age category included children aged 5–17 months; younger age category included infants aged 6–12 weeks. M0=time of the first dose administration in the initial study. M20=20 months after the first dose in the initial study. M21=21 months after the first dose in the initial study. Error bars represent 95% Cis[33]

Overall, the extended follow-up study showed that over the 6–7-year period following RTS,S/AS01 vaccination, the incidence of severe malaria declined in children regardless of treatment group. Although there was no evidence of continued vaccine efficacy against severe malaria during the additional three years of follow-up, neither was there evidence of increased susceptibility (age shift to older children). During the entire 6-7 year period, vaccine efficacy against severe malaria remained significantly positive for children receiving 4 doses in both age categories, and for those receiving 3 doses in the 6-12 week age group. Although there was an age shift with an increase in clinical malaria relative to the control group during the extended follow-up period in the vaccinated 5 to 17 month-old children at the only intensely seasonal transmission site (Nanoro), the overall benefit of vaccination

against clinical malaria during the whole trial period remained. Thus, children in areas with moderate to high perennial malaria transmission who received 3 or 4 doses of RTS,S/AS01 benefitted for at least 7 years after vaccination, and did not have an excess risk of clinical or severe malaria. In some intensely seasonal settings, where almost all of the malaria transmission occurs in a 4-5 month period, vaccinated children may experience a limited period of increased risk of clinical malaria relative to unvaccinated children, but overall would benefit from vaccination with a 4 dose schedule. Noting these results, MPAG assessed that these data provided providing further reassurance on the absence of an age shift effect in immunized children and reinforced the safety profile of the vaccine[34].

8.2 Revisiting the need for a 4th dose

As noted in Section 7, vaccine efficacy over the full follow-up period was higher in 5-17-month-old children who received a 4th dose; efficacy appeared to decline in the period following the fourth dose in a way similar to that seen following the first three doses. Thus, the impact on clinical malaria with a fourth dose would be greater than without a fourth dose.

In addition, among 5–17-month-old-children who only received three doses of RTS,S, the initial reduction in severe malaria was counterbalanced by an increase in severe malaria around 18 months after the initial vaccine course, presumably due to waning immunity. This age shift effect has been noted among recipients of other malaria-control interventions when the intervention is withdrawn. Presumably when the intervention group is then compared to a contemporaneously followed control group in the same population who did not receive the intervention and who develop immunity through repeated episodes of natural infection, the intervention group is at comparatively higher risk of malaria and severe disease for a limited period.

This age shift in severe malaria was most marked in higher transmission settings, possibly because participants in the control group developed immunity through natural infection more rapidly. Importantly, an age shift in severe malaria was not observed up to the end of the follow-up period among children vaccinated at 5-17 months of age who received a fourth dose. It remained unclear at the time of the 2015 WHO recommendation whether there would be a substantial age shift in severe malaria following waning immunity after the 4th dose or whether there might be an excess in severe malaria cases overall among children who received 3 doses compared with children in the control group. As noted previously, subsequent information from long-term follow-up showed the lack of an age shift in severe malaria after the 4th dose and demonstrated that the age shift after 3 doses was time limited and without excess severe malaria cases.

At the time of the 2015 WHO recommendation, based on the expected added protection from clinical malaria and overall lack of efficacy against severe malaria among children who received the 3-dose schedule, a 4th dose of RTS,S/AS01 was felt to be essential. However, additional data exploration and analyses have provided an opportunity to revisit this assumption.

First, at the time of the initial analysis of severe malaria risk in 5–17-month-old children between the 3 and 4 dose groups, it was assumed that up until the time of the 4th dose, the 3 and 4 dose groups were equivalent, and thus were treated as a single group in analysis. However additional analysis revealed

that, in the pre 4th dose period, there was a higher risk of severe malaria in those randomized to the 3-dose arm than those randomized to the 4-dose arm (Figure 14).

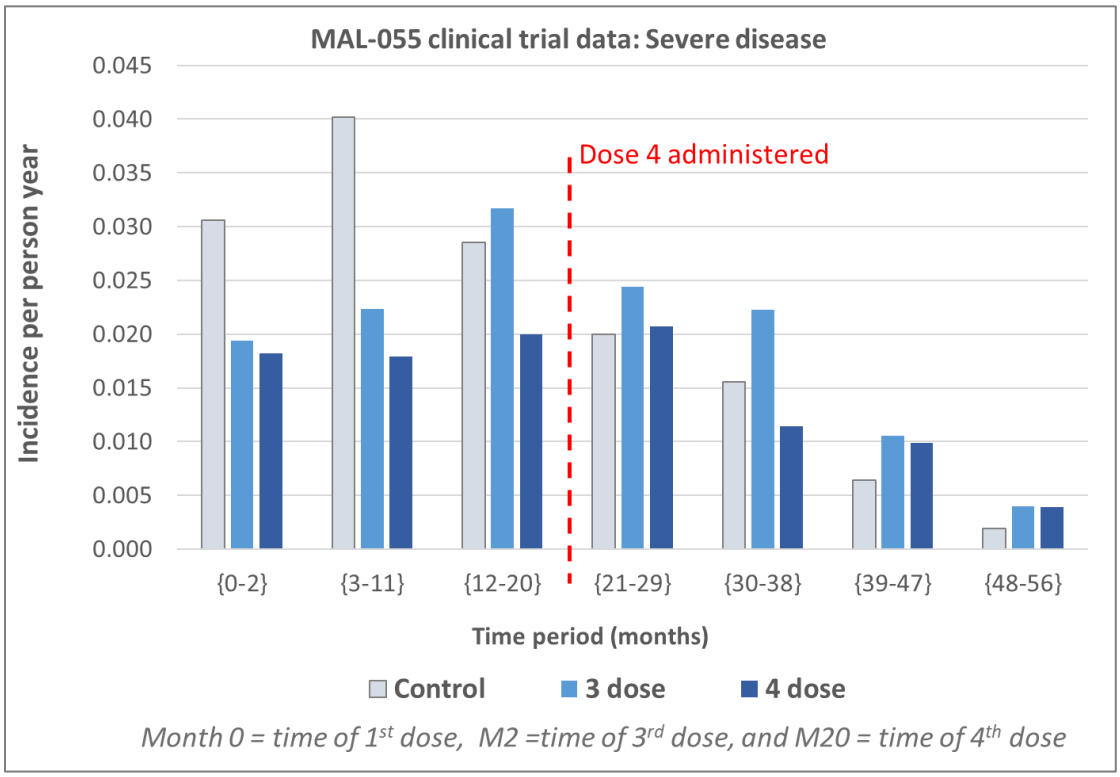


Figure 14: Vaccine impact before and after receiving the 4th dose (intention-to-treat population). Severe disease incidence per person year (MAL 055, aggregated over all clinical trial sites for 5-17 month cohort ITT population) plotted every 8 months after dose 1 is administered. The dotted line represents when dose 4 is given, month 0 indicates time of dose 1, month 2 completion of dose 3 and month 20 administration of dose 4. A difference between the 3-dose and 4-dose groups is apparent before the fourth dose is given (Annex 1).

Further analysis by GSK at the request of WHO indicated no problem with randomization, the difference therefore arose by chance. The risk of clinical malaria was similar in the 2 arms. However, this unexpected difference may have complicated the interpretation of the data over the whole study period and contributed to a potential overestimation of the importance of the 4th dose.

Second, the modelling groups at Swiss TPH and Imperial College were engaged to estimate thresholds of vaccine coverage that predict impact—in particular, what levels of coverage (overall and for the fourth dose) were sufficiently high to be considered good public health value. The models (which were validated with data from the extended follow-up of a subset of children from the Phase 3 trial) predicted a small incremental impact of the fourth dose, with over 90% of impact achieved with the administration of the first 3 doses[5]. The modelers were unable to reproduce the extent of the age shift observed in the Phase 3 trial. These estimates and inability to reproduce the extent of the age shift are consistent with the 2015 modelling analysis[28]. Given these observations, which, along with data from the long-term follow-up study of a subset of Phase 3 participants demonstrating a lack of any excess of

severe malaria among children who did not receive a fourth dose suggest that receipt of a fourth dose is not critical, the Framework for WHO Recommendation on RTS,S/AS01 concludes “The policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose). High coverage for a newly introduced vaccine is frequently not attained until several years after the start of implementation.” Further information on the impact of the 4th dose will be generated during the last two years of the MVIP.

