Malaria Policy Advisory Group Meeting
4—7 October 2021, Geneva, Switzerland
Background document for Session 6
Also published in the SAGE Yellow Book for October 2021 (5.1_Malaria)

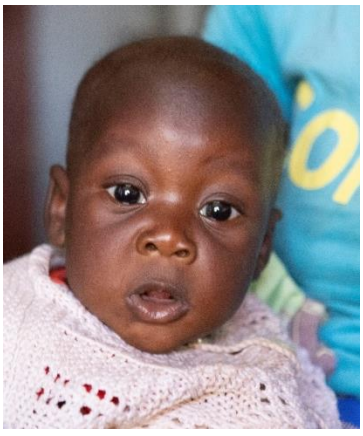
World Health Organization

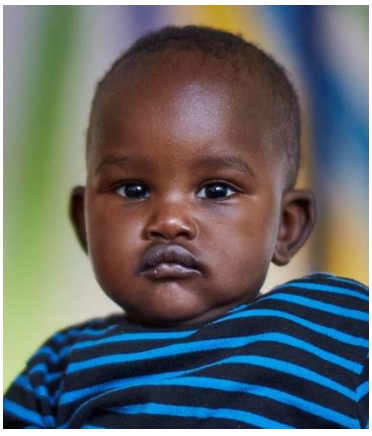
Background Paper

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).

September 2021





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)

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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.

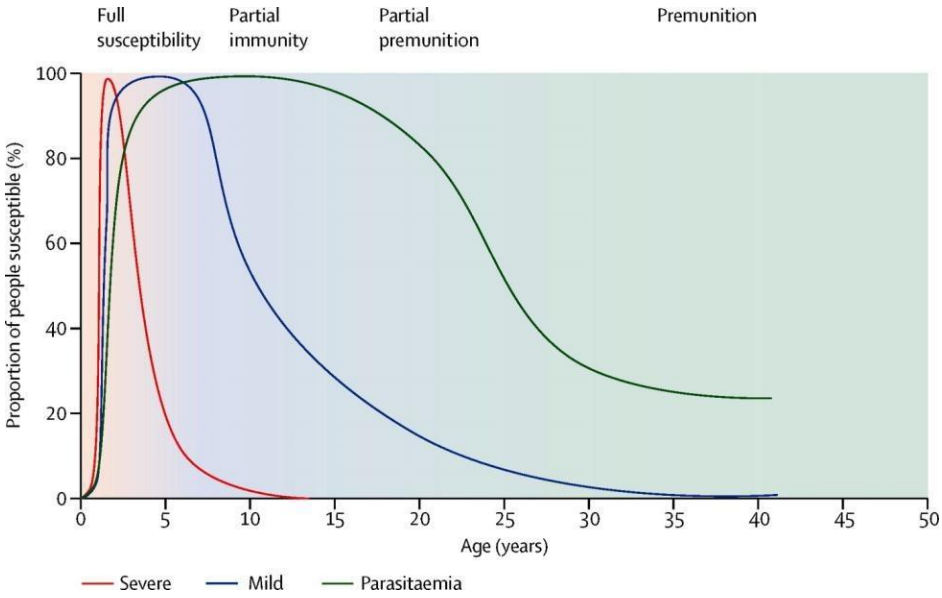


Figure 1: Relation between age and malaria severity in an area of moderate transmission intensity. From White *et al.* 2014[11].

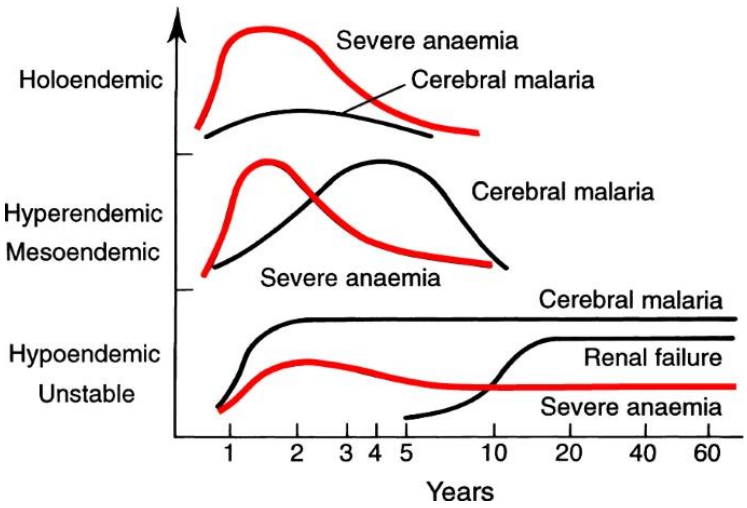


Figure 2: Relationship of severe falciparum malaria manifestations to age at different levels of malaria transmission From White *et al.* 2018[11].

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

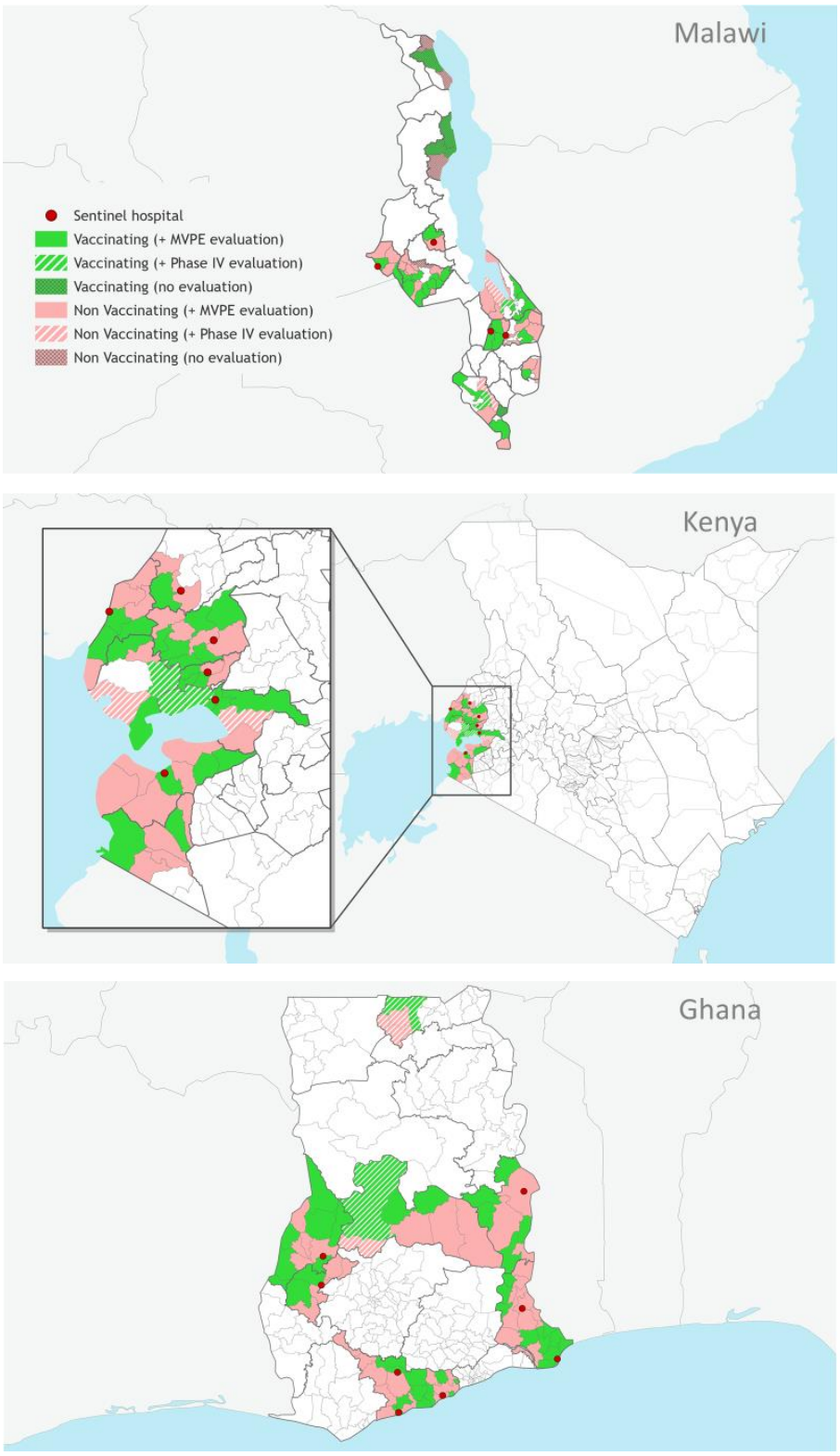
5.1 Overview of design

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.
Error! Reference source not found. 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.

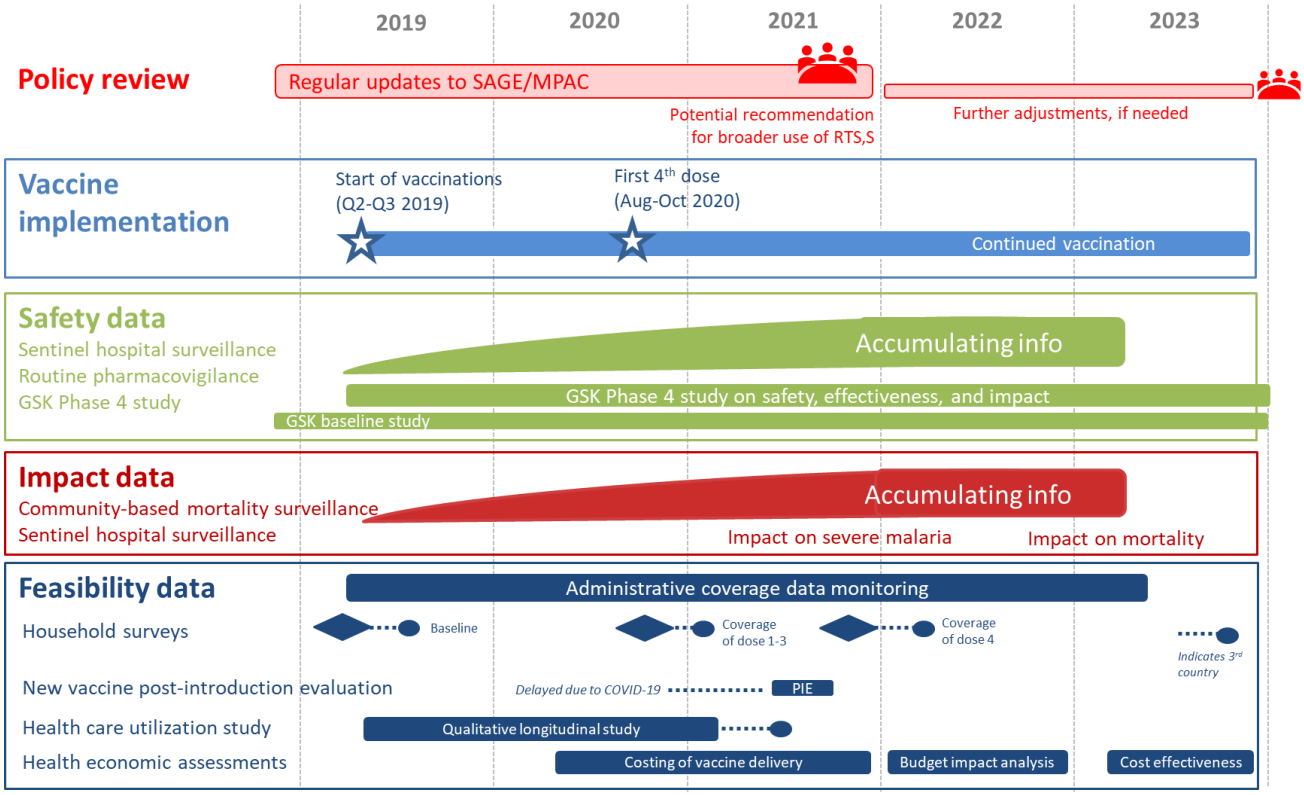


Figure 3: Timeline for evidence generation and review

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.

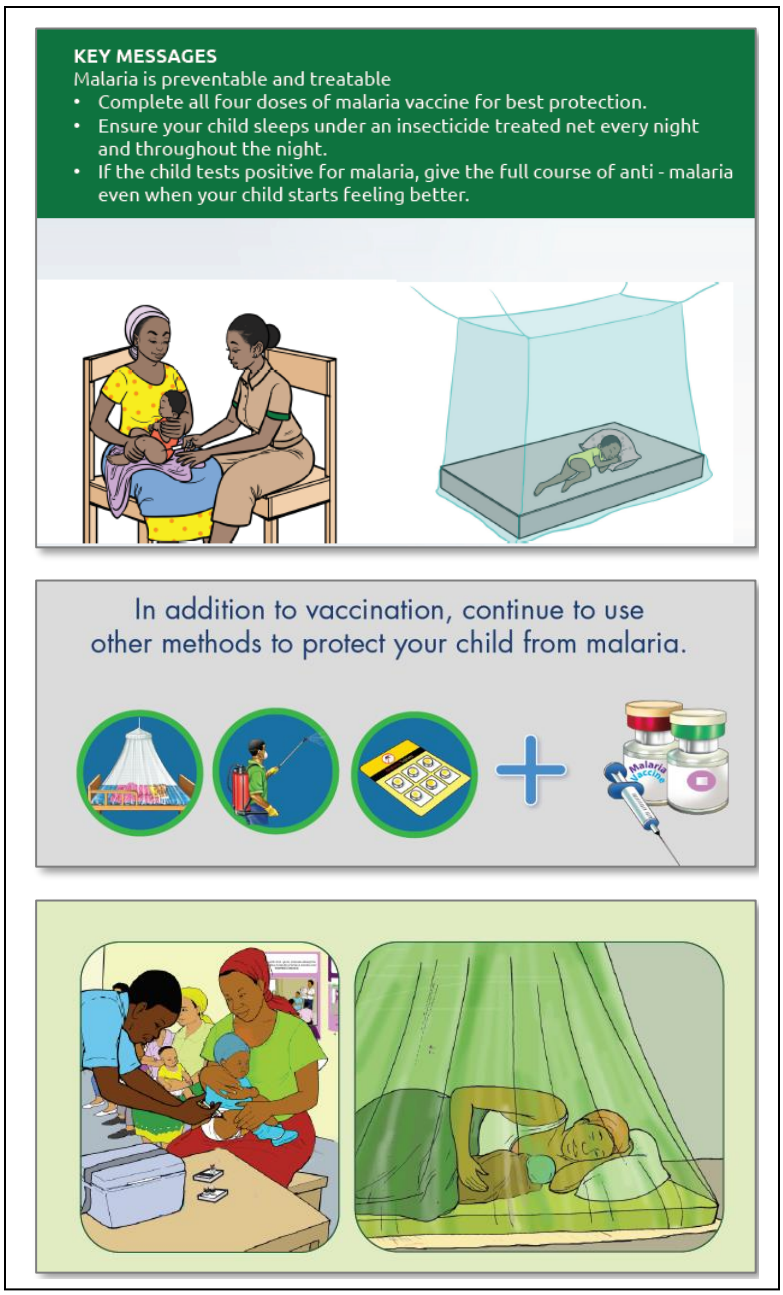


Figure 5: Extracts from countries' communication materials, developed under the leadership of the MOH, highlighting the complementarity of RTS,S/AS01 with other malaria control interventions.
From top to bottom: Ghana Flip Chart; Kenya Flyer; Malawi Flyer and Key Facts Booklet

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.). The analysis followed a pre-defined analysis plan that has been s 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 (**Error! Reference source not found.**). 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 (**Error! Reference source not found.**).