8.3 Seasonal use

As noted previously, the anti-CSP antibody kinetics for RTS,S/AS01 show peak levels shortly after completion of the 3-dose regimen with rapid decline over the ensuing six months, associated with correspondingly high initial vaccine efficacy during this period. In the pivotal Phase 3 trial, vaccine efficacy against clinical malaria in 5-17 month old children was 67.6% in the 6 months following the third dose[3].This observation has stimulated interest in consideration of use of RTS,S/AS01 in areas of highly seasonal malaria transmission, such as the Sahel region in Africa, or other areas with high seasonality. The proposed strategy would be to deliver a primary 3 dose regimen in young children (5-17 months) immediately prior to the onset of the 4-6 month transmission season. Subsequent booster doses could then be delivered to these children annually, again just prior to the transmission season, to provide additional protection over and above what could be achieved with ITNs during this period of greatest risk[35].

To evaluate a seasonal vaccination strategy, an individually-randomized, controlled trial was conducted in young children (5-17 months) in Burkina Faso and Mali to assess whether vaccination with the malaria vaccine RTS,S/AS01 was non-inferior to seasonal malaria chemoprevention (SMC) with monthly amodiaquine plus sulfadoxine-pyrimethamine in preventing uncomplicated malaria and/or whether the interventions combined were superior to either alone in preventing uncomplicated malaria and severe malaria-related outcomes (Annex 4). SMC is a strategy recommended by WHO for malaria prevention in areas of highly seasonal malaria transmission, where most malaria cases occur during an approximate 4 month period; SMC is approximately 75% efficacious in preventing uncomplicated and severe malaria[14]. A total of 6861 children were randomized to receive SMC (2287), RTS,S/AS01 (2288), or both (2286). Of these, 1965, 1988 and 1967 children respectively received the first dose of study vaccines and were followed over a three-year period.

The incidence of uncomplicated clinical malaria in the SMC, RTS,S/AS01 and combined groups was 305, 278 and 113 per 1000 person-years at risk, respectively. The hazard ratio (HR) comparing RTS,S/AS01 to SMC was 0.92, (95% confidence interval (CI): 0.84, 1.01), which excluded the pre-specified non-inferiority margin of 1.20. The incidence of clinical malaria, hospital admissions with severe malaria and deaths from malaria was 62.8% (95% CI 58.4, 66.8), 70.5% (95% CI: 41.9, 85.0) and 72.9% (95% CI: 2.91, 92.4) lower in the combined group than the SMC alone group. The incidence of these outcomes was 59.6% (95% CI: 54.7, 64.0), 70.6% (95% CI: 42.3, 85.0) and 75.3% (95% CI: 12.5, 93.0) lower in the combined group than the RTS,S/AS01 alone group.

Five children given RTS,S/AS01 developed febrile convulsion the day after vaccination but recovered without sequelae. No other serious adverse events were assessed by the investigator to be related to

vaccination. Eight cases of clinically suspected meningitis occurred: four in the chemoprevention alone, three in the RTS,S/AS01 alone, and one in the combined group. These were investigated by lumbar puncture, but none had proven meningitis. There was no evidence of increased mortality or hospital admissions in girls who received RTS,S/AS01.

In this large study, seasonally targeted RTS,S/AS01 was safe and non-inferior to SMC in preventing uncomplicated malaria. The safety signals observed in the Phase 3 trial were not observed in this trial. In addition, the combination of these interventions was associated with substantially lower incidence of uncomplicated malaria, severe malaria and death from malaria.

8.4 Fractional dose RTS,S/AS01

The first RTS,S/AS01 CHMI trial was conducted over 20 years ago to evaluate three different adjuvant formulations using AS02 formulation (a water-in-oil precursor to the liposome based AS01). Although significant high VE was shown after CHMI challenge 3 weeks following vaccine dose 3, it was hypothesized that the observed high vaccine efficacy in one arm that received a fractional dose (1/5 normal) was a chance finding due to small numbers, and was not further investigated at that time.

The potential value of a fractional third dose was revisited two decades later in another CHMI study in a Phase 2a controlled open label study in the US when 16 adults were vaccinated using different vaccine schedules (one with delayed dose 3). Results showed highest efficacy after CHMI at 3 weeks post dose 3, in the group that received a delayed dose 3 (VE 86.7% [95% CI 66.8-94.6]).

Following this, five different fractional dose regimens (n=26 participants per arm) were explored in another CHMI study, using two different formulations: paediatric (RTS,S/AS01$_E$ = 25ug RTS,S and an adjuvant system containing 25 ug of Monophosphoryl Lipid A, QS-21, and liposomes in a 0.5 ml dose) and adult (RTS,S/AS01$_B$ = 50ug RTS,S and an adjuvant system containing 50 ug of Monophosphoryl Lipid A, 50 ug of QS-21, and liposomes in a 0.5 ml dose[36]. Regimen timing and dosages are summarized in Table 2.

Table 2. Vaccine dose details for all study treatment groups (Moon et al)[34]

Study Group	Vaccination Months	RTS,S Antigen Administered, µg		Adjuvant Administered, µg		Volume Administered per Vaccination, mL
		Per Vaccination	Total	Per Vaccination	Total	
AduFx	0-1-7	50-50-10	110	50-50-10	110	0.5-0.5-0.1
2PedFx	0-1-7	50-50-10	110	50-50-10[a]	110	1.0-1.0-0.2
PedFx	0-1-7	25-25-5	55	25-25-5	55	0.5-0.5-0.1
Adu2Fx	0-1-7	50-10-10	70	50-10-10	70	0.5-0.5-0.1
Adu1Fx	0-…-7	50-…-10	60	50-…-10	60	0.5-…-0.1

[a]Administered in 1.0ml (double) doses.

Challenge was conducted 3 months after the last vaccination. The vaccine efficacies of the different regimens are summarized in Figure 15.

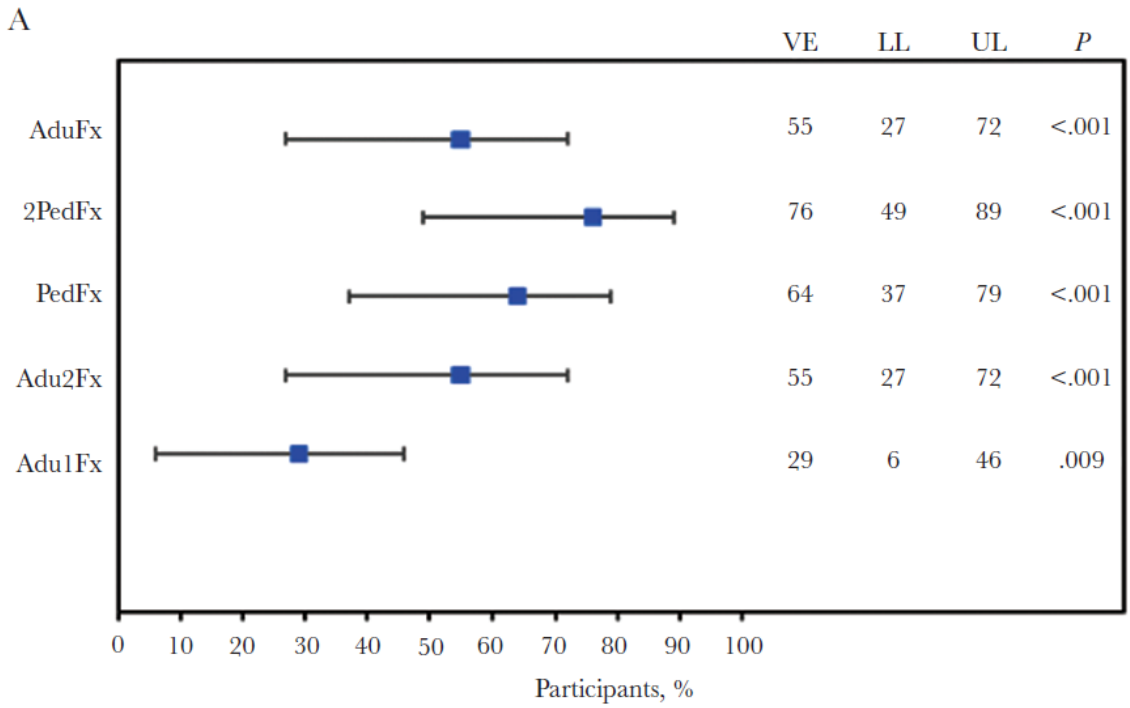


Figure 15: Vaccine efficacy in the prevention of *P. falciparum* parasitaemia for all five study groups. Error bars indicate 95% confidence intervals[36].