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 **Error! Reference source not found.**. 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.

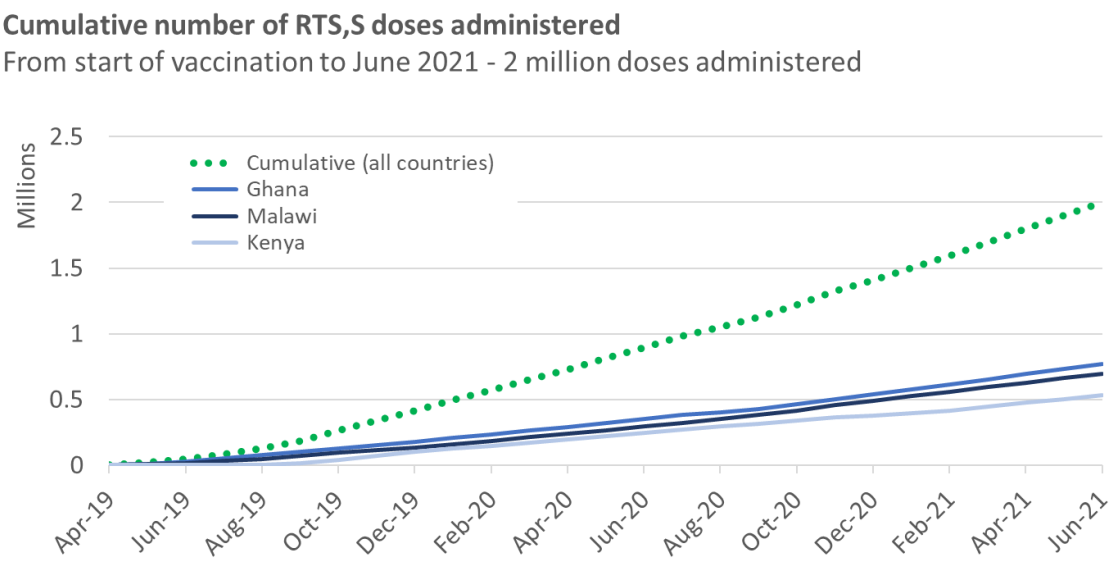


Figure 6*: Cumulative number of RTS,S administered since start of the programme*

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.

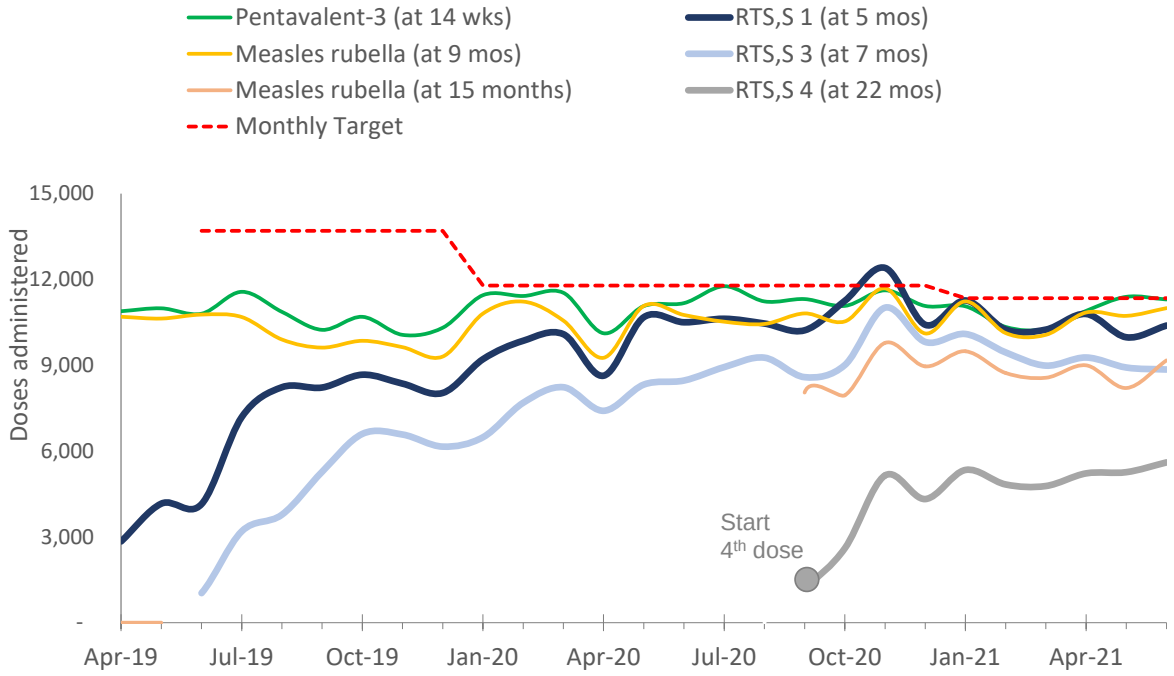


Figure 7*:* Number of doses administered for selected antigens including RTS,S from April 2019 to June 2021 among MVIP target population, Malawi, administrative data

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.

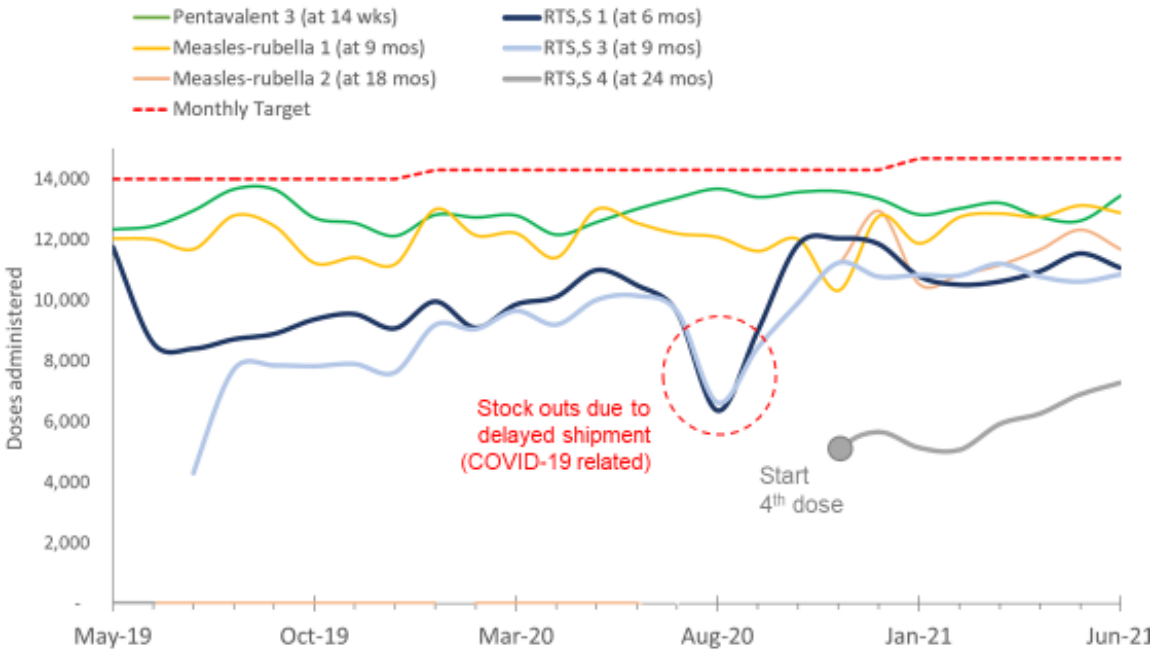


Figure 8: Number of doses administered for selected antigens including RTS,S from May 2019 to June 2021 among MVIP target population, Ghana, administrative data

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.

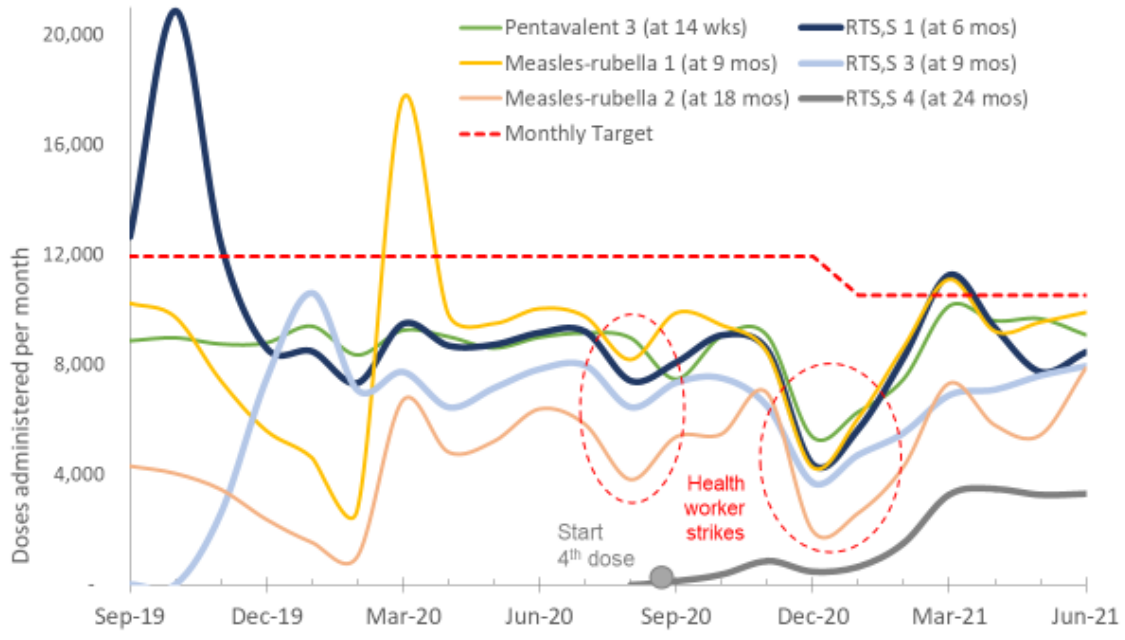


Figure 9*:* Number of doses administered for selected antigens including RTS,S from September 2019 to June 2021 among MVIP target population, Kenya, administrative data

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).

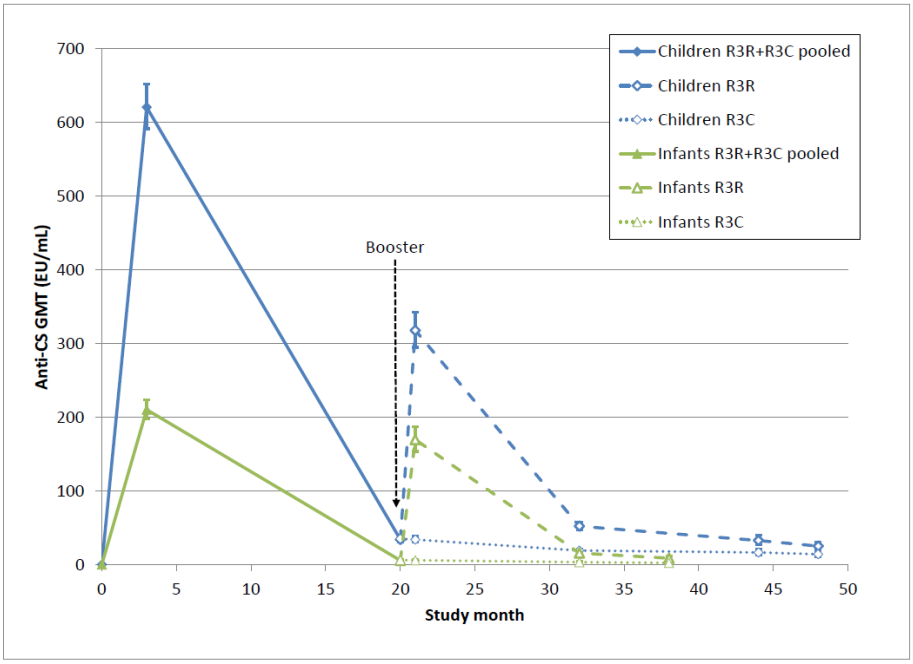


Figure 11: Anti-CS geometric mean titres in 5–17-month age category (labelled as “children”) and 6–12-week-old age category (“infants”) in pivotal Phase 3 trial (per-protocol population for immunogenicity). Provided by GSK

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).

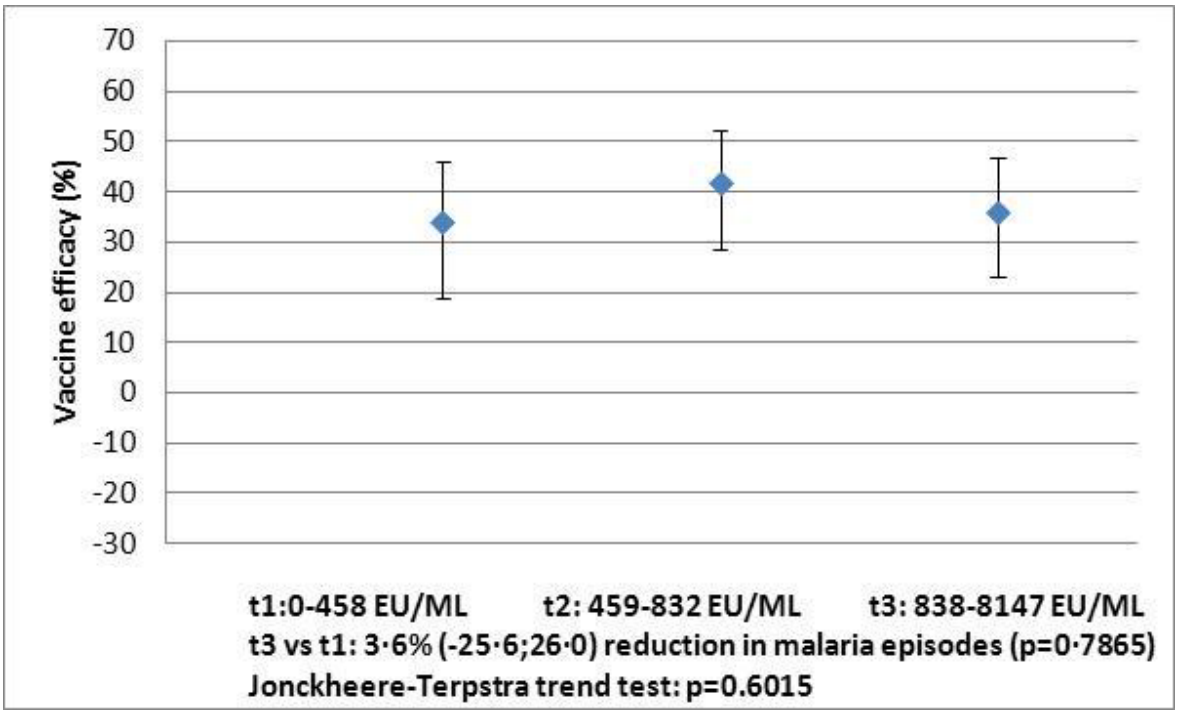


Figure 12: Vaccine efficacy by tertile of anti-CS antibody concentration (ATP population) in 5-17 month age category (R3C, 3-dose schedule). Error bars represent 95% confidence interval. t1-3: tertile 1-3 of anti-cs titre post vaccination. Provided by GSK on request

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.