Vaccine efficacies were similar among the 3-dose groups, with the lowest point estimate of efficacy in the 2-dose group (Adu1Fx), suggesting that a universal 3-dose formulation could be used across age groups. Although these VEs were lower than the result seen in the previous two fractional dose trials, it is important to note that challenge in those studies occurred 3 weeks after the last dose, as opposed to 3 months; thus, a lower VE would be expected.

A field trial is currently ongoing in Kenya and Ghana evaluating fractional dose regimens in children 5-17 months of age. Five study groups (n=300 each) have been enrolled:

1. Control: Rabies vaccine at 0,1,2 months
2. R012-20: RTS,S/AS01 at 0,1,2 months full dose with full dose booster at 20 months (Phase 3 trial regimen)
3. R012-14: RTS,S/AS01 at 0,1,2 months full dose with full dose booster at 14 months
4. R01-Fx2-14: RTS,S/AS01 at 0,1 full dose, 1/5 fractional dose at 2 months with fractional booster at 14 months
5. R01-Fx7-20: RTS,S/AS01 at 0,1 full dose, 1/5 fractional dose at 7 months with fractional booster at 20 months

A preliminary interim analysis at 20 months showed that:

- The fractional dose regimens were not superior to the standard regimen over either 6.5 or 12 months for the same outcomes

Vaccine efficacy against clinical malaria was significant in all groups compared to rabies control group: Reactogenicity was similar as with the Phase 3 trial, and no safety signals were noted. Antibody kinetics were similar to what was observed in the Phase 3 trial, and there were no significant differences in antibody avidity among RTS,S/AS01 groups. The incidence of severe malaria was reduced by ~40% in all RTS,S/AS01 groups compared with the control group (Personal communication, Christian Ockenhouse, MD, PATH).

9 Modelled public health impact and cost-effectiveness estimates

Mathematical modelling of the public health impact and cost effectiveness of RTS,S has been updated for perennial settings (Section 9.1) by Imperial College and SwissTPH and for seasonal settings (Section 9.2) by Imperial College. The reports for each are available in Annex 8.

9.1 Perennial settings

9.1.1 Overview

Beginning in 2015 with the conclusion of the Phase 3 trial, modelled predictions of RTS,S/AS01 malaria vaccine public health impact and cost-effectiveness were produced to complement empirical observations from trial data and, more recently, the MVIP. Initial modelled predictions were produced by multiple groups using harmonized inputs that drew on data from the RTS,S/AS01 Phase 3 clinical trials and malaria disease burden studies. Results from the 2015 analysis predicted a substantial public health impact and high cost-effectiveness of the RTS,S/AS01 vaccine across the wide range of settings modelled. At US$ 5 per dose and a *Pf*PR_{2-10} of 10–65%, the estimated median incremental cost-effectiveness ratio was $25 (16–222) per clinical case averted and $87 (48–244) per DALY averted respectively, for the four-dose schedule[28].

The modelling analysis was updated to generate impact and cost-effectiveness estimates across a range of generic transmission settings using a combination of existing RTS,S/AS01 evidence and MVIP data, including the following: previously validated, modelled disease and vaccine parameters, and assumptions and cost of delivery estimates from the MVIP.

9.1.2 Model inputs and data sources

Model inputs and assumptions are summarized in Table 3 below. For both the OpenMalaria and Imperial College models, the underlying model structure and vaccine parameterization has remained stable since the previous round of modelling. Key differences in model inputs include more comprehensive coverage and cost of delivery data that have become available from the MVIP. In previous analyses, RTS,S/AS01 costs were estimated based on vaccine and immunization supplies including freight and wastage only, and were a likely underestimate of the cost of delivery. Here, the recurrent cost of delivery as observed during the MVIP was added to the vaccine costs. The recurrent cost of delivery, which excludes the introduction/initial set-up costs, may be more representative of the program delivery cost in the long run as the set-up costs for the MVIP countries were a substantial component of overall costs. Furthermore, modelers relied on recurrent costs because the sub-national introduction of RTS,S/AS01 in pilot countries meant that introduction costs were spread across a smaller number of doses delivered during the MVIP, particularly when compared to a full national roll out. Where applicable, ranges shown in parentheses in Table 3 (vaccine coverage, cost of delivery) were explored in a sensitivity analysis. All costs are in US dollars. In addition to using updated cost of delivery estimates, revised assumptions for vaccine coverage were used to produce updated modelled predictions. In 2015, vaccine coverage for the first 3 doses was assumed to be 90%, with a drop of 20% from the third dose to the fourth, resulting in 72% coverage of the fourth dose. Using data from the MVIP, and feedback from the 2015 model, for this analysis vaccine coverage was assumed to be 80% for

the first three doses, with a 20% drop off from the third dose to the fourth dose, resulting in 64% coverage for the fourth dose. It should be noted however, that as yet MVIP data on fourth dose coverage is limited. For all scenarios, fully vaccinated children were defined as those who received the first 3 doses of the schedule.

Table 3: Data sources and model assumptions.

	Assumption	**Data Source**	**Changed since 2015 report**
Demographics	Constant population size and demography with an average life expectancy at birth of 46.6 years.	Penny et al (2015)	No
Transmission intensity	Parasite prevalence among 2–10-year-olds between 3% and 65%, representing current transmission levels in Africa.	Malaria Atlas Project	No
Case management	Effective coverage (i.e., treatment with parasitological cure) for clinical malaria is 45%. Access to care for severe malaria varied by model.	Penny et al (2015)	No
Other interventions (ITN, IRS, ACT, SMC, health care access)	Predictions assume that current interventions in place at the start of vaccination remain at static levels.	Penny et al (2015)	No
Vaccine efficacy and waning	Model predictions of RTS,S efficacy against infection profiles based on fitting to Phase 3 trial efficacy.[1]	Penny et al (2015)	No
Vaccine schedule	Three doses of vaccine given at 6, 7.5, and 9 months old (6–9-month implementation) with a scheduled fourth dose at month 27[2] The first two doses of the primary series are assumed to have 0% efficacy.	Penny et al (2015)	No
Vaccine coverage	80% (range 50%–90%) coverage assumed for the first three-doses; we assumed a 20% drop-off in coverage for the fourth dose (64% coverage, range 40%–72%).	MVIP	Yes
Seasonality	Perennial transmission (no seasonality). Seasonal trends in rainfall, and therefore mosquito density, were assumed to be constant throughout the year.[3]	Penny et al (2015)	No
Vaccine price	US$ 5 (range $2–$10) per dose. $6.52 (range $2.69–$12.91) when including injection and reconstitution syringes, safety boxes, freight, insurance, and wastage.	Penny et al (2015)	No
Cost of delivery estimate	We assumed an (economic, recurring) cost of delivery per dose of US$ 1.62 (range $0.96–$2.67).	Interim cost of delivery estimates from MVIP	Yes
Cost of malaria case management	Costs are estimated by severity of illness and cover first-line antimalarial drugs, diagnostics, and related supplies including freight and wastage. We assumed full compliance and adherence with the age dosage. The same costs were applied to all settings, ranging from US$ 1.07 to $2.27 per uncomplicated case, and from $21.78 to $55.58 per severe case.	Penny et al (2015)	No

[1] The Phase 3 trial included data from 11 trial sites with different transmission intensities, and observations of efficacy against clinical and severe disease at 3-month intervals in each trial site for a median of 48 months follow-up. In 2015, both modelling groups calibrated the efficacy properties, including decay, of RTS,S, by replicating the trials in-silico and matching to uncomplicated malaria impact in the trials site.

[2] This is not the schedule of 6, 7, 9 and 24 months, but the previous model uses 27 months and that was assumed for the updated analysis as well.

[3] Results of the seasonal use case for RTS,S are included elsewhere in this report.

9.1.3 Results

The vaccine impact and cost-effectiveness predictions in 2-10 year old children are summarized across parasite prevalence levels ranging from 10%–50% (Table 4, Figure 16). Predictions of the potential public health impact of the RTS,S/AS01 vaccine remain largely unchanged, as both modelling groups used the same malaria transmission and vaccine impact models that were used for the analyses performed in 2015, with minor adjustments to some parameters. The cost per DALY averted and cost per clinical case averted predictions (Table 4, Figure 16: D, E and F) have marginally increased based on the updated additional cost of delivery predictions. Central estimates of cost-effectiveness from individual models still fall within the range of those presented in 2015, and are consistent with a prediction that RTS,S/AS01 is cost-effective compared with standard norms and thresholds. The relative impact of the added cost of delivery predictions is larger at the lower (US$ 2) assumed cost per dose level.

Table 4: Public health impact and incremental cost-effectiveness ratios (ICER) for 4-dose schedule at 15 years of follow-up in regions with a parasite prevalence among 2–10-year-olds of 10–50%.

	Median estimate (range)	
	Swiss TPH model	**Imperial College Model**
Percentage of malaria deaths averted in children younger than 5 years	9.2% (8.7% to 10.1%)	18.6% (13.6% to 20.8%)
Percentage of clinical cases averted in children younger than 5 years	13.2% (11.2% to 14.6%)	20.9% (20.1% to 23.6%)
Malaria deaths averted per 100 000 fully vaccinated children (receives at least 3 doses)[1]	417 (205 to 540)	448 (315 to 534)
Malaria clinical cases averted per 100 000 fully vaccinated children	108,824 (46978 to 121182)	101,413 (57839 to 145301)
ICER (US$) per DALY averted		
$2 per dose	$50 (42 to 120)	$52 (43 to 78)
$5 per dose	$97 (81 to 230)	$103 (86 to 151)
$10 per dose	$175 (146 to 412)	$187 (157 to 274)
ICER (US$) per clinical case averted		
$2 per dose	$31 (25 to 46)	$14 (10 to 26)
$5 per dose	$59 (48 to 89)	$28 (19 to 50)
$10 per dose	$105 (87 to 160)	$52 (35 to 91)

[1] The SwissTPH model deaths include those directly attributable to the disease and those caused by co-morbidities. The absolute number of deaths (and how RTS,S impacts them) can differ between models which can result in similar deaths averted per 100 000, despite there being a different percent of deaths averted

Estimates show the median and range of model predictions across transmission settings. Of note, summary statistics are not directly comparable between the current analysis and Penny *et al* (2015)[28], because of the way the estimates are presented. These updated predictions show the median and range

of model predictions (at 80% coverage), whilst predictions from Penny *et al* (2015)[28] show the median (range) across four models' medians (at 90% coverage). Additionally, the estimates in Table 4 show the summary statistics over a *Pf*Pr range of 10-50%, whereas in the previous predictions a *Pf*Pr range of 10-65% was used.

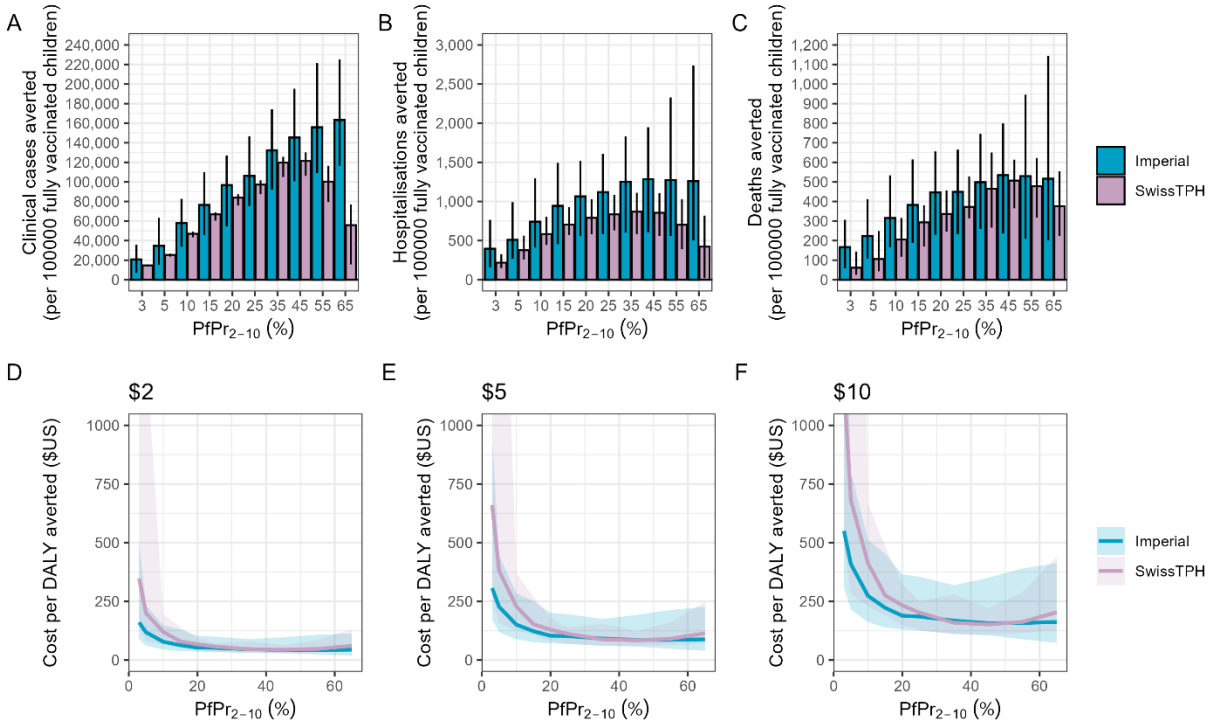


Figure 1610. Summary of impact and cost-effectiveness predictions for RTS,S/AS01 across transmission settings of 3-65%.

Figure 16 reflects the full range of possible *Pf*Pr from 3% to 65%. Panels in the top row show predictions of impact of A) clinical cases, B) hospitalizations, and C) malaria deaths averted per 100 000 fully vaccinated children, as a function of baseline parasite prevalence among 2–10-year-olds (*Pf*Pr_{2-10}) from Imperial (blue bars) and Swiss TPH (mauve bars) models. Bars represent the median estimate and the error bars represent the 95% credible intervals. Panels in the bottom row show the cost per DALY averted as a function of *Pf*Pr_{2-10} for an assumed cost per dose of D) US$ 2, E) $5 and F) $10 for Imperial (blue lines) and Swiss TPH (mauve lines) models. Lines represent the median estimate and shaded areas represent the 95% credible intervals.

9.1.4 Interpretation of results

Both the Swiss TPH and Imperial College models predict a positive public health impact of the introduction of RTS,S/AS01 in settings with *Pf*Pr_{2-10} between 10% and 50% over a 15-year time horizon, which is consistent with previously published estimates. Vaccine impact increased with increasing coverage. Compared with the previous 2015 analysis, the cost per case and DALY averted have slightly increased due to the inclusion of more comprehensive information on cost of delivery, RTS,S/AS01 is still considered cost-effective by general thresholds and standards.

9.2 Seasonal settings

9.2.1 Background

Data from a trial assessing the individual and combined impact of seasonal use of RTS,S/AS01 and SMC (Annex 4) as well as the Imperial College individual-based transmission model of *P. falciparum* malaria were used to estimate the population level impact of a seasonally targeted RTS,S schedule. Details on the model validation results, transmission model parameters, impact and cost-effectiveness estimates are provided in Annex 8. The cost-effectiveness of this approach was considered either alone or in combination with SMC. Model comparisons were made across two seasonality archetypes, characteristic of the seasonality patterns across the Sahel and Sub-Sahel region. Three potential vaccination strategies were considered (see Table 5).

Table 5: Potential vaccination strategies modelled for a seasonally targeted schedule

Vaccination Strategy	Key features (potential advantages)
EPI vaccination: age-based priming series, age-based additional doses.	• Age at first vaccination fixed at 5 or 6 months of age. • Uses existing EPI vaccine infrastructure and current contacts to deliver RTS,S.
Seasonal vaccination (SV): seasonal priming series, seasonal fourth and fifth doses	• Calendar month of first vaccination fixed. • Peak vaccine efficacy of primary series and additional doses are aligned with time of peak risk. • Once the infrastructure for seasonal doses is established, it may be possible to provide more vaccine doses in childhood. • Dose schedule changes could result in heightened efficacy of additional doses compared to EPI scheduling.
Hybrid vaccination: age-based priming series, seasonal fourth and fifth doses	• Age at first vaccination fixed at 5 or 6 months of age. • Uses EPI vaccine infrastructure. • Peak efficacy of additional doses are aligned with time of peak risk. • Once the infrastructure for seasonal doses is established, it may be possible to provide more vaccine doses in childhood.

The model structure cannot capture Hybrid vaccination strategies with the main results showing only EPI and seasonally targeted RTS,S schedule deployment. Further population-level modelling of a Hybrid strategy is underway.