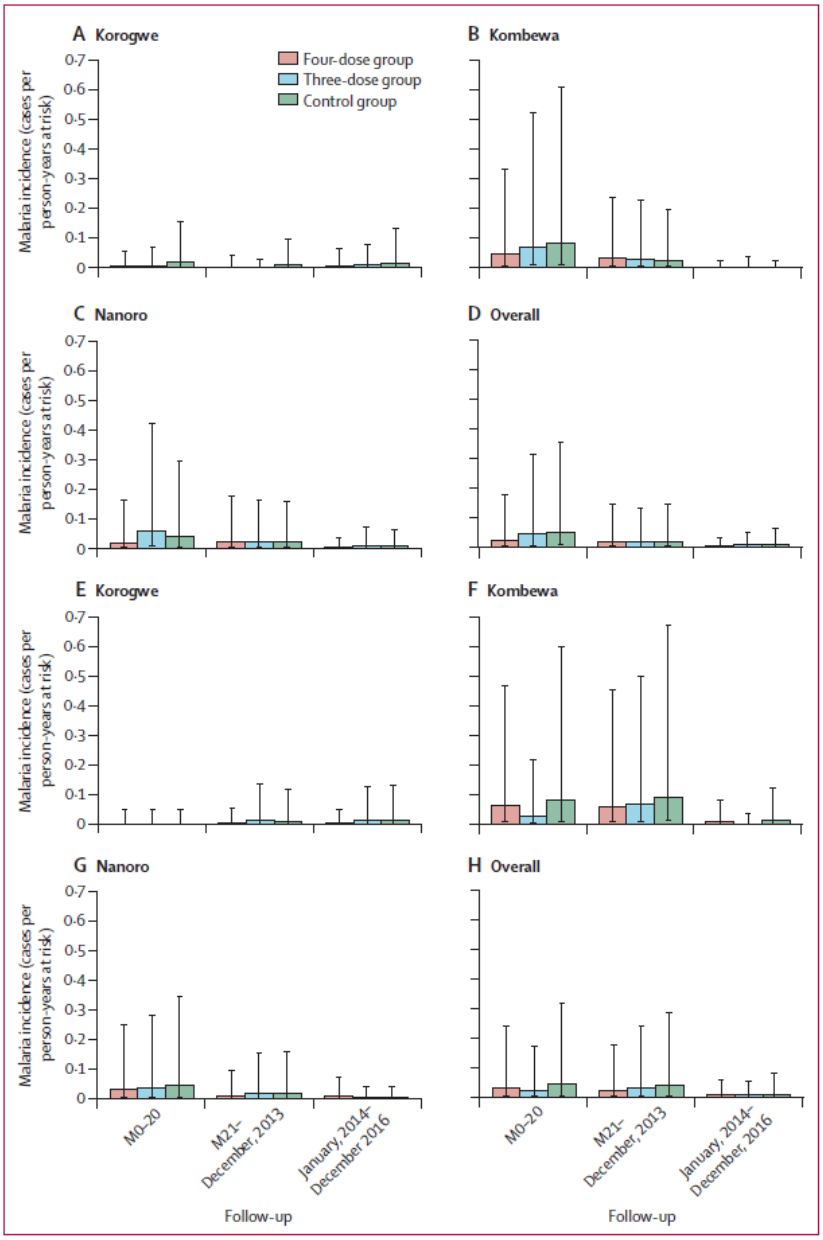


Figure 13: Incidence of severe malaria in children from the older age category (A–D) and the younger age category (E–H) in the intention-to-treat population (A, E) Korogwe. (B, F) Kombewa. (C, G) Nanoro. (D, H) Overall. Older age category included children aged 5–17 months; younger age category included 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).

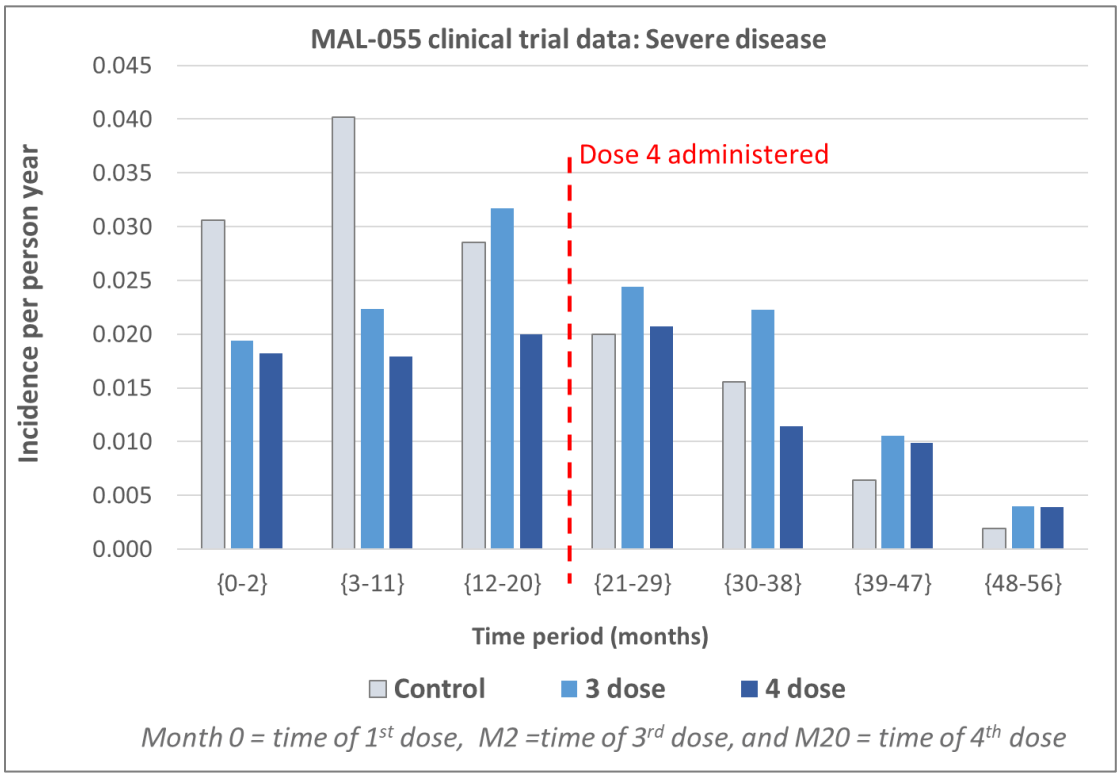


Figure 14: Vaccine impact before and after receiving the 4th dose (intention-to-treat population). Severe disease incidence per person year (MAL 055, aggregated over all clinical trial sites for 5-17 month cohort ITT population) plotted every 8 months after dose 1 is administered. The dotted line represents 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.

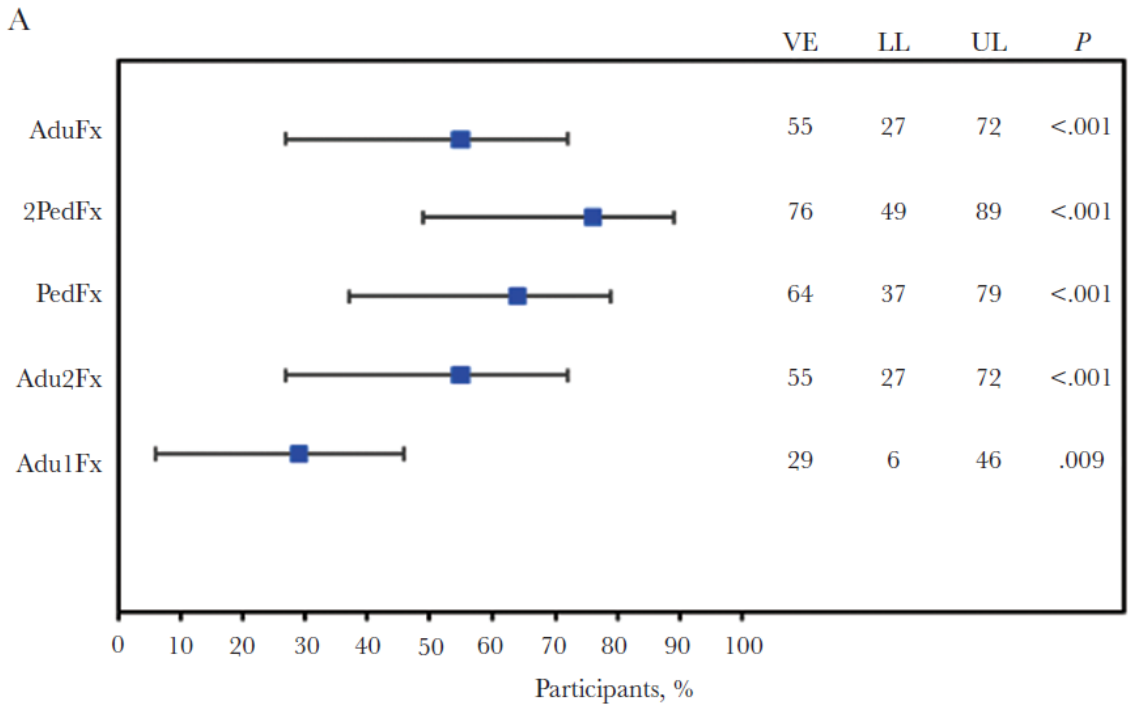


Figure 15: Vaccine efficacy in the prevention of *P. falciparum* parasitaemia for all five study groups. Error bars indicate 95% confidence intervals[36].

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.

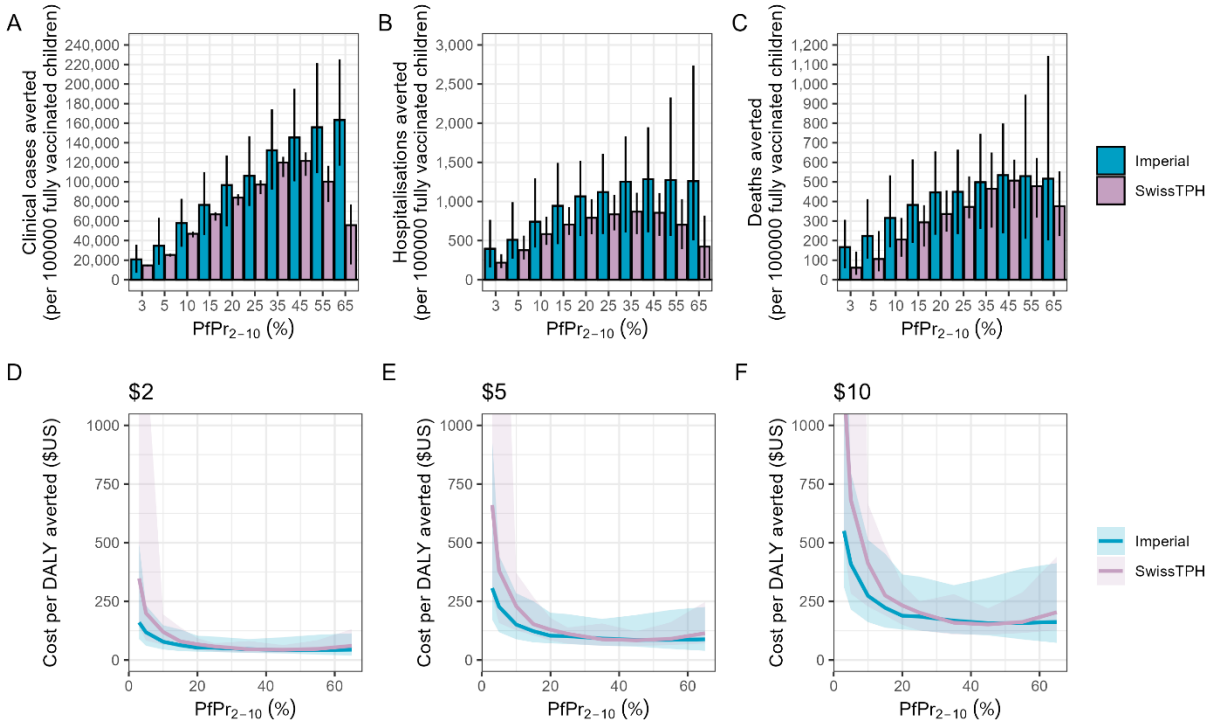


Figure 1610. Summary of impact and cost-effectiveness predictions for RTS,S/AS01 across transmission settings of 3-65%.

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).

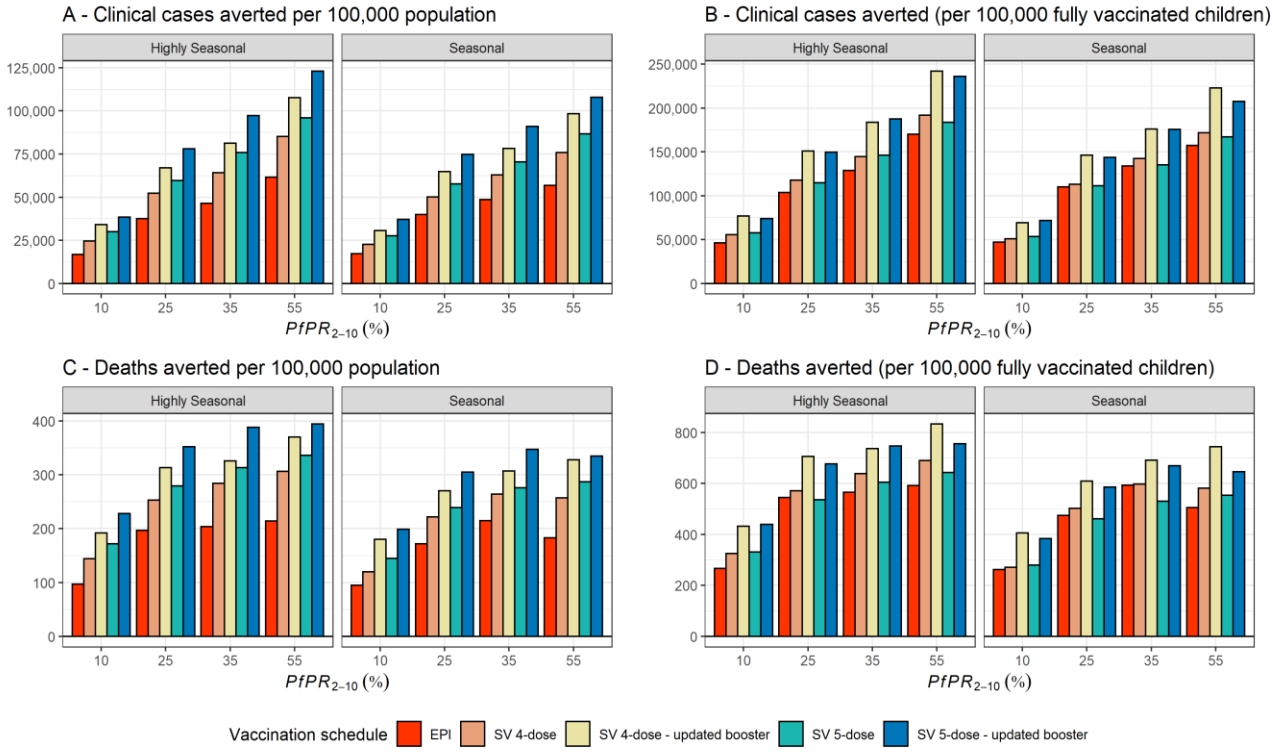


Figure 17: Cumulative clinical cases averted over 15 years as a function of baseline PfPR2-10 (four settings representative of medium to high transmission intensity are shown) and seasonality A&C) per population and B&D) per 100 000 fully vaccinated children. Coverage is fixed at 80% for the first three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

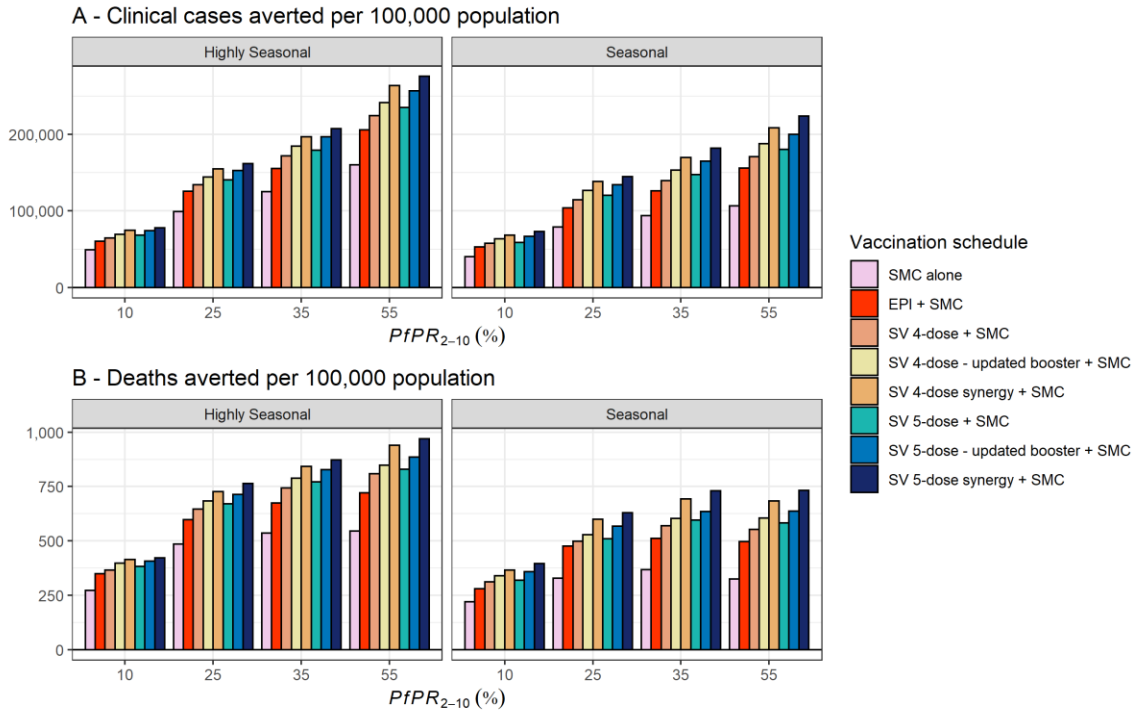


Figure 18: Cumulative clinical cases and deaths averted over 15 years per population as a function of baseline $PfPR_{2\text{-}10}$ (four representative of medium to high transmission intensity are shown) and seasonality. Coverage is fixed at 80% for the first three doses with a 20% drop off for the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

Leadership and key contributions have been provided by the evaluation partners consortia from Ghana (Kintampo Health Research Centre; Navrongo Health Research Centre; School of Public Health, University of Ghana; Ghana Health Service; Noguchi Memorial Institute for Medical Research; University of Health and Allied Sciences), Kenya (CDC Foundation, Centers for Disease Control and Prevention (CDC), Kenya Medical Research Institute (KEMRI), KEMRI Wellcome Trust Research Programme; Walter Reed Army Institute of Research) and Malawi (College of Medicine, University of Malawi; University of North Carolina at Chapel Hill (UNC) Project, Lilongwe) who implemented the WHO-commissioned

evaluation studies, provided data in a timely fashion and participated in the analysis led by the LSHTM. Important contributions were made by the invasive Bacterial Vaccine Preventable Diseases (IB-VPD) reference laboratories (NICD, South Africa and MRC Gambia), who provided quality assured molecular analysis for cerebrospinal fluid in the diagnosis of meningitis. External monitoring was provided by Pharmalys and ClinWin Research Services, who oversaw the quality assurance of the WHO-led evaluation studies. The team at the London School of Hygiene and Tropical Medicine (LSHTM) made essential contributions: Dr Paul Snell provided ongoing data management and Professor Paul Milligan and Dr Kerryn Moore led the development of the statistical analysis plan for the Malaria Vaccine Pilot Evaluation and conducted the analysis for the statistical report.

Valuable additional insights were obtained through the PATH-commissioned qualitative studies by the University of Cape Coast, the Kumasi Centre for Collaborative Research, and the University of Energy and Natural Resources together with the University of Health and Allied Sciences in Ghana, Malawi-Liverpool-Wellcome Clinical research Programme in Malawi and; KEMRI, CDC and Liverpool School of Tropical Medical collaboration in Kenya. In addition, the health economics group at PATH led the costing studies and the teams at the Swiss Tropical and Public Health Institute and the Imperial College, UK, conducted the mathematical modelling to estimate the vaccine's public health impact and cost-effectiveness.

Continuous oversight and monitoring of safety data from the MVIP, and expert advice on the vaccine's safety profile, was provided by the members of the MVIP Data Safety and Monitoring Board (DSMB) - Professor Cynthia Whitney Dr Jane Achan, Dr Esperança Sevene, Professor Charles Newton, Professor Larry Moulton.

Gemma Villanueva and Nicholas Henschke from the Cochrane Response supported the systematic review of evidence and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) used to inform the recommendations. Finally, Dr Laurence Slutsker had a crucial role in consolidating the evidence and drafting this report.

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

MALARIA VACCINE IMPLEMENTATION PROGRAMME (MVIP)

PROPOSED FRAMEWORK FOR POLICY DECISION ON RTS,S/AS01 MALARIA VACCINE

FOR THE STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE) ON IMMUNIZATION AND THE MALARIA POLICY ADVISORY COMMITTEE (MPAC)

PREPARED BY THE FRAMEWORK FOR POLICY DECISION ON RTS,S/AS01 WORKING GROUP AND THE WHO SECRETARIAT

11 March 2019

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I. EXECUTIVE SUMMARY

The intention of this proposed Framework for Policy Decision (FPD) document is to provide relevant background and information and to present the Working Group recommendations to the World Health Organization (WHO)'s Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) on how the data generated by the Malaria Vaccine Implementation Programme (MVIP) can be used, as they become available, to inform policy decisions. The Framework will provide an opportunity for discussion and alignment of views prior to key time points for recommendations by the SAGE and MPAC to WHO regarding the broader use of the RTS,S/AS01 malaria vaccine.

To develop the Framework, a Working Group was established of representatives from WHO advisory bodies involved in malaria vaccine policy decision making. They reviewed data and information that led to the 2016 WHO malaria vaccine position paper, and data and information that has emerged since then. Background was provided on the MVIP, along with a summary of policy precedents on malaria interventions and prior SAGE policy decisions on vaccines, to facilitate Working Group discussions around a series of FPD key questions.

Existing data and information – leading up to and incorporated in the 2016 WHO malaria vaccine position

Phase 3 trial: RTS,S/AS01 has been developed over more than three decades by GlaxoSmithKline (GSK), including through a collaboration, begun in 2001, with PATH's Malaria Vaccine Initiative. 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 (MAL-055). This multisite trial was conducted at 11 sites in seven African countries and showed a vaccine efficacy, when given in four doses to children aged 5–17 months at first vaccination, of 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 [1]. 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)[4]. The Phase 3 data indicated 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 [1].

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. Among participants aged 5–17 months at first vaccination who received a 3-dose 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 vaccinees, respectively. 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 [1].

During the Phase 3 trial, the vaccine was associated with an increased risk of febrile seizures within seven days of vaccination; overall, the risk of seizures was similar among children who received RTS,S/AS01 and those who received the comparator vaccine (possibly due to a reduction in malaria-

related seizures). Two safety signals were identified during the trial for which causality has not been established: meningitis (any cause) and cerebral malaria. Among 5 to 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). In the same age group, 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[1].[1] A *post hoc* analysis showed an imbalance in mortality among girls (all ages), with about 2-fold higher death rate 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 [2]. The Phase 3 trial was conducted in settings with improved access to quality care and there was very low mortality among children enrolled in the trial. The WHO advisory groups and the European Medicines Agency (EMA) concluded that all of these described safety signals may have arisen by chance [2].

Regulatory: The EMA, under a process known as Article 58, reviewed data on the quality, safety and efficacy of RTS,S/AS01 and issued a positive scientific opinion in July 2015. The positive scientific opinion means that the quality of the vaccine and its risk/benefit profile is favourable from a regulatory perspective. In its assessment, the EMA applied the same rigorous standards as for medicines to be marketed within the European Union [3]. The EMA's assessment is being updated as new data become available and has remained valid since the original issuance.

Policy: In January 2016, following a joint review of evidence by WHO's SAGE and MPAC following review by the Joint Technical Expert Group on Malaria Vaccines (JTEG), WHO published its position for RTS,S/AS01. WHO recommended pilot implementation of the RTS,S/AS01 vaccine in distinct settings in sub-Saharan Africa in order to generate critical evidence to enable decision-making about potential wider scale use.

The 2016 WHO position paper called for pilot implementation of the malaria vaccine through phased designs and in the context of ongoing high coverage of other proven malaria control measures. The pilot implementations would demonstrate the extent to which the protection demonstrated in children aged 5–17 months in the Phase 3 trial can be replicated in the context of routine health systems, particularly in view of the need for a 4-dose schedule that requires new immunization contacts. Other questions identified by WHO to be addressed as part of pilot implementations include the extent to which RTS,S/AS01 vaccination impacts all-cause mortality, which could not be adequately assessed in the Phase 3 trial owing to the very low overall mortality in the trial; whether there is a differential impact in boys and girls; and whether there are excess cases of meningitis and cerebral malaria, as identified during the Phase 3 trial, which would suggest that these effects are causally related to RTS,S/AS01 vaccination [2].

[1] Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa' (Human Vaccines & Immunotherapeutics; in press)

As part of its recommendation from the 2015 review process, the JTEG advised WHO to monitor emerging data from the pilot implementations and noted that it would be appropriate for WHO to recommend country-wide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose [4].

New data and information – since the January 2016 position paper

Pilot implementation: Following a call for expressions of interest, Ghana, Kenya and Malawi were selected, using standardized criteria, to participate in the pilot implementations [5]. The Programme is being implemented over multiple years with activities begun in 2017 and evaluations expected to be completed by 2023. RTS,S/AS01 vaccine introduction is anticipated to start in the first half of 2019 in all countries, upon confirmation of readiness of all relevant components. The Programme consists of three components:

1) Vaccine introduction through national immunization programmes in selected areas of each country with moderate to high malaria transmission. The vaccine has received special authorization for use in context of the pilot implementations by each country's national regulatory authority following a joint convening by the African Vaccine Regulatory Forum (AVAREF). The aim is to reach approximately 360,000 children per year in the selected areas.
2) A WHO-sponsored pilot evaluation master protocol has been developed for ongoing implementation by country-based research partners to conduct studies to:
    - Assess the programmatic feasibility of delivering a four-dose schedule, including new immunization contacts, in the context of routine health service delivery;[2]
    - Evaluate the vaccine's impact on severe malaria and all-cause mortality;[3] and
    - 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.[4]
3) GSK-sponsored Phase 4 studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and the EMA to further assess vaccine safety, effectiveness and impact in routine use [6]. In addition to enhanced hospitalization surveillance, the Phase 4 study will include active surveillance through home visits and continuous monitoring of outpatient visits and hospitalisations at health care facilities in a subset of areas in which the vaccine is and is not being administer. The WHO-sponsored pilot evaluations complement the GSK-sponsored Phase 4 study.

Evidence and experience from the pilot implementations will inform recommendations on the vaccine's potential use on a wider scale in Africa. The FPD Working Group reviewed expected pilot data availability and power calculations of key safety and impact end points. The calculations were based on current assumptions included in the statistical analysis plan under development (see Annex

[2] Routine coverage data from the health information systems will be available as the programme unfolds and household surveys in 2020/2021 and 2021/2022 will document coverage of doses 1-3 and 4, respectively.
[3] The evaluation of impact on survival will be through community mortality surveillance and is powered to detect a 10% reduction in all-cause mortality in each country. This is expected to be complete in 2023.
[4] The potential safety signals identified through the Phase 3 trial will be monitored at a number of sentinel hospitals. Adverse events following immunization will also be assessed through routine pharmacovigilance at all health facilities in the pilot areas.

4) related to expected rate of accrual of relevant disease events and vaccine introduction timelines across the three MVIP countries.

Long-term follow-up of children from 3 of the 11 sites included in the Phase 3 trials (MAL-076): The soon-to-be published results of GSK's MAL-076 study were shared with the FPD Working Group. Continued open label monitoring of children who were enrolled in the Phase 3 clinical trial at 3 of the 11 trial sites[5] showed that there was protection against clinical and severe malaria over the total of 7 years of follow-up and in the 3 additional years of follow-up there was no further imbalance observed in meningitis, cerebral malaria, nor sex-specific mortality. Notably, there were very few cases of severe malaria observed after the 4 years of follow-up during the Phase 3 trial, presumably due to the development of acquired immunity, regardless of whether children received RTS,S/AS01 or comparator vaccine. These long-term follow-up results showed no evidence of an overall excess of severe malaria in RTS,S/AS01 recipients [7] who received three RTS,S/AS01 doses and no rebound of disease after the fourth vaccine dose. The MAL-076 results indicate that the previously observed excess in severe malaria among children who received only three doses of RTS,S/AS01, from the time that the fourth dose would have been given to the end of the Phase 3 trial, was time limited (see Section V for more on MAL-076).[6]

Background information on malaria reviewed by the FPD Working Group and on policy precedents for introduction of vaccines against other diseases (see Annex 5)

Immunization: Vaccines are among the most successful public health interventions. Millions of lives have been saved and substantial disability averted due to the implementation and scale-up of vaccines against other diseases. The FPD Working Group reviewed prior SAGE policy decisions on other vaccines to inform questions pertinent to RTS,S/AS01 with attention to the type and quality of data available at the time of a recommendation. Rotavirus vaccines, pneumococcal conjugate vaccines (PCVs), and dengue vaccine case studies were the most relevant examples for this exercise.

Malaria: The FPD Working Group reviewed the current status of malaria transmission as well as policy precedent for malaria interventions. The 2018 World Malaria Report estimates that over 400,000 people, mainly young African children, died from malaria in 2017. This is despite considerable progress in malaria control since 2000 with the implementation and scale-up of interventions to combat the disease. Currently recommended malaria prevention tools—long lasting insecticidal nets (LLINs), Intermittent Preventive Treatment in infants (IPTi), Intermittent Preventive Treatment in pregnancy (IPTp), indoor residual spraying (IRS), and in areas with highly seasonal malaria, seasonal malaria chemoprevention (SMC)—provide substantial protection against malaria morbidity and mortality but are at risk due to emerging biological resistance in the malaria parasites and anopheline vectors. The last two years have seen a plateau in progress in malaria control and an increased urgency to develop and implement new strategies to get malaria control back on track [8]. In contrast to the process for SAGE vaccine policy decisions published in position papers, malaria intervention policy decisions have not followed a consistent procedure or format for publication.

[5] 3 of the 11 Phase 3 trial sites (Korogwe (Tanzania); Kombewa (Kenya); Nanoro (Burkina Faso)) had an additional 3 years of follow up.
[6] MAL-076 study results submitted for publication (GSK)

The RTS,S/AS01 vaccine may be an important new intervention to add to the current package of malaria control interventions - one that is neither drug nor insecticide based, and that can be delivered through the existing immunization delivery system. A malaria vaccine provided through the routine childhood vaccination programme could reach children not otherwise reached with malaria control interventions, including those in the lowest socio-economic strata.

Below is a summary of the FPD Working Group recommendations; all are further discussed in Section III:

1) The SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging pilot data (see Figure 1).
   - Step 1: A WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when:
     i. concerns regarding the safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria and sex-specific mortality) are satisfactorily resolved, by demonstrating either the absence of a risk of an important size during RTS,S/AS01 pilot implementation or an assessment of a positive risk-benefit profile despite adverse event(s); and
     ii. severe malaria data trends are assessed as *consistent with a beneficial impact* of the vaccine; or
     iii. mortality data trends are assessed as *consistent with beneficial impact* of the vaccine.