9.2.2 RTS,S impact – seasonally targeted vaccination compared to EPI vaccination

Over a 15-year period, the model simulations showed that seasonally targeted RTS,S schedule resulted in greater reductions in cases and deaths than EPI vaccination across all endemicity settings in both seasonal and highly seasonal settings. An additional fifth dose and higher fourth and fifth dose efficacy increased this impact (Figure 17).

Considering the effect of seasonality, the incremental benefit of seasonally targeted RTS,S schedule over EPI (defined as the proportion of additional events averted with a seasonally targeted RTS,S schedule versus EPI schedule) was larger in highly seasonal settings compared to seasonal settings (average 75%

additional cases and 64% additional deaths averted vs 60% additional cases and 55% additional deaths averted).

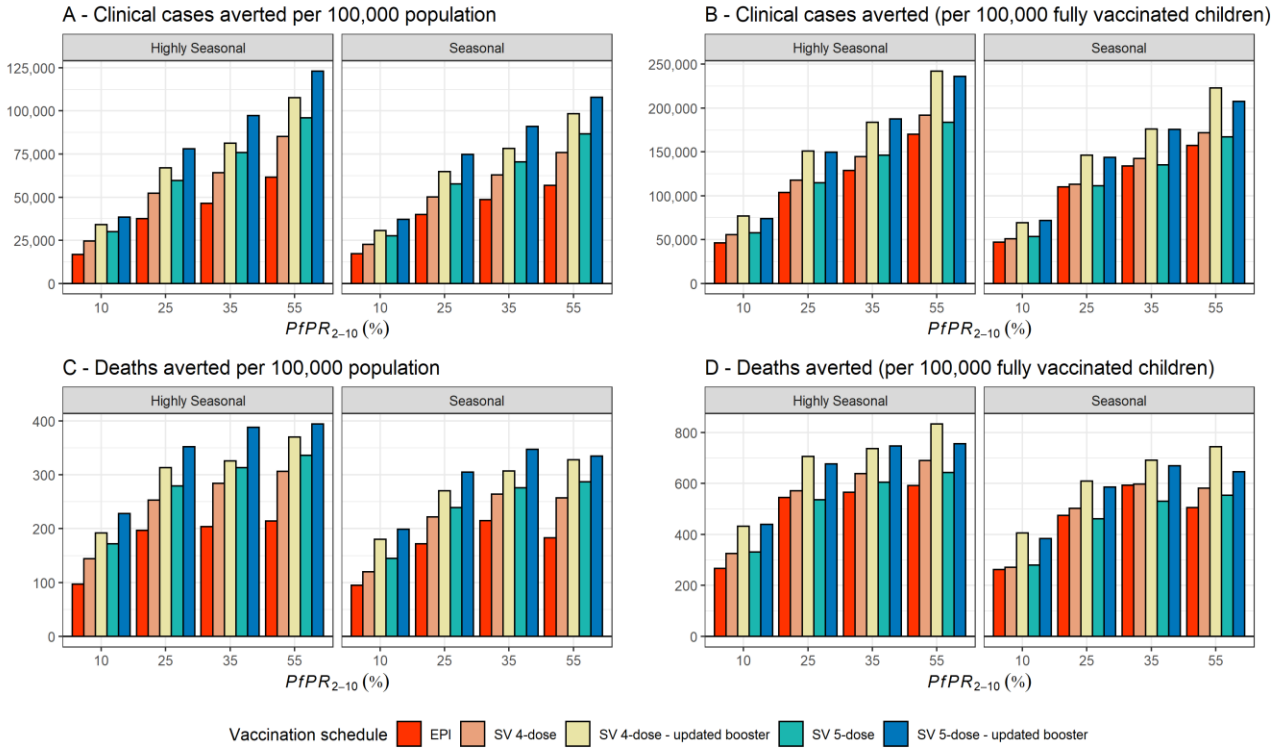


Figure 17: Cumulative clinical cases averted over 15 years as a function of baseline PfPR2-10 (four settings representative of medium to high transmission intensity are shown) and seasonality A&C) per population and B&D) per 100 000 fully vaccinated children. Coverage is fixed at 80% for the first three doses with a 20% drop off for the fourth and fifth doses

This is likely a result of the burden of malaria being concentrated in a shorter time period in highly seasonal settings compared to in seasonal settings where burden is more uniformly spread over 5–6 months. The benefit of seasonally targeting vaccines was reduced when considering the impact per 100 000 fully vaccinated children due to the increased number of doses delivered in the seasonally targeted RTS,S schedule (Figure 17: 1B, 1D).

However, despite seasonally targeted RTS,S schedule resulting in the largest reductions in malaria cases and deaths, modelling results showed the EPI vaccination strategy to be more beneficial during 10–20 months of age (when children are at higher risk of severe malaria outcomes), due to the disparity in ages of the first vaccine dose between strategies (Annex 8). A Hybrid strategy that uses EPI delivery for the primary series could potentially be more impactful than seasonally targeted RTS,S schedule by preserving a young age at first vaccination and retaining the benefits of seasonally targeted fourth and fifth doses (Annex 8).

9.2.3 RTS,S impact with SMC delivery

The model simulations indicated the combination of RTS,S and SMC to be significantly more impactful than either intervention alone in seasonal settings. The combination of seasonally targeted RTS,S vaccination strategy + SMC resulted in a greater number of cases and deaths averted compared to EPI vaccination strategy + SMC (Figure 18). The inclusion of SMC alongside a vaccination schedule also reduces the effect of disparity in age at first vaccination between seasonally targeted RTS,S vaccination and EPI vaccination (Annex 8).

On average, the seasonally targeted RTS,S vaccination strategy averted an additional 61% more cases than SMC alone with the EPI vaccination strategy averting an additional 31%. When interventions were combined, the additional impact of vaccination over SMC was higher in seasonal settings than in highly seasonal settings. This may reflect the greater importance of protection conferred by RTS,S outside the peak transmission season, in areas where transmission is less seasonal, when SMC is in place to address the burden during the peak months.

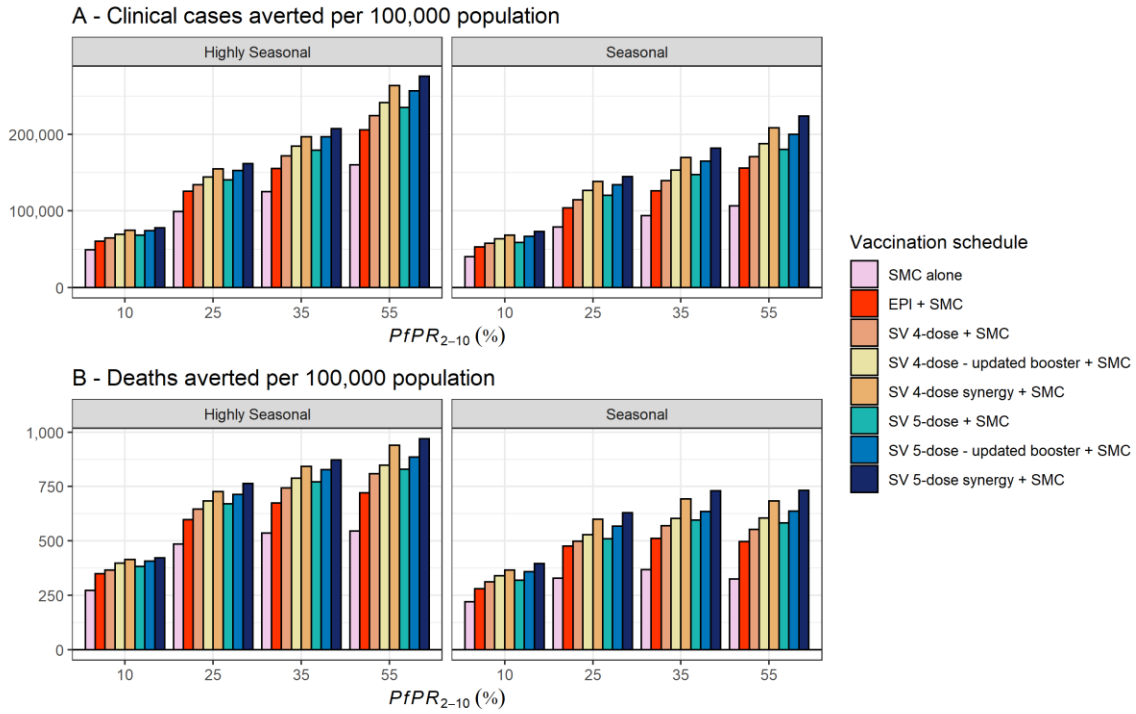


Figure 18: Cumulative clinical cases and deaths averted over 15 years per population as a function of baseline $PfPR_{2\text{-}10}$ (four representative of medium to high transmission intensity are shown) and seasonality. Coverage is fixed at 80% for the first three doses with a 20% drop off for the fourth and fifth doses. SMC coverage at 75%.