   Based on current assumptions across the three MVIP countries' related to the expected rate of accumulating events and vaccine introduction timings, such data on safety and impact trends could be available approximately 24 months after RTS,S/AS01 vaccine introduction in the Programme. Updated estimates will be confirmed within a statistical analysis plan when there are preliminary data on event rates (see Annex 4).

   - Step 2**:** Adjustments or refinements to the policy recommendation for broader use of RTS,S/AS01 can be made based on the final MVIP data set, with particular focus on the value of the fourth dose, expected to be available approximately 50 months after start of vaccination in the third MVIP country.
2) There is a need to resolve safety concerns on meningitis, cerebral malaria, and sex-specific mortality to establish the risk-benefit profile of the vaccine, as reassuring safety data are required for a policy recommendation.
3) The policy recommendation for broader use could be made in the absence of data showing vaccine impact on mortality. Impact on severe malaria is an acceptable surrogate indicator for impact on mortality, and could support a policy recommendation if assessed as consistent with a beneficial impact.
4) A 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.
5) Barring substantial adverse impact on the coverage of other vaccines or malaria control interventions, the impact of RTS,S/AS01 introduction on the coverage of these interventions should not influence the policy recommendation. Rather these indicators should inform strategies for implementation, including areas to call attention to or to provide opportunities for improvement.

6) Cost effectiveness estimates should be regularly refined, as data become available for increasingly precise calculations, and presented at appropriate time points.

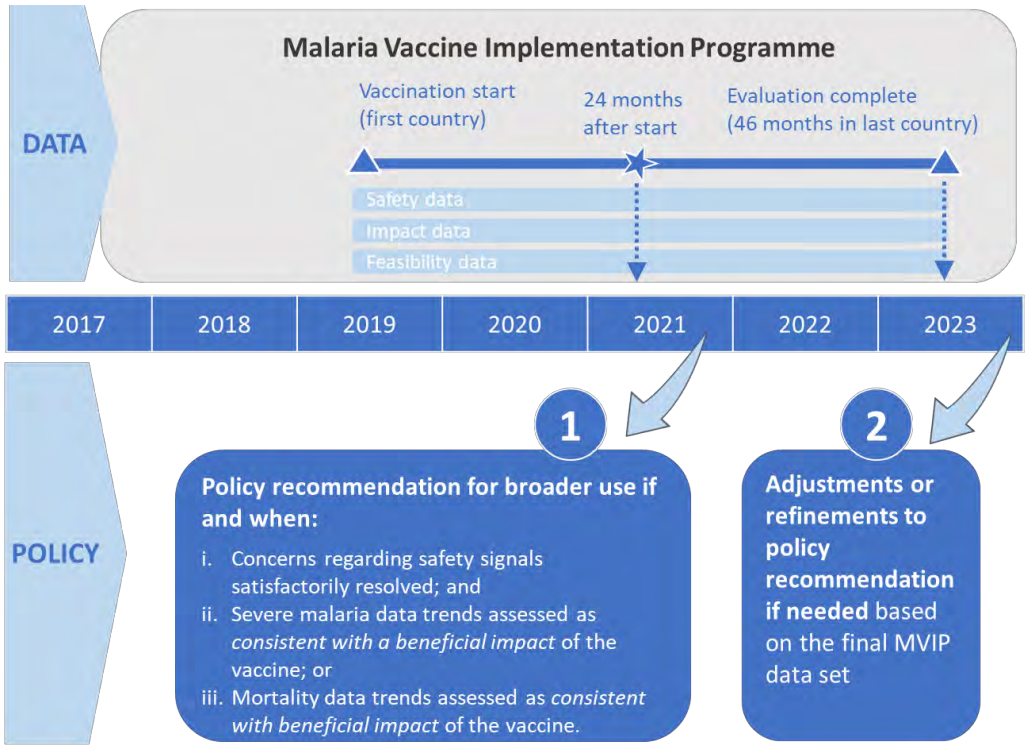
7) Expansion within MVIP countries should be synchronized with recommendation for broader use across sub-Saharan Africa.

8) In the context of the step-wise approach to policy recommendations, the pilots should continue on to complete data collection to establish the public health value of the fourth dose, including assessment of the vaccine's impact on mortality.

9) Conflicting data among the MVIP countries would require careful investigation into the reasons for differences. The pilots should continue with plans for analysis even if data are delayed or not available in all countries.

10) Criteria that could result in WHO not recommending RTS,S/AS01 vaccine for use or that may lead to a decision to defer a policy recommendation to a later time point were recommended by the Working Group.

Figure 1: Proposed step-wise approach to policy recommendation



II. INTRODUCTION

In January 2016, WHO published its first malaria vaccine position paper, adopting the joint recommendations by the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) [2]. Recognizing the importance of malaria as a major cause of morbidity and mortality, particularly in sub-Saharan Africa, the need for new malaria control tools, and the potential significant contribution of the RTS,S/AS01 malaria vaccine to further reduce malaria burden, WHO recommended pilot implementation of the vaccine in sub-Saharan Africa.

The Malaria Vaccine Implementation Programme (MVIP) has been developed in line with these recommendations to address the identified outstanding questions related to the public health use of the vaccine. The Programme supports introduction of the malaria vaccine in selected areas of Ghana, Kenya and Malawi accompanied by rigorous evaluation of the vaccine's feasibility, safety and impact in routine use. The primary aim of the Programme is to generate additional data to enable a WHO policy decision on the broader use of the RTS,S/AS01 malaria vaccine in sub-Saharan Africa.

A. Purpose of the Framework for Policy Decision

The Framework for Policy Decision (FPD) on RTS,S/AS01 aims to describe how and when data collected through the MVIP will be used to inform a WHO policy recommendation on vaccine use beyond the pilots.

The Framework considers the relative contribution of the collected data on feasibility, safety, and impact to a future policy recommendation. It also provides clarity on the expected use of the data in anticipation of potential changes in SAGE and MPAC membership between the time the SAGE/MPAC recommendations were made (2015) and availability of data from the pilot implementations. It is anticipated that funders, potential funders, and manufacturers can refer to the Framework for planning purposes. Finally, the Framework is non-binding as other factors might impact a policy decision (such as a new highly efficacious intervention). Both SAGE and MPAC supported the development of such a Framework during their 2018 meetings.[7]

B. FPD Working Group

The FPD on RTS,S/AS01 Working Group includes representatives from the SAGE, MPAC, IVIR-AC, modelling groups, and the MVIP Programme Advisory Group (PAG). The Working Group Terms of Reference (see Annex 1) define its operations and specific responsibilities.

Working group members have reviewed relevant background information and other considerations for the RTS,S/AS01 policy decisions. Discussion were structured around key questions for the working group to consider in the context of RTS,S/AS01 (see Annex 3).

The subsequent sections present the Working Group's recommendations and summarize the background information that informed the Framework.

[7] SAGE and MPAC meeting reports, October 2018

III. WORKING GROUP RECOMMENDATIONS

The Working Group is comprised of representatives from advisory bodies involved in malaria vaccine policy decision making (See Annex 1 and 2). The following background and information were provided during their meetings (see Annex 2) to facilitate their deliberations:

- *Existing data and information that led to the current policy position (Section IV)*
- *Data and information that have emerged since then (Section V)*
- *Questions posed to the FPD Working Group (Annex 3)*
- *Expected availability of evidence from the pilot implementations (Annex 4)*
- *Considerations based on precedent from malaria interventions policies, prior SAGE policy decisions on other vaccines, and immunization coverage trajectories following new vaccine introductions (Section V and Annex 5)*

Recommendation 1: The SAGE and MPAC should consider recommending a step-wise approach for review and policy decision on broader use of RTS,S/AS01 based on emerging pilot data.

Step 1: A WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when:

i. concerns regarding the safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria and sex-specific mortality) are satisfactorily resolved, by demonstrating either the absence of a risk of an important size during RTS,S/AS01 pilot implementation or an assessment of a positive risk-benefit profile despite adverse event(s); and
ii. severe malaria data trends are assessed as *consistent with a beneficial impact* of the vaccine; or
iii. mortality data trends are assessed as *consistent with beneficial impact* of the vaccine.

Based on current assumptions across the three MVIP countries' related to the expected rate of accumulating events and vaccine introduction timings, such data on safety and impact trends could be available approximately 24 months after RTS,S/AS01 vaccine introduction in the Programme. Updated estimates will be confirmed within a statistical analysis plan when there are preliminary data on event rates (see Annex 4).

Step 2: Adjustments or refinements to the policy recommendation for broader use of RTS,S/AS01 can be made based on the final MVIP data set, with particular focus on the value of the fourth dose, expected to be available approximately 50 months after start of vaccination in the third MVIP country.

Table 1 includes the potential timing of review and key available data from the MVIP based on the step-wise approach to policy recommendation.

Table 1. Step-wise approach to policy recommendation

	Step 1	Step 2
Policy decision	**Initial policy decision on broader use of RTS,S/AS01** if safety signals satisfactorily resolved and severe malaria impact data trends are assessed as consistent with findings from the Phase 3 trial, and mortality data are compatible with a beneficial effect of the vaccine	**Update or refinement of the policy recommendation, if needed, with particular focus on value of fourth dose**
Potential timing of review*	In late 2021, approximately 30 months after vaccine introduction in the first country, based on approximately 24 months of data across MVIP.	In late 2023, at the end of the pilots, based on approximately 50 months of data after vaccine introduction in 3rd MVIP country.
Key available data from MVIP	– Data on potential safety signals identified through the Phase 3 trial (meningitis, cerebral malaria, sex-specific mortality) – Impact on severe malaria and trends in impact on mortality – Coverage of first 3 doses from representative sample household survey and from administrative data – Approximately 6 months of administrative coverage data for dose 4 – Contextual and behavioural factors related to RTS,S/AS01 uptake through first 3 doses – Costs of delivering first 3 doses – AEFI[1] and pre-specified AESI[2] reported through MoH routine pharmacovigilance systems – AEFI and AESI data collected through active surveillance as part of GSK-sponsored Phase 4 study	– Information on fourth dose coverage – Added value of the fourth dose with respect to impact on severe malaria and mortality – GSK-sponsored Phase 4 study interim analysis
Not yet available	– Impact on mortality – Dose 4 coverage from representative sample household survey & administrative data	

**based on current assumptions across the 3 MVIP countries related to expected rate of accrual of relevant disease events and vaccine introduction timelines. Updated estimates will be made when there are preliminary data on event rates.*

The FPD Working Group based its recommendation for a step-wise approach on the principle that a decision on broader use of the RTS,S/AS01 malaria vaccine beyond the pilot countries be made at the earliest possible timepoint when robust evidence is available to ascertain a positive risk-benefit profile of the vaccine. In developing these recommendations, the FPD Working Group established a hierarchy of data requirements:

[1] Adverse events following immunization (AEFI)
[2] Adverse events of special interest (AESI)

1. Reassuring safety data are considered of primary importance and a pre-condition for a positive policy recommendation; it is critical to understand whether there are causal associations between RTS,S/AS01 and any of the safety signals observed in the Phase 3 trial.
2. Impact is an important consideration, with impact on severe malaria considered an acceptable surrogate indicator for impact on mortality; trends should be assessed as *consistent with beneficial impact* of the vaccine. There should be recognition that the impact of the vaccine on severe malaria may not necessarily be the same because of what can be achieved during clinical trials as compared to pilot implementation.
3. 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.

Providing a policy recommendation as soon as there is sufficiently robust evidence is important not only in view of the vaccine's potential public health impact, but also to provide the advanced signal to the manufacturer that may be needed to maintain vaccine production, increase likelihood of uninterrupted supply, and trigger financing mechanisms should there be a recommendation for broader use of RTS,S/AS01. The FPD seeks to reduce some of the uncertainty around the timing of a policy recommendation by indicating a potential policy roadmap as reference for the manufacturer and funders' advanced decision making. The likely dependencies of the policy recommendation need to be considered and anticipated, specifically:

- Manufacturer's considerations for supply:

Unlike other vaccines, there is no dual market for RTS,S/AS01. Continued vaccine production by GSK after the 10 million doses committed for the Programme are dependent on the outcome and timing of: a) policy recommendation for broader use of RTS,S/AS01; b) MVIP countries' decisions on continuous vaccination and expansion to comparison areas; and c) purchase order or funding commitment to maintain manufacturing production capacity beyond 2020. GSK will not be in the position to maintain on-going manufacturing activities until there is formal commitment to procure the vaccine beyond the MVIP. Without continued manufacturing, there will be a gap in supply between end of the pilot and start of broader use of the vaccine due to the time required to re-start the facility, along with uncertainty around the increased costs. Though endorsement of a FPD does not guarantee positive results, a step-wise policy recommendation approach may further enable discussions and risk-sharing options among public health partners to ensure continuous supply of RTS,S/AS01. Transparency and advance notice are required between GSK and key stakeholders on the timing of forthcoming manufacturing decision points.

- Financing decisions

Endorsement of a FPD provides guidance on the potential timing of a WHO policy recommendation, enables advanced planning on financing decisions and windows for broader roll-out, and also support for MVIP countries continuing to vaccinate.

Furthermore, the endorsement of a FPD could serve as a positive signal while fundraising in 2019 for the resources required to complete the Programme. Currently, the MVIP is funded between 2017 and 2020, but due to the timing of funding cycles there were few commitments made beyond this point to complete the Programme from 2021 to 2023.

Recommendation 2: There is a need to resolve safety concerns on meningitis, cerebral malaria, and sex-specific mortality to establish the risk-benefit profile of the vaccine, as reassuring safety data are required for a policy recommendation.

Under the Article 58 procedure, the EMA's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of the vaccine outweigh its risks and issued a positive scientific opinion [3] in July 2015. The CHMP noted it had not established that the safety signals identified in the Phase 3 trial were causally linked to the vaccine, and they could be due to chance. They recommended that further data on the signals be obtained through the Manufacturer's post-marketing Risk Management Plan. The January 2016 WHO position paper identified key questions to be addressed as part of pilot implementations, including "whether excess cases of meningitis and cerebral malaria identified in the Phase 3 trial are causally related to the vaccine" and to determine impact of the vaccine on mortality by sex [2]. The WHO-led pilot evaluations[8] and the GSK-sponsored Phase 4 study[9] have been designed to address the safety signals identified in the Phase 3 trial. Additionally, reports of AEFI and pre-specified AESI captured through the Ministry of Health routine pharmacovigilance systems or the GSK-sponsored phase 4 study will be reviewed and assessed by the ministries of health and/or national regulatory authorities. The MVIP Data Safety and Monitoring Board (DSMB) will review data from all of these sources on an ongoing basis and, should safety concerns arise in the pilot implementations, could recommend stopping vaccinations to the Programme Advisory Group and WHO leadership.

The FPD Working Group agreed that resolution of the safety signals is of key importance for a recommendation on broader use of the vaccine. Based on current assumptions related to the expected rate of accrual of disease events and vaccine introduction timings in the three MVIP countries, it is estimated that, if there is no true excess of meningitis, cerebral malaria, and mortality in girls, it would be possible to rule out relative risks of these respective events of an acceptable magnitude approximately 24 months after vaccine introduction, based on the upper 95% confidence level on the relative rate estimates (see Annex 4).

If an excess of one or more of these adverse events were to be found during the Programme, discussions would be required around whether any observed benefits of the vaccine (i.e. reductions in severe malaria, anaemia, blood transfusions) would still justify a recommendation for broader use. Benchmarking against other vaccines with known risks (e.g. rotavirus vaccine risk of intussusception) would be useful.