9.2.4 Cost-effectiveness

Details on cost-effectiveness modelling are provided in Annex 8. As no seasonal delivery cost data or introduction data are yet available for RTS,S, seasonal costs were assumed equivalent to EPI vaccination costs informed by MVIP data.

Incremental cost-per-case and cost-per-DALY averted for each intervention compared with no vaccine, for an assumed cost per dose of US$5, were lowest at intermediate to high levels of baseline $PfPR_{2\text{-}10}$. ICERs were generally less than $100 per DALY averted and $20 per case averted for a $PfPR_{2\text{-}10}$ of more than 20% for all vaccination schedules (Annex 8, Figure A14). Overall, the model estimated that ICERs were marginally lower for the seasonal vaccination strategies (i.e., more cost-effective) despite the higher number of overall doses delivered (Annex 8, Table A5).

When added to SMC, the cost of vaccination was generally less than $160 per DALY averted and $50 per case averted for all vaccination schedules (Annex 8b, Figure A14). ICERs were lower for seasonally targeted RTS,S schedules compared to EPI schedules (Annex 8b, Table A6).

9.2.5 Interpretation of results

Population-level modelling indicates that seasonally delivered RTS,S vaccination in seasonal settings results in greater absolute reductions in malaria cases and deaths over 15 years compared to RTS,S delivery though an EPI vaccination strategy. However, although seasonal vaccination strategy may avert more cases than the EPI strategy, further exploration of seasonal vaccination clinical trial data and model results highlight the potential for seasonal vaccination strategies to result in delayed first vaccination depending on birth month leaving children at risk of malaria in their first transmission season.

Reductions in malaria morbidity and mortality are greatest when vaccines are delivered in combination with Seasonal Malaria Chemoprevention (SMC), with seasonal vaccination strategy + SMC predicted to result in the largest burden reductions.

Cost-effectiveness analysis, while illustrative, suggests that all delivery strategies (routine EPI, SV, hybrid) are cost-effective at a cost per dose of US$ 5 in seasonal settings with medium to high transmission intensity. Both trial and modelling results indicate RTS,S vaccination would be a cost-effective addition to existing SMC programmes. When considering RTS,S vaccination in seasonal settings the potential achievable coverage will likely determine the most beneficial delivery approach.

10 Equity considerations

The vast majority of malaria illness and death occur in Africa and in children under 5 years of age. Malaria disproportionately affects the poor and those living in rural areas. HIV exposure, HIV infection or chronic malnutrition, all of which frequently overlap geographically with areas of malaria endemicity, are additional risk factors for malaria illness or death[37, 38]. Although progress has been made in improving equity for malaria control interventions, in some countries, access to malaria control measures differ by SES and rural/urban settings[6]. The RTS,S malaria vaccine has been tested and proven safe in children with HIV or those with malnutrition.

Evidence from the midline household surveys in the 3 pilot countries show that the RTS,S vaccine was delivered equitably by sex and by socio-economic status, the exception being Malawi, where vaccine coverage during the first 24 months of vaccine introduction was 58% for children in the lowest socio-economic status and 68% among children in the highest socio-economic status. Because of the broad reach of the vaccine, and relatively rapid uptake to reach a high proportion of age-eligible children, layering of the malaria vaccine and ITNs has increased access to at least one malaria prevention tool (ITN or malaria vaccine) among vulnerable children.

11 Overall RTS,S SAGE/MPAG Working Group assessment and summary of key recommendations for SAGE/MPAG consideration

11.1 Assessment of vaccine safety

A substantial amount of new information is now available to address the questions raised by SAGE/MPAG in 2015 following the Phase 3 trial on the safety, impact, and feasibility of RTS,S/AS01 as a malaria prevention intervention, to inform a potential recommendation on broader use of the vaccine. In particular, in the first two years of the MVIP, designed to respond specifically to the outstanding questions on the public health use of the vaccine, it has been demonstrated that the vaccine can be delivered successfully. The RTS,S/AS01 vaccine has been incorporated by the MoH in the EPI programmes in Ghana, Kenya, and Malawi using the routine systems for new vaccine introduction, and uptake has been good in all three countries, reaching or exceeding expectations for a new vaccine with a novel schedule, even in the context of the COVID-19 pandemic and response. The MVPE has been conducted according to protocol and at high quality. The statistical analysis was conducted according to the published Statistical Analysis Plan.

Additional data on safety from sources outside of the MVIP have also become available since the last SAGE/MPAG meeting in 2015. These additional data include: 1) long-term follow-up of a subset (>3000 children) of the Phase 3 trial participants for an additional three years after conclusion of the main study; 2) a seasonal use study in more than 6000 children assessing the individual and combined impact of RTS,S/AS01 and SMC; and 3) a trial in about 1200 children of different fractional dose regimens of RTS,S/AS01.

Based on the safety data available from the MVIP, a large, structured pilot introduction, through which more than 1.7 million RTS,S/AS01 vaccine doses were provided, and from these additional sources, the Working Group concurs with the MVIP DSMB that no evidence of a causal relationship between the RTS,S/AS01 vaccine and the 3 potential safety signals – cerebral malaria, meningitis, or mortality by gender, has been found.

This conclusion comes following the DSMB and Working Group review of the primary outcome measures on safety from the MVPE, 24-months after vaccine introduction (Annex 6). Analysis of the data showed that the safety signals seen among 10,306 infants and children who received RTS,S/AS01 in the Phase 3 clinical trial of RTS,S/AS01 (2009-2014), and which were considered possible chance findings, were not present. The signals were not seen in the pilot implementation after 652,673 children received their first dose (and 494,745 their third dose) in implementation areas where the vaccine was provided, or among the 10,032 age-eligible children admitted to the sentinel hospitals (4,870 from implementation areas), during the period from start of vaccination in 2019 until 30 April 2021.

The DSMB and Working Group concluded that the MVPE results showed comparable burden for meningitis, cerebral malaria, and gender-specific mortality among age-eligible children living in implementation areas and those in the comparison areas, with results consistently showing risk ratios near 1 (i.e., no association) for probable meningitis, cerebral malaria, and the vaccine-gender interaction with mortality. In addition, estimates comparing the risks in intervention areas with those in comparison

areas were inconsistent with the corresponding risk ratio point estimates (adjusted for vaccine coverage) observed in the Phase 3 trial. In other words, the hypotheses that there was a causal association between the vaccine and those specific three risks were rejected. Consistent with this observation, no safety signals were detected during the extension period of the long-term (7-year) follow-up study of a subset of children enrolled in the Phase 3 trial, nor in the seasonal use or fractional dose trials.

The GSK-sponsored Phase 4 post-authorization study continues, as part of the risk management plan with the EMA, and will accrue additional data on safety, with data cleaning and an interim analysis planned for 2023, around the end of the MVIP and a final analysis planned in 2025.

The Working Group does not consider it necessary to wait until further data have accrued to conclude on the safety of the RTS,S/AS01 vaccine. The primary concern regarding the 4th dose was around the loss of protection against severe malaria among children who received only 3 doses during the Phase 3 trial. However, the long-term follow-up study and re-analysis of the Phase 3 data indicate that the age shift in severe malaria cases was limited in duration, without an excess in severe malaria cases in children who received only 3 doses. The Working Group notes that in the Phase 3 trial there was no excess in meningitis cases in the children who received 3 doses vs 4 doses after month 20, when the 4th dose was provided (3 meningitis cases in the 3-dose arm and 2 cases in the 4-dose arm after month 20 until study end); there was no excess in possible cerebral malaria in the children who received 3 doses vs 4 doses in the Phase 3 trial after month 20 (8 cases in the 3-dose arm and 7 cases in the 4-dose arm); and the gender imbalance in mortality was observed prior to month 20, and if causally associated with the vaccine, should have been observed during the first 24 months after vaccine introduction.