Recommendation 3: The policy recommendation for broader use could be made in the absence of data showing vaccine impact on mortality. Impact on severe malaria is an acceptable surrogate indicator for impact on mortality, and could support a policy recommendation if assessed as consistent with a beneficial impact.

[8] WHO-sponsored pilot evaluations: there will be 4 to 8 sentinel hospitals per country conducting active in-patient surveillance with focus on monitoring of meningitis and cerebral malaria. To ensure quality, an external monitor will report standards on adherence to clinical algorithms for diagnosis. Community-based mortality surveillance will engage village reporters to document all deaths in children (included the sex of the deceased). Verbal autopsy teams, village reporting supervisors, and reference laboratories will also provide quality assurance.

[9] In the GSK-sponsored Phase 4 programme, a cohort will be enrolled into a prospective study with 10 home visits over a two-year time period and active in-patient surveillance in sentinel hospitals to measure AESI, AEFI, and association of meningitis and cerebral malaria.

It is unlikely that a significant country-specific impact on mortality will be demonstrable before the end of the pilot evaluations (46 months in each country), if the mortality reduction is of the size the Programme is powered to detect (10% reduction in all-cause child mortality).[10] Data trends on the impact on severe malaria may be available earlier (approximately 24 months after vaccine introduction). The measured benefit in terms of severe malaria at this time could possibly be reduced by apparent later rebound effects in children who receive only three vaccine doses. Overall benefit against severe malaria will be available after 46 months of evaluation in each MVIP country. It is anticipated that sufficient data on the safety signals may have accrued by 24 months after the first vaccination to rule out adverse effects, as described above, if there is no true increased risk.

The FPD Working Group considered impact on severe malaria to be an acceptable surrogate indicator for likely impact on mortality. Impact trends in data on severe malaria and mortality, with associated levels of uncertainty, could be presented to inform policy decisions. The recommendations on impact on severe malaria and mortality align with MPAC recommendations made in Oct 2018 [7].

There are several reasons for not waiting until all evaluations are completed in 2023 before WHO recommends policy on broader use of the RTS,S/AS01 vaccine:

1) For no other vaccine has the SAGE required and WHO stipulated demonstration of mortality impact prior to making an initial recommendation for vaccine use. Rather, data on mortality impact has resulted in modifications of recommendations as those data became available.

2) The previous concern, expressed in the SAGE/MPAC recommendations from October 2015, around a potential excess risk of severe malaria in long-term follow-up of children who miss the fourth dose has been reduced by the findings from the MAL-076 seven year follow-up study. MAL-076 data showed that the previously observed apparent rebound in severe malaria among those children who received three doses of RTS,S/AS01 was time limited with no overall excess in severe malaria, very few severe malaria cases after four years of follow up, and no additional imbalance observed in safety signals or deaths. Overall, children benefited from three or four doses of the vaccine, with more benefit in terms of protection against clinical or severe malaria observed among children who received four doses.[11] This is new information that was not available at the time of the October 2015 SAGE/MPAC recommendations and provides reassurance that children who receive only three doses benefit overall, with respect to clinical malaria, and are not at higher risk of severe malaria than children who received no vaccine doses [4].

The FPD Working Group recognised that the impact of the vaccine on severe malaria would not necessarily be the same as that measured during the Phase 3 clinical trials because of what can be achieved during clinical trials as compared to programme implementation. If less than expected impact is due to low vaccine coverage, programmatic improvements to increase RTS,S/AS01 vaccine coverage will be required.

[10] This endpoint will be evaluated through community-based surveillance systems relying on village reporters. Verbal autopsies on reported deaths will confirm age, RTS,S/AS01 vaccination status, and attempt to ascertain the cause of death. Mortality data are powered for country-specific estimates, and will also be aggregated across countries.
[11] MAL-076 study results submitted for publication (GSK)

Recommendation 4: A policy recommendation for broader use of RTS,S/AS01 need not be predicated on attaining high coverage (including coverage of the fourth dose).

A FPD Working Group review of the SAGE policy recommendations on other vaccines showed that feasibility data are rarely available at time of initial policy recommendation. Instead, revisions to prior recommendations have incorporated findings from post-marketing studies on feasibility as they become available. Furthermore, at least several years of implementation are typically required to achieve high vaccine coverage and in some settings this may not be achieved for many years. Challenges can be expected in particular for new vaccine introduction outside the Expanded Programme on Immunization (EPI)'s current schedules, however there was agreement among the FPD Working Group that feasibility can be improved with time. Implementation challenges have been met and addressed with other vaccine introductions as well as malaria control interventions. Data on vaccine coverage and lessons learned on implementation will be collected during the pilot and used for programmatic improvement going forward.

Data reviewed by the SAGE and MPAC in 2015 indicate that children who did not receive the fourth dose of RTS,S/AS01 would experience benefit against clinical malaria but not significant benefit against severe malaria from vaccination [4]. Data available from the MAL-076 long term follow up study[12] indicate that the previously observed apparent rebound in severe malaria among children who received only three doses of RTS,S/AS01 was time limited, with very few severe malaria cases after four years of follow up, and no further imbalance observed in safety signals or deaths.[13] MPAC reviewed these data in October 2018 and concluded that they provide further reassurance on the absence of a rebound effect after the fourth dose, or a persistent rebound effect after only three doses, and give further reinforcement of the safety profile of the vaccine, and its apparent benefit in children who receive three or four doses [7].

For these reasons, in the context of the FPD, the Working Group concluded that it is not desirable or feasible to define a target threshold for vaccine coverage, including fourth dose coverage, to predict impact or to inform a policy decision. Rather, anticipated coverage levels should be factored into the projected data availability of the safety and impact endpoints. Vaccine coverage attained, and methods used to increase coverage, serve as lessons learned to improve vaccine implementation, rather than to determine the policy decision.

Recommendation 5: Barring substantial adverse impact on the coverage of other vaccines or malaria control interventions, the impact of RTS,S/AS01 introduction on the coverage of these interventions should not influence the policy recommendation. Rather these indicators should inform strategies for implementation, including areas to call attention to or to provide opportunities for improvement.

The RTS,S/AS01 vaccine is proposed as a potential additional tool to complement the existing package of WHO-recommended preventive, diagnostic and treatment measures for malaria in children. The Phase 3 trial occurred in the context of high bed net coverage and good access to quality health care [2].

[12] 3 of the 11 Phase 3 trial sites (Korogwe (Tanzania); Kombewa (Kenya); Nanoro (Burkina Faso)) had an additional 3 years of follow up.
[13] MAL-076 study results submitted for publication (GSK)

Delivery of RTS,S/AS01 through the ministries of health, led by the EPI and in coordination with the National Malaria Control Programme (NMCP), could serve as a unique opportunity to reach children who have not been reached with other malaria interventions. The RTS,S/AS01 immunization regimen provides new contacts for children in their second year of life, enhancing opportunities to increase coverage of other childhood vaccines and other health interventions. The Programme will utilize cross-sectional household surveys to measure RTS,S/AS01 uptake and coverage, impact on coverage of other vaccines, insecticide-treated nets (ITN) use, and health care seeking behaviour, as well as a qualitative assessment through interviews of parents and health workers to understand the obstacles and opportunities for vaccine delivery. A measured reduction in health intervention uptake, coverage or use associated with RTS,S/AS01 introduction could be addressed with targeted interventions and/or messaging.

Therefore, barring any substantial adverse impact to the use of malaria control interventions and coverage of other childhood vaccines, pilot data should be used to inform programmatic improvements and vaccine implementation, rather than to inform policy decision.

Recommendation 6: Cost effectiveness estimates should be regularly refined, as data become available for increasingly precise calculations, and presented at appropriate time points.

Based on currently available data, RTS,S/AS01 compares favourably in relation to global cost effectiveness estimates of several other vaccines. While RTS,S/AS01 was found to be less cost-effective overall than some other malaria interventions, RTS,S/AS01 is expected to be highly cost-effective in moderate to high transmission settings and may play an important and cost-effective role alongside other interventions [9]. Gavi, the Vaccine Alliance, has included RTS,S/AS01 in their analyses of potential vaccine investment strategies and has continued to examine both the potential impact and cost effectiveness of the vaccine.

A review of policy precedents show that cost-effectiveness is rarely incorporated into an initial policy recommendation for broader use. Rather there should be refinement of the cost effectiveness estimates for RTS,S/AS01, including risk of adverse events, as more pilot data become available. These refined cost effectiveness estimates should be presented at appropriate time points to the SAGE and MPAC. During the pilot implementation, economic analyses will be conducted on the delivery costs and budget impact of the malaria vaccine on routine health systems to inform ministries of health. These data, with evidence from the evaluations (i.e. impact on severe malaria and/or mortality end point, dose regimen, etc.) will be used to validate and/or update existing modelled estimates on public health impact and cost-effectiveness of the malaria vaccine.

Data and economic analyses for cost effectiveness will be completed regardless of the timing of a policy recommendation for broader use. They will likely be used to inform decisions by stakeholders, such as countries and financing agencies. WHO and PATH are continuing to work with relevant agencies to explore future funding mechanisms for the vaccine (the major cost driver), should WHO recommend the vaccine for broader use.

Recommendation 7: Expansion within MVIP countries should be synchronized with recommendation for broader use across sub-Saharan Africa.

As stipulated in the pilot evaluation master protocol, to meet the evaluation objectives, the vaccine

will be made available through routine immunization services in vaccination areas[14] of the Programme for a minimum of 30 months following the start of vaccination. In line with the January 2016 WHO position paper calling for a "phased design," ministries of health in the MVIP countries view pilot implementation as a phased vaccine introduction. The EPI Programmes have voiced their preference to continue vaccinations (provided there are no safety signals and there are positive trends of impact) as any start/stop is detrimental to programme operations and community mobilization. MVIP countries could therefore decide to continue vaccinations in these areas beyond the minimum 30 months of routine immunization.

Expansion of vaccinations to the comparison areas was advised by the WHO Research Ethics Review Committee, should the vaccine be found to have a positive risk/benefit profile. The FPD Working Group suggested that expansion to comparison areas could occur at the time when broader use of RTS,S/AS01 beyond the pilot countries is recommended because the same criteria would need to be met. Countries will likely rely on the SAGE and MPAC recommendations for broader use before making decisions on introduction in the comparison areas.

There should be regular briefings with the SAGE and MPAC on the Programme's plans for comparison area expansion as, ideally, this expansion would be synchronized with recommendation for broader use. Provided there is sufficient supply available, the national regulatory authorities are in agreement, and a positive risk/benefit profile is maintained, it would not make sense to withhold vaccinations from the pilot comparison areas until after the end of the Programme.

The vaccine donation offered by GSK for the pilot implementations would be sufficient to allow for continuous vaccination within implementation areas and vaccination of comparison areas through the end of the Programme, if desired by MVIP countries. It is important to address the risk of vaccination start/stop in advance due to time required for decision making, financing, vaccine availability, and implementation planning (see Recommendation 1). Creative mechanisms should be considered to ensure supply and funding are available for expanded vaccination, as well as continued vaccination, within the MVIP countries until recommendations and financing are in place for broader use.

Recommendation 8: In the context of the step-wise approach to policy recommendations, the pilots should continue through to completion of data collection to establish the public health value of the fourth dose, including assessment of the vaccine's impact on mortality.

The MVIP should continue to generate data throughout the entire implementation and evaluation periods (expected to be 46 months in each country) regardless of whether an earlier policy recommendation is provided (barring a safety concern resulting in earlier pilot end). Impact on all-cause mortality along with updated cost effectiveness estimates can be incorporated into the final dataset for review by advisory bodies. These real-life data will also be of interest to countries and funding agencies.

Completion of the MVIP beyond an initial recommendation will also provide important information on the role of the fourth dose. Contrary to the findings in the Phase 3 trial, mathematical models predict a relatively small incremental impact of the fourth dose on severe malaria, with over 90% of

[14] The pilot area in each country is comprised of areas (districts or sub-counties) that introduce the vaccine at the beginning of the programme and areas initially without the vaccine acting as comparison.

the modelled impact achieved through administration of the first three doses. These results are consistent with the 2015 modelling analysis presented to the SAGE and MPAC. Modelling indicates that the largest difference in impact between the four-dose and three-dose group in the Phase 3 trial would have been expected at study end in the Phase 3 trial, with impact decaying in both groups following this time, as age incidence curves are also decreasing. This is consistent with observed trends in the MAL-076 study that little difference is seen between the three-dose and four-dose groups in the longer follow-up. Further analysis of the Phase 3 MAL-055 data indicated a difference between the three-dose and four-dose group in regard to impact against severe disease (but not clinical disease) before the fourth dose was given. However, this difference is most likely due to chance.

If it is found upon completion of the Programme that the fourth dose provides little incremental benefit in real life settings, the recommendation could be modified (e.g. to a three-dose regimen).

Recommendation 9: Conflicting data among the MVIP countries would require careful investigation into the reasons for differences. Continue forward with plans for analysis even if data are delayed or not available in all countries.

Recommendation 10: Criteria that could result in WHO not recommending RTS,S/AS01 vaccine for use or that may lead to a decision to defer a policy recommendation to a later time point were recommended by the Working Group.

To issue a recommendation not to implement the RTS,S/AS01 vaccine:

- When there is a clear safety risk (e.g. meningitis) assessed to be unfavourable in context of risk-benefit profile
- If there is something in the risk-benefit profile that could critically undermine the confidence and trust in the national immunization programme

To defer a decision on RTS,S/AS01 to the end or near the end of the pilot evaluations:

- If there is significant uncertainty about safety issues (meningitis, cerebral malaria, sex-specific mortality)
- If impact is not assessed as consistent with a beneficial effect

IV. BACKGROUND ON THE RTS,S/AS01 MALARIA VACCINE: PHASE 3 TRIAL TO PILOT IMPLEMENTATIONS

A. Phase 3 RTS,S/AS01 Trial

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 [1]. 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 [1]. The data presented in the 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. 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). The Phase 3 data indicated 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 [1].

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 vaccinees, respectively.[15] [16] 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. 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.

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 [9]. 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.[14] 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 $PfPR_{2-10}$ between 10% and 65%.[17] In these settings, median modelled estimates range

[16] The impact of RTS,S/AS01 vaccination has been assessed by an estimation of cases averted in the Phase 3 clinical trial, and by use of mathematical models to predict the impact of RTS,S/AS01 when administered through the routine EPI programme. The estimated number of cases averted by RTS,S/AS01 in the trial was the sum of differences in the number of cases between the control and the RTS,S/AS01 groups, expressed per 1000 participants vaccinated.

[17] Prevalence of infection as measured by cross-sectional surveys in those aged 2–10 years. Prevalence of infection in children is a commonly used measure of malaria parasite transmission.

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 $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.

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 [4].

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). In the same age group, 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[1].[18]

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 [10] nor has the potential meningitis signal been seen in the more than 4000 children who have received RTS,S/AS01 in ongoing trials to evaluate alternative dosing regimens or to measure efficacy with annual boosters in highly seasonal areas.[19] The pilot evaluations and a Phase 4 study (further explained below) have been designed to provide further information.

[18] Safety profile of the RTS,S/AS01 malaria vaccine in infants and children: additional data from a phase III randomized controlled trial in sub-Saharan Africa' (Human Vaccines & Immunotherapeutics; in press)
[19] Personal communication on 27 Feb 2019 with Sir Brian Greenwood

B. SAGE/MPAC recommendations leading up to 2016 WHO position paper

In accordance with the WHO's mandate to provide guidance to Member States on health policy matters, WHO is tasked with developing evidence-based immunization policy recommendations. The SAGE is an independent advisory group charged with advising WHO on overall global vaccination policies and strategies, ranging from vaccines and technology, research and development, to delivery of vaccination and its linkages with other health interventions. The subsequent recommendations are then reflected in WHO vaccine position papers. The MPAC was established in 2011 to provide independent advice to WHO on developing policy recommendations to control and eliminate malaria. MPAC has deliberated and provided advice on the usefulness of important potential malaria control tools, including seasonal malaria chemoprevention (SMC) and mass drug administration (MDA), and has guided the development or revision of guidelines for current malaria control tools. The Joint Technical Expert Group on malaria vaccines (JTEG) was jointly established by the Initiative for Vaccine Research (IVR) and the Global Malaria Programme (GMP) to provide advice to WHO on activities related to the development of malaria vaccines at or nearing the pivotal Phase 3 trial stage.

In October 2015, the MPAC and the SAGE recommended that data be collected through the pilot implementations of RTS,S/AS01 to answer remaining questions on feasibility, safety, and impact of the vaccine to inform a policy recommendation on wider use of RTS,S/AS01. WHO adopted the MPAC/SAGE recommendations in its first Malaria Vaccine Position Paper in January 2016 [2]. WHO recommended pilot implementation of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings, in order to generate critical evidence to enable decision-making about potential wider scale use.

WHO recommended that these pilot implementations be done with phased designs and in the context of ongoing high coverage of other proven malaria control measures. The pilot implementations would demonstrate the extent to which the protection demonstrated in children aged 5–17 months in the Phase 3 trial can be replicated in the context of routine health systems, particularly in view of the need for a 4-dose schedule that requires new immunization contacts. Other questions WHO recommended to be addressed as part of pilot implementations include the extent to which RTS,S/AS01 vaccination impacts all-cause mortality (including sex-specific mortality), which could not be adequately assessed in the Phase 3 trial owing to the very low overall mortality in the trial; and whether the excess cases of meningitis and cerebral malaria identified during the Phase 3 trial are causally related to RTS,S/AS01 vaccination.

The Joint Technical Expert Group on Malaria Vaccines (JTEG) advised WHO to monitor emerging findings and indicated that, if appropriate, the SAGE and MPAC may broaden recommendations on the basis of these emerging findings. As part of its recommendation from the 2015 review process, the JTEG advised WHO to monitor emerging data from the pilot implementations and noted that it would be appropriate for WHO to recommend country-wide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose [4]. However, no specific thresholds or guidance were provided to ascertain the meaning of the terms 'resolved safety concerns', 'favourable implementation data' or 'high coverage of the fourth dose.

Based on the efficacy data from the Phase 3 trial, WHO did not recommend the use of the RTS,S/AS01 vaccine in the younger (6—12 weeks) age category, as the vaccine efficacy was found to be low in this age category.

C. Malaria Vaccine Implementation Programme (MVIP)

The Programme has been developed to execute the 2016 WHO recommendation for pilot implementation of the RTS,S/AS01 malaria vaccine to address several outstanding questions related to the public health use of the vaccine.

WHO initiated the country selection process by issuing a call for expressions of interest addressed to ministries of health in Sub-Saharan Africa in December 2015. Of the ten countries that expressed interest, three were selected for the Programme based on pre-specified criteria. Key among these criteria was the desire to engage in the pilot implementations by national stakeholders – particularly the Ministry of Health – and well-functioning malaria and immunization programmes. Other criteria included: good coverage of recommended malaria control interventions and childhood vaccinations; moderate-to-high malaria transmission despite good implementation of WHO-recommended malaria interventions; a sufficient number of infants living in the malaria-transmission areas where the vaccine will be introduced; strong implementation research or evaluation experience in the country; and capacity to assess safety outcomes. Participation in the Phase 3 RTS,S/AS01 trial was an additional element considered during the country selection process.

The selection of Ghana, Kenya and Malawi to participate in the pilot implementations was made public on 24 April 2017, just ahead of World Malaria Day and during African Vaccination Week [5].

The Programme consists of three components: 1) Ministry of Health-led vaccine introduction; 2) WHO-sponsored pilot evaluations; and 3) GSK-sponsored Phase 4 study.

1) Vaccine introduction

The malaria vaccine introduction is country-led with implementation by the Ministry of Health through the national immunization programme in selected areas characterized by medium-to-high malaria transmission. Immunization authorities in the three pilot countries have specified the vaccination schedule, based on WHO recommendations (See Table 4). A 4-dose schedule is required, with the first dose given as soon as possible after 5 months of age followed by doses 2 and 3 at approximately monthly intervals and the fourth dose near the child's second birthday. RTS,S/AS01 can be co-administered with other vaccines in the national immunization programme.

Close collaboration with the NMCP will ensure that existing WHO-recommended prevention tools, such as LLINs and artemisinin-based combination therapies (ACTs), continue to be deployed on a wide scale.

The vaccine has received special authorization for use in context of the pilot implementations by each country's national regulatory authority following a joint convening by AVAREF. The aim is to reach approximately 360 000 children per year in the selected areas.

2) Pilot evaluations

While it is critical that the MVIP represents routine vaccine implementation through the national immunization programmes, the evaluation components must be conducted in a scientifically rigorous manner to generate answers to the remaining questions. For this reason, RTS,S/AS01 will be introduced in some areas at the beginning of the programme with other areas, initially without RTS,S/AS01 introduction, acting as comparison. The division into vaccine implementation or comparison areas has been completed through randomization to generate the strongest possible evidence on the impact and safety of the vaccine. Identical and established monitoring systems in

both implementation and comparison areas will record impact and safety outcomes through observational and cross-sectional studies. Surveillance over the course of 46 months will allow evaluation of key variables more than 1 year following the administration of the fourth vaccine dose in a sufficiently large number of children to meet sample size needs.

A master protocol for the pilot evaluations was developed by WHO and received approval by the WHO Research Ethics Review Committee in February 2018. Country-based research partners have been contracted to implement country-specific protocols. The subsequent sections provide further information about the three evaluation components: a) feasibility; b) impact; and c) safety.

a) Assess the programmatic feasibility of delivering a four-dose schedule, including new immunization contacts, in the context of routine health service delivery

The operational feasibility of providing RTS,S/AS01 at the recommended 4-dose schedule will be evaluated in the context of routine health service delivery. The primary objective of the feasibility evaluation is to estimate the coverage of RTS,S/AS01 in the implementation areas, defined as the proportion of children aged 12-23 months who had received 3 doses of RTS,S/AS01 by 12 months of age, and the proportion of children aged 27-38 months who had received their fourth dose of RTS,S/AS01 by 27 months of age. The secondary feasibility objectives measure, in implementation and comparison areas, the coverage of recommended EPI vaccines; the coverage and utilization of ITN/LLIN and IRS; changes in malaria diagnosis and treatment practices; and the patterns of health-seeking behaviour for febrile children. In addition to ongoing monitoring of facility-based administrative uptake and coverage data, three cross-sectional household surveys will be conducted in each pilot country over the course of the programme.

As for most new vaccine introductions, a New Vaccine Post-Introduction Evaluation (PIE) will be conducted approximately 6 to 12 months after introduction of RTS,S/AS01 to evaluate programmatic performance.

In addition, a qualitative study will explore a range of factors (socio-economic, cultural, demographic, systemic and health-related) that may impact on how the vaccine is delivered and accepted. Using Qualitative Longitudinal (QL) methods, the study will run alongside and track the introduction of the vaccine, gathering information from health care professionals as they promote and deliver the new vaccine, and following households as they receive it. In particular, it will track a panel of households with eligible children over time, as the programme is introduced and established. In this way, the study will shed light on the factors that influence the sustained engagement of families in the vaccine programme, and what (if any) impact the introduction of the vaccine has on their health-related practices and understandings.

Finally, the Programme will collect economic data to estimate the incremental cost of adding RTS,S/AS01 to the routine schedule, its budgetary impact and to provide updated estimates of the vaccine's impact and cost-effectiveness.

b) Evaluate the vaccine's impact on severe malaria and all-cause mortality[20]

The second evaluation component aims to estimate the impact of RTS,S/AS01 on all-cause mortality in children aged 5-39 months, malaria mortality, and rate of hospitalization with malaria (as an indicator of severe malaria) and the sex-specific effect of RTS,S/AS01 on all-cause child mortality. Data on all-cause and sex-specific mortality will be captured at the community level through resident Village Reporters (VR) specially trained to document and report deaths in the target age group. Trained VR supervisors will conduct Verbal Autopsies, using WHO-recommended methods.

Malaria mortality and the rate of hospitalization with malaria will be captured at sentinel hospitals for all children in the relevant age group presenting to the hospital. The randomized vaccine introduction will enable a comparison of the rate of these events between the areas that have introduced RTS,S/AS01 and those which have not yet introduced the vaccine.

c) 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

In addition to data collected by the ministries of health through strengthened routine pharmacovigilance, and through the GSK Phase 4 study (see #3 below), safety data will be captured in up to 24 sentinel hospitals across the three pilot countries by means of systematic, prospective, monitoring of all paediatric admissions, paying particular attention to meningitis and cerebral malaria. Safety data will be reviewed regularly by a Data Safety and Monitoring Board (DSMB).

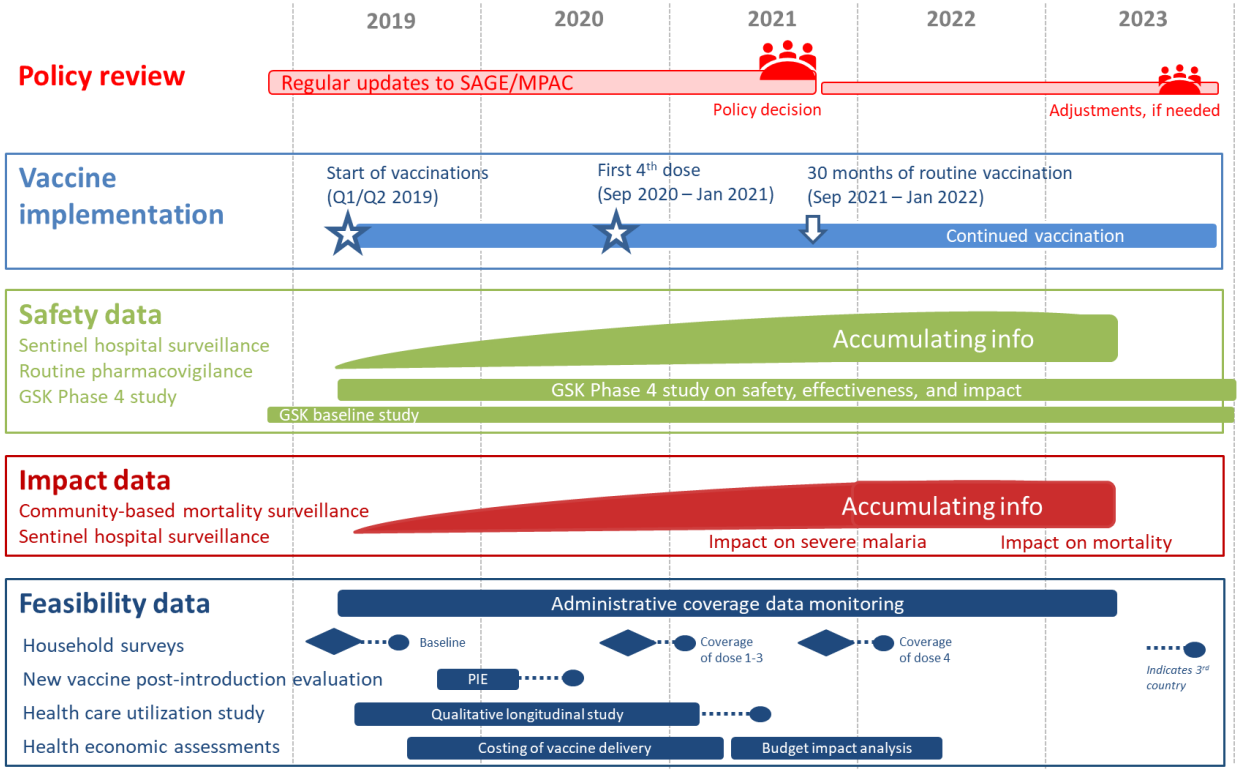
3) GSK-sponsored Phase 4 study

The GSK-sponsored Phase 4 studies form part of the RTS,S/AS01 Risk Management Plan agreed between GSK and EMA to further assess vaccine safety, effectiveness and impact in routine use. In addition to enhanced hospitalization surveillance, the Phase 4 study will include active surveillance through home visits and continuous monitoring of outpatient visits and hospitalisations at health care facilities in a subset of vaccinating and comparison areas. The WHO-sponsored pilot evaluation has been designed to complement the GSK-sponsored Phase 4 study which will take place in a small sub-set of the pilot area of each country.

Evidence and experience from the pilot implementations will be provided to the SAGE and MPAC to inform recommendations on the vaccine's potential use on a wider scale in Africa. (See Figure 2)

[20] The evaluation of impact will depend on community mortality surveillance and is powered to detect a 10% reduction in all-cause mortality in each country. This is expected to be complete in 2023.

Figure 2: Timeline of MVIP data generation and review



V. DATA AND INFORMATION USED BY THE WORKING GROUP TO INFORM RECOMMENDATIONS

A. New data available since the 2015 SAGE/MPAC recommendation for pilots

Results from Phase 3 long-term follow-up study (MAL-076)

MAL-076 was a long-term open-label follow-up study conducted in 3 out of the 11 Phase 3 trial sites (Korogwe [Tanzania], Kombewa [Kenya] and Nanoro [Burkina Faso]). Children 5–17 months of age at first vaccination who were enrolled in the trial were followed for a median of four years during the Phase 3 trial and then followed for an additional three-year period for the MAL-076 study (for a total follow-up time of approximately seven years after administration of the first three RTS,S/AS01 doses) [11]. The primary objective of the MAL-076 study was to describe incidence of severe malaria over the additional three-year follow-up period. Secondary objectives were to assess clinical malaria incidence, malaria hospitalization, fatal malaria, and cerebral malaria during the additional three-year period and overall seven years of follow-up. Selected serious adverse events (SAEs) were also recorded during follow up. In addition to prospective data collection, retrospective data were collected during the gap period between the end of the Phase 3 MAL-055 and the start of MAL-076 study.

The three MAL-076 study groups were comprised of children who were participants in the Phase 3 trial at these three long-term follow up sites and whose parents had consented to their participation in the long-term study follow-up. Children who had been randomized to the 4-dose and the 3-dose malaria vaccine groups or the control group for both age categories were eligible to participate in MAL-076. Out of the 2512 children aged 5–17 months vaccinated in the 3 participating sites from Phase 3 MAL-055 trial, 1739 were enrolled in the MAL-076 study. The incidence of severe malaria was low in all study sites for both age categories during the three-year period of long-term follow up. In the 5–17-month age group vaccine efficacy (VE) against severe malaria decreased over time, and overall during the seven years of follow-up was 37% (95%CI: 15; 53) in the 4-dose group and 10% (95% CI: 18; 32) in the 3-dose group (Table 3). VE against clinical malaria also decreased over time; overall during the seven years of follow-up in the 5–17 months age category, VE against clinical malaria was 24% (95% CI: 16; 31) in the 4-dose group and 19% (95% CI: 11; 27) in the 3-dose group. In the 5–17 months age category, a statistically significant increased incidence of clinical malaria in RTS,S/AS01 recipients versus controls was observed over the last three years of the seven year follow-up only in Nanoro (VE: -37% [95% CI: -44; 73]), an area of highly seasonal malaria transmission, and only for the 3-dose group. VE against malaria hospitalizations was similar to the VE against severe malaria.