11.2 Assessment of impact

The DSMB and Working Group concluded that the MVPE findings demonstrated clinically and statistically significant effectiveness of the RTS,S/AS01 vaccine against severe malaria and that this effect was assessed as consistent with the effect observed in the Phase 3 trial and indicated a beneficial impact of the vaccine. As expected, there was insufficient power at this point to detect an effect on mortality (~13 500 child deaths were recorded through the mortality surveillance system, while to achieve 90% power to demonstrate a 10% reduction in mortality, 24 000 deaths will need to have accumulated). Nonetheless, the 7% impact on mortality (not statistically significant) measured through the MVPE is consistent with what would be expected if malaria contributes to about 30% of deaths in young children (based on a 25% reduction in severe malaria as a proxy for malaria related mortality). The conclusions regarding a positive impact of the vaccine in routine use were based on the following:

- The number of events accrued were adequate to demonstrate significant benefit for preventing severe malaria. For mortality, the number of accrued events had not yet reached the target sample size, so the analysis was not yet adequately powered.
- The pooled analysis indicated that RTS,S/AS01 vaccine significantly reduced the incidence of severe malaria in the implementation areas, and hospital admissions with a positive malaria test; a non-statistically significant reduction in all-cause mortality (excluding accidents/trauma) was also seen.

The Working Group recognizes the added benefit of delivering the RTS,S/AS01 vaccine using a seasonal vaccination strategy in areas of highly seasonal transmission, with demonstrated VE against clinical and severe malaria, malaria-specific mortality and all-cause mortality. The Working Group also acknowledges the potential benefit of seasonal vaccination in areas of perennial transmission with seasonal peaks.

11.3 Assessment of feasibility

At this juncture, the decisions regarding a broader recommendation for RTS,S/AS01 are to be based primarily on safety and impact considerations. However, the available feasibility data are very encouraging. This assessment is based on the following observations:

- Despite RTS,S/AS01 being a new vaccine delivered through EPI and requiring an expanded schedule, reasonably high coverage of the first three doses was achieved in all three pilot countries. This was achieved in a relatively short time period and in the context of substantial challenges to the health system due to the COVID-19 pandemic, indicating strong demand by parents and acceptance by health workers who deliver the vaccine.
- It is too early to assess fourth dose coverage, although preliminary information suggests drop-out rates between dose 3 and dose 4 have been around 19-30%, not an unexpected range for the first months of implementation of a new vaccine provided during the 2nd year of life, and provided using routine strategies alone without supplemental activities. It is notable that the coverage rates reached were in the context of an ongoing pandemic. The level of uptake of the fourth dose indicates that the fourth dose can be delivered; the continuation of the pilots will provide lessons learned on best practices to increase fourth dose coverage.
- Malaria vaccine introduction did not have an impact on the uptake of other routine childhood vaccinations, ITN use, health care seeking behaviours for febrile illness, or other child health interventions such as the provision of vitamin A or deworming.
- The malaria vaccine was delivered equitably, with no difference in delivery by sex, nor major difference by socio-economic status.
- Malaria vaccine uptake during the first 18 months of implementation was 69-75% among children who had not used an ITN, suggesting the intervention was reaching children who have lower access or use of other malaria prevention measures. Thus, the malaria vaccine increases the reach and reduced inequities to access to malaria prevention interventions.
- In general, care givers and health care providers had positive attitudes towards the vaccine. Further work is required with health care providers to look for opportunities to provide missed vaccine doses (for all childhood vaccines), and improved understanding on how to ensure the provision of doses to children who present late for vaccination. Proper data recording tools are needed to assist with the implementation of the above.
- Estimates on cost of RTS,S/AS01 delivery during the MVIP were comparable to costs of HPV vaccine pilot implementation; comparisons of these estimates to those available from routine new vaccine introductions (outside of pilots) should be made with caution, as methods and delivery strategies may differ during routine new vaccine introduction.

11.4 RTS,S/AS01 in the context of other malaria control interventions

RTS,S/AS01 is a complementary tool for prevention. LLINs remain a proven and cost-effective intervention. SMC is an effective intervention for areas with highly seasonal malaria. IPTi, although not widely deployed, provides added protection during the first year of life. And IRS, although limited in use, also is efficacious. Access to quality case management is essential when malaria illness occurs regardless of the preventive measures in place. The WHO Global Malaria Programme supports malaria control approaches that are flexible and tailored to local context. Adequate funds for the recommended malaria control interventions, and to support the tailored approach to malaria control, should be allocated to ensure their deployment and coverage to maximize impact.

11.4.1 RTS,S/AS01 and seasonal malaria chemoprevention

When RTS,S/AS01 was delivered, in the context of a controlled trial, as a primary series before the seasonal increase in malaria incidence in highly seasonal transmission settings in Burkina Faso and Mali, followed by yearly booster doses before the start of the malaria transmission season, it was demonstrated to be non-inferior to four annual courses of seasonal malaria chemoprevention (SMC) with SP-AQ in protecting against uncomplicated clinical malaria over a period of three years. Furthermore, a combination of RTS,S/AS01 and SMC was superior to RTS,S/AS01 or SMC alone in reducing the incidence of uncomplicated clinical malaria, hospital admissions with severe malaria and deaths from malaria.

The combined impact of RTS,S/AS01 and SMC was impressive; compared to SMC alone, the combination significantly reduced episodes of severe malaria by 70%, severe malaria anaemia by 68%, all cause deaths by 53%, and malaria deaths by 73%. Importantly, subsequent single annual doses of RTS,S/AS01 delivered just prior to the seasonal incidence increase provided continued additional benefit of a similar magnitude in the three years following the initial primary series. The trial has entered an extension phase to measure the added benefit of continuing annual dosing beyond 2 booster doses. Modelled estimates of impact are high, including when the initial 3 dose series is provided as part of routine immunizations followed by annual boosts, and the strategy is estimated to be cost-effective.

Thus, the combination of seasonal chemoprevention and seasonal vaccination with RTS,S/AS01 (primary series and annual boosting) , appears to be a promising approach to increase the operational effectiveness of the malaria vaccine by deploying it just prior to the high transmission seasons. This strategy may be well-suited to areas in Africa with highly seasonal malaria transmission or with perennial transmission with seasonal peaks, though it has yet to be evaluated in these settings. For example, in such areas, it is possible that it could be used as an alternative to the 4-dose schedule as evaluated in MVIP, with the primary series either being provided just before the peak season, through a campaign, followed by two (or more) annual boosts, or it could be provided through the routine EPI programme, with the primary series beginning around 5 months of age, and followed by two annual boosts.

11.5 Conclusions and recommendations for SAGE/MPAG consideration

The RTS,S SAGE/MPAG Working Group recommends that RTS,S/AS01 should be provided at a minimum of 4 doses to reduce malaria disease and burden in children from 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission. The RTS,S/AS01 vaccine has an acceptable safety profile, and its introduction results in a significant reduction in severe malaria, an acceptable surrogate indicator for the likely impact on mortality. The Working Group notes that the vaccine provides substantial added protection against malaria illness and death even when provided in addition to a package of existing interventions which are known to reduce the malaria burden. The introduction of a vaccine at this time would come when progress in recent years has stalled in malaria control in Africa, when our current tools are threatened by drug and insecticide resistance, and when malaria remains a primary cause of illness and death in African children, with more than 260 000 child deaths from malaria annually.

In areas of moderate to high, perennial malaria transmission, the vaccine should be provided as a 3-dose primary series, starting from around 5 months of age and with a minimal interval between doses of 4 weeks. For children who are delayed in receiving their first dose, vaccination should be started before 18 months of age. A fourth dose should be given between about 12 and 18 months after the 3rd dose (i.e., at around 18 months to 2 years of age), however there can be flexibility to optimize delivery. The minimal interval between the 3rd and the 4th dose should be 4 weeks.

In areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks, the RTS,S SAGE/MPAG Working Group recommends that consideration should be given to the option of providing the RTS,S/AS01 vaccine seasonally, with potential 5-dose strategies including:

1) For all children under 5 years of age who have already completed the 3-dose primary series through routine administration, provide annual dose(s) just prior to the peak transmission season, or
2) For all children 5-17 months of age, give the 3-dose primary series monthly as a “campaign” just prior to the peak transmission season and then in subsequent years provide an annual dose just prior to peak seasons.

The RTS,S SAGE/MPAG Working Group makes this recommendation for possible 5-dose seasonal malaria vaccination strategies based on available data. The Working Group understands that this trial is continuing with additional doses provided to children up until the age of 5 years, and final results will contribute evidence on vaccine efficacy beyond 5 doses. The Working Group also notes that providing the first dose from 5 months of age may limit opportunities for integration with the delivery of other vaccines and/or for protection of children slightly younger (i.e., 4 months).

The Working Group notes that the careful and intentional monitoring for the safety signals seen in the Phase 3 trial, through quality data collection at sentinel hospitals and through community-based mortality surveillance, has revealed no evidence that the safety signals observed in the Phase 3 trial were causally related to the RTS,S/AS01 vaccine. Thus, the Working Group does not recommend special mechanisms be put in place to look for these signals during expansion of vaccine use or adoption by other countries.

WHO should lead the development of a Framework to guide where the initial limited doses of a malaria vaccine should be allocated, through a transparent process that incorporates input by key parties, with appropriate representation and consultation. This Framework should include dimensions of market dynamics, learning from experience, scientific evidence for high impact, implementation considerations, and social values, including fairness, and equity.

The MVIP should continue as previously planned for an additional two years to 1) measure the impact of the introduction of RTS,S/AS01 on mortality; and 2) measure the added benefit of the fourth dose (the Working Group noted that in the Phase 3 clinical trial, the impact on severe malaria was only seen among children who had received 4 doses of the vaccine but there was impact on clinical malaria among children who received only 3 doses, though lower than that observed on children who had received 4 doses). Data collection on severe malaria and safety endpoints should continue. Any revisions or modifications concerning the recommendation for the fourth dose can be made at the end of the pilots.

11.6 Research recommendations

The Working Group recommended a number of areas for monitoring, evaluation, and research. None of these are meant to be obstacles to the broader implementation of the RTS,S/AS01 vaccine.

- Data from the MVPE and other studies show no evidence that the safety signals observed in the Phase 3 trial were causally related to the RTS,S/AS01 vaccine. Strengthening of national pharmacovigilance systems is highly desirable to detect unanticipated adverse effects of this vaccine and any other newly introduced vaccines, as well as for vaccines already in use.
- The MVIP will continue to monitor for or collect data on safety and impact, and on the value of the fourth dose through to the end of the programme and in the planned case control study.
- Based on experience in the three pilot countries, the MVIP will also provide information on how best to achieve coverage of the 4th dose.
- Monitoring and evaluation around flexible schedules and implementation strategies are encouraged; this includes monitoring and evaluation around implementation strategies for RTS,S/AS01 seasonal vaccination.
- Vaccine effectiveness studies following widespread introduction of RTS,S/AS01 are encouraged.

The following research are recommended for the following areas, with the PAG noting that none are prerequisite prior to expanded use of RTS,S/AS01.

(1) areas with moderate to high malaria transmission with perennial transmission

- Through the MVIP, continued collection and monitoring data on safety and impact through the end of the programme and in the planned case control study, and on the added benefit of the fourth dose.
- Through the MVIP, collect additional information on how best to achieve coverage of the 4th dose, and its impact on severe malaria and mortality.
- Added or synergistic effect of RTS,S/AS01 when given in conjunction with expanded IPTi.

(2) areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks

- Operations research around the delivery of seasonal vaccine dosing, including around annual pre-season dosing after a primary series given through the routine health clinics in areas of perennial or seasonal transmission.
- Further evaluation will be required to determine how best to deliver the combination of SMC and seasonal malaria vaccination in areas of high malaria burden in the Sahel, sub-Sahel, and areas of perennial transmission with seasonal peaks.
- Safety, immunogenicity, and effectiveness of annual doses beyond dose 5.
- Planned follow-up of the ongoing seasonal malaria vaccination trial and case-control study, and evaluation of any age shift effect of clinical or severe malaria cases in immunized children (relative to the control group) after ceasing vaccination.

(3) both areas (1) and (2):

- Parasite genotype monitoring to detect any emergence of vaccine escape mutants – in context of broader use of RTS,S/AS01
- Co-administration of RTS,S/AS01 with typhoid conjugate, Meningococcal, and inactivated polio vaccines, and other antigens as appropriate.

12 Acknowledgements

The successful planning, conduct and analysis of the Malaria Vaccine Implementation Programme (MVIP) has depended on the contributions of multiple organizations and individuals.

The MVIP and the generation of additional evidence on the first malaria vaccine described in this report would not have been possible without the generous financial support received from Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid. All three organizations demonstrated vision and leadership by contributing jointly towards an ambitious, large-scale pilot programme for a vaccine developed exclusively for children in Africa.

The partnership between the World Health Organization, PATH and GSK, the vaccine manufacturer, was crucial for the implementation of the MVIP. The RTS,S/AS01 vaccines used in the MVIP were generously donated by GSK. The leadership by, and staff of, the Ministries of Health of Ghana, Kenya and Malawi ensured the successful introduction of the vaccine into their immunization programmes and provided routine vaccine administrative data enabling the continuous monitoring of vaccine uptake as well as the sharing of learnings along the way. UNICEF made important contributions, ensuring the timely shipment of the malaria vaccines, despite the logistical difficulties posed by the COVID-19 pandemic.

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13 List of supportive materials and annexes

Supportive materials – via links

Background paper on RTS,S/AS01 Malaria vaccine, prepared by the Joint Technical Expert Group (JTEG) on Malaria Vaccine and WHO Secretariat, September 2015
Available at:
https://www.who.int/immunization/sage/meetings/2015/october/1_Final_malaria_vaccine_background_paper_v2015_09_30.pdf

An evaluation of the cluster randomized pilot implementation of RTS,S/AS01 through routine health systems in moderate to high malaria transmission settings in sub-Saharan Africa: a post-authorization observation study (MVPE Master Protocol v9.0)
Available at: https://clinicaltrials.gov/ProvidedDocs/65/NCT03806465/Prot_ICF_000.pdf

Statistical analysis plan for the MVPE v3.4
Available at: https://clinicaltrials.gov/ProvidedDocs/65/NCT03806465/SAP_002.pdf

Annexes

Annex 1: Framework for WHO Recommendation on RTS,S/AS01 Malaria Vaccine

Annex 2: Malaria vaccine targets and pipeline

Annex 3: Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced (September 2021, v1.2)

Annex 4: Publication Chandramohan et al. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. NEJM. 2021;

Annex 5: Health Utilisation Study (HUS) Round 2 - *cross-country report on findings from the Primary Child Caregiver cohort sample*

Annex 6: MVIP Data Safety and Monitoring Board meeting recommendations following review of malaria vaccine pilot evaluation results (July 2021)

Annex 7: Reports of the extraordinary meetings by the African Advisory Committee on Vaccine Safety (AACVS) and the Global Advisory Committee on Vaccine Safety (GACVS) (August 2021)

Annex 8: Modelled public health impact and cost effectiveness of RTS,S/AS01 in seasonal and perennial settings (August 2021)

Annex 9: GRADE and Evidence to Recommendation table on the use of malaria vaccine

14 RTS,S SAGE/MPAG Working Group Membership and Terms of Reference

Members of the MVIP Programme Advisory Group (PAG) in its capacity as the RTS,S SAGE/MPAG Working Group, include:

- Prof Ifedayo Adetifa, KEMRI-Wellcome Trust Research Programme, Kenya
- Prof Nick Andrews, Public Health England, United Kingdom
- Dr Dafrossa Cyrily Lyimo, Independent consultant (and former National Immunization and Vaccine Development Programme Manager, Tanzania
- Dr Corine Karema, Independent consultant (and former Director of the Rwanda National Malaria Control Programme, Rwanda
- Dr Eusébio Macete, Centro de Investigação em Saúde de Manhiça, Mozambique (Co-Chair)
- Prof Kim Mulholland, Murdoch Children's Research Institute, Australia
- Prof Kathleen Neuzil, Center for Vaccine Development and Global Health (CVD), University of Maryland School of Medicine, USA
- Prof Peter Smith, London School of Hygiene & Tropical Medicine, United Kingdom (Chair)
- Prof S. Patrick Kachur, Mailman School of Public Health, Columbia University, USA

Past members have included:

- Prof Graham Brown, University of Melbourne, Australia
- The late Ms Adelaide Shearley, John Snow Inc., Zimbabwe
- Prof Fredrick Were, University of Nairobi and Kenya Paediatric Research Consortium, Kenya

Terms of Reference is accessible here: https://www.who.int/initiatives/malaria-vaccine-implementation-programme/programme-advisory-group

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