Table 3. Results for Severe Malaria* in the MAL-076 study, 5–17 month age category

Group	4 doses RTS,S/AS01			3 doses RTS,S/AS01			Control
N	**594**			**561**			**593**
Period	**n**	**% VE**	**(95% CI)**	**n**	**% VE**	**(95% CI)**	**n**
M0-M20 Mal-055 pre-dose 4	**32**	50.58	(24.52; 67.65)	**57**	10.61	(-27.6; 37.38)	**65**
M21-M48 (SE) Mal-055 post dose 4	**31**	-2.28	(-68.3; 37.85)	**28**	6.06	(-56.7; 43.67)	**31**
M48 - 3 years Mal-076 only	**7**	53.68	(-13.7; 81.13)	**11**	23.33	(-67.1; 64.82)	**15**
Total (overall 7 years)	**70**	**36.69**	**(14.6; 53.07)**	**96**	**10.14**	**(-18.1; 31.64)**	**111**

*Case definition 2: *P. falciparum* asexual parasitemia >0 (within -1 to +3 days of admission) and at least one marker of severe disease **OR** SAE report (within -1 to +3 days of admission) including preferred term of "Malaria", "*P. Falciparum* infection" or "Cerebral malaria"

SAEs were similar between 4 dose, 3 dose, and control groups; none were vaccine-related. Fatal SAEs were reported in 1/2/2 (R3R/R3C/C3C) children in the 5–17 months age category. One case of meningitis was reported in the control group of the 5–17 months age category and was not fatal. No cases of cerebral malaria were reported.

Based on these results, VE against severe malaria remains positive during the 7 years following initial vaccination when 4 doses are provided and VE against clinical malaria remains positive for 7 years when 3 or 4 doses are provided. MAL-076 data indicate no indication of an age shift (or rebound) of severe malaria following 4 vaccine doses. The observed age shift in severe malaria following vaccination among children who received only 3 vaccine doses in MAL-055 was limited in time. Furthermore, over the entire period, there was no excess in severe malaria cases. Incidence of severe malaria declined considerably when children grew older regardless of the study/vaccine group. This decline was observed in the Phase 3 trial as well (Figure 3). One site with strong seasonal malaria (Nanoro, Burkina Faso) showed a period of increased risk for uncomplicated malaria, but this was not preceded by, nor did it result, in an increased risk for severe malaria.

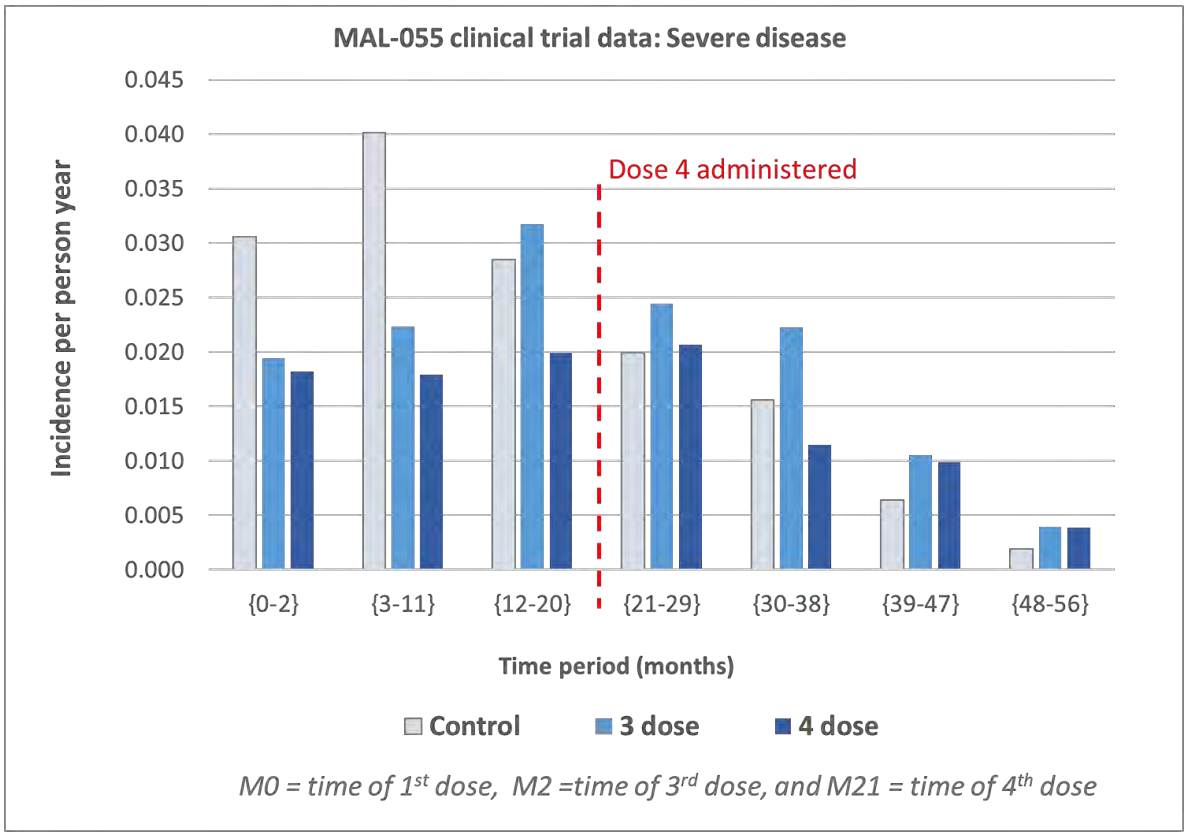
Further analysis of MAL-076 and MAL-055 data

The modelling groups at Swiss TPH and Imperial College were engaged to estimate thresholds of vaccine coverage that predict impact—in particular, on what levels of coverage (overall and for the fourth dose) are sufficiently high to be considered good public health value. The models (which were validated with MAL-076 data) predict small incremental impact of the fourth dose, with over 90% of impact achieved with the administration of the first 3 doses. The modelers were unable to reproduce the extent of the rebound observed in the Phase 3 trial. These estimates and inability to reproduce the extent of the rebound are consistent with the 2015 modelling analysis.

Data presented from the Phase 3 trial, showing severe malaria incidence per person-year, plotted in 6-monthly intervals show a marked decline in severe malaria incidence, with very low incidence of severe malaria by months 48-56 months follow-up in all three study arms (Figure 3).

After reviewing the modelling results and data from the MAL-076 study, the Working Group requested from GSK additional statistical analysis of the MAL-055 data (1) to better understand the difference between modelling results and Phase 3 trial results, and (2) to try to quantify the incremental benefit of the fourth dose for clinical or severe malaria relative to the first three doses, over time and to end of MAL-055. The additional analysis was reviewed by the Working Group, but provided little definitive information to better understand the benefit of the fourth dose.

Figure 3. Vaccine impact before and after receiving the 4th dose (intention-to-treat population).



Source: Modelling groups with permission from GSK

Severe disease incidence per person year plotted every 6 months after dose 3 is administered. The dotted line represents when the fourth dose is given. We see a difference between the 3-dose and 4-dose groups before the fourth dose is given. Additional analyses did not reveal a reason for this difference, which is considered a chance finding.

B. Policy considerations for the Working Group

Annex 5 includes the full summary of the malaria intervention policy background, prior SAGE policy decisions on vaccines, and considerations around operational feasibility.

Standards applied for other vaccine policy recommendations

Prior SAGE policy decisions on other vaccines were reviewed to inform questions pertinent to RTS,S/AS01 with attention to the type and quality of data available at the time of a recommendation. Rotavirus vaccines, PCVs, and dengue vaccine case studies were the most relevant examples for this exercise. Specifically the group focused on the following issues in prior policy decisions:

- Assessment of safety signals for risk-benefit assessment
- Availability of mortality impact data
- Consideration of disparate efficacy or impact results across study sites/countries
- Availability of feasibility and cost-effectiveness data

As illustrated by the case studies in the Annex, global policies for vaccine use evolve after initial licensure, prequalification, and SAGE recommendations, as additional information, including mortality data, are generated over time.

Malaria intervention policy recommendations

The Malaria Policy Advisory Committee advises WHO on recommendations for malaria control interventions. Currently recommended malaria prevention tools include long lasting insecticidal nets (LLINs), Intermittent Preventive Treatment in infants (IPTi), Intermittent Preventive Treatment in pregnancy (IPTp), indoor residual spraying (IRS), and in areas with highly seasonal malaria, seasonal malaria chemoprevention (SMC). Increased rollout of malaria control methods had led to over 50% reduced malaria mortality in sub-Saharan Africa since 2000 [2], but ongoing gaps in access to preventive, diagnostic and treatment measures continue to exist.

C. Operational feasibility: Expected MVIP coverage based on Immunization coverage trajectories over time following new vaccine introductions

Definition of "high" coverage

The JTEG has recommended that "high" immunization coverage be documented in order to recommend continued implementation. However, as the SAGE has previously recognised (SAGE, April 2018), the relatively low coverage levels of the second dose of measles-containing vaccine (MCV2) provided to children aged 15–18 months in MVIP countries could indicate challenges in reaching children in the second year of life with the fourth dose of RTS,S/AS01. Receiving all four doses of the vaccine provides optimal benefit of the vaccine and appears to prevent the age-shift in timing of severe disease that was observed in the Phase 3 trial among children randomized to receive only 3 vaccine doses. Long-term follow up data from the MAL-076 study are reassuring, showing no excess risk of severe malaria among those who receive only 3 doses and modeling estimates based on Phase 3 data predict that the added benefit of a fourth dose may be small compared to that of the first three doses. Nonetheless, given uncertainty around the added benefit of a fourth dose, efforts at maximizing coverage of the full four dose series during the Programme is desirable.

Considering experience with introduction of other childhood vaccines, the definition of "high" coverage is challenging, and would be expected to differ for the third and fourth doses of RTS,S/AS01. Coverage is expected to be lower for the fourth dose of RTS,S/AS01 compared to the third dose because of healthcare visits during the second year of life are less well established than those in infancy. Examples from other vaccine introductions were reviewed to determine realistic goals for coverage based on the strength of the immunization system to support the additional vaccine introduction and new immunization schedule.

Documentation of achieving high coverage is not typically a prerequisite for a WHO policy recommendation for vaccine introduction (see section V), unless there is an epidemiological rationale. For example, with vaccines that induce population-level protection ("herd immunity"), suboptimal childhood vaccination coverage can lead to an age shift in disease at the population level, but this principal does not apply to malaria vaccination as the RTS,S/AS01 vaccine is expected to provide individual protection only and not expected to have an effect on malaria transmission.

Strength of routine immunization in the pilot countries

After responding to call for expressions of interest, Ghana, Kenya, and Malawi were selected for participation in the pilot implementations based on standardized criteria, including demonstration of a strong EPI programme. Coverage levels for diphtheria-tetanus-pertussis (DTP) and MCV are considered indicators of health system performance. Vaccines given in the second year of life, such as MCV2 and meningococcal A vaccine are relevant when considering potential RTS,S/AS01 coverage (see Table 7 in Annex 5). The additional visits to be introduced for RTS,S/AS01 can be leveraged as opportunities to reach children at critical time points for well child exams, including weight monitoring, and to provide vitamin A and deworming recommended at two years of age.

Table 4. Integration of RTS,S/AS01 into the childhood vaccination schedule /1

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	❶											
Oral polio	❶	❶	❷	❸								
DTP-HepB-Hib (penta)		❶	❷	❸								
Pneumococcal conj.		❶	❷	❸								
Rotavirus		❶	❷									
Inactivated Polio				❶								
Meningococcal A conj.										❶		
Measles-Rubella								❶		❷		
Yellow Fever								❶				
Vitamin A						❶			❷	❸		❹
RTS,S/AS01 in Ghana						❶	❷	❸				❹
RTS,S/AS01 in Kenya						❶	❷	❸				❹
RTS,S/AS01 in Malawi					❶	❷	❸				❹	

1/ The upper part of the table reflects Ghana's vaccination schedule

Based on the WHO recommendations, the EPI Programmes defined the most appropriate target age for children to receive each dose of RTS,S/AS01 given the existing routine immunization schedule (see Table 4). Ghana and Kenya will provide the four doses at 6, 7, 9, and 24 months of age. Delivery of the second dose at 7 months of age will be a new vaccination contact point in these two countries.

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 partial protection against malaria- as early as possible; this requires three new vaccination contacts.[21]

ACKNOWLEDGEMENTS

The WHO secretariat would like to thank the FPD Working Group members, and Professor Peter Smith as chair, for their thoughtful deliberations in the development of the Framework for Policy Decision on RTS,S/AS01. This document reflects their expertise in child health, insight into the policy process, and critical thinking around the questions and data presented for their consideration. WHO also appreciates the MVIP Programme Advisory Group for their review of the document, and the input from Drs. Laurence Slutsker and Scott Gordon of PATH. WHO appreciates the technical and administrative support provided by Cynthia Bergstrom, PATH, to ensure effective delivery on the Working Group's Terms of Reference.

The FPD Working Group would like to acknowledge the openness and responsiveness of the manufacturer in providing access to data and performing additional analyses requested by the Working Group and the WHO secretariat.

The Working Group thanks Dr. Melissa Penny and colleagues from the SwissTPH as well as Drs. Azra Ghani and Alexandra Hogan from Imperial College, with coordination from Farzana Muhib of PATH, for analysis and modelling of the MAL-076 and MAL-055 data that spurred Working Group discussions and input into this document.

Furthermore, there were several valuable contributions to the content of this document. Drs. Jenny Waldorf and Rebecca Casey of the United States Centers for Disease Control and Prevention prepared the policy precedent on immunization and presented to the Working Group. Key inputs on the malaria policy precedent were prepared by Ryan Thompson of the Johns Hopkins Bloomberg School of Public Health.

[21] Malawi decided to schedule the first dose at 5 months in order to reach children at the earliest age for which the vaccine is recommended. The target age of 22 months for the fourth dose reflects the minimal interval of 15 months from the third dose.

Annex 1: FPD Working Group Terms of Reference

World Health Organization
Terms of Reference
Malaria Vaccine Implementation Programme
Framework for Policy Decision – Working Group

Background on the Malaria Vaccine Implementation Programme

In January 2016, following a joint review of evidence by WHO's Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC), WHO published its policy recommendation for RTS,S/AS01, the first malaria vaccine. WHO recommended pilot implementation of the RTS,S/AS01 vaccine in distinct settings in sub-Saharan Africa in order to generate critical evidence to enable decision-making about potential wider scale use.

The Malaria Vaccine Implementation Programme (MVIP) has been developed to execute the 2016 WHO recommendation for pilot implementation of the of the RTS,S/AS01 malaria vaccine to address several outstanding questions related to the public health use of the vaccine. The MVIP supports routine introduction of the malaria vaccine in selected areas of 3 countries (Ghana, Kenya and Malawi) and rigorous evaluations to:

- Assess the programmatic feasibility of delivering a four-dose schedule, including new immunization contacts, in the context of routine health service delivery;
- Evaluate the vaccine's impact on severe malaria and all-cause mortality; and
- 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.

As part of the 2015 review process, the Joint Technical Expert Group (JTEG), comprised of MPAC and SAGE members, advised WHO to monitor emerging data from the MVIP; "If concerns about safety are resolved, implementation data are favourable and fourth dose coverage is high, WHO might recommend broader introduction prior to pilot end."

WHO assumes the overall scientific and technical leadership and is responsible for coordinating and overseeing all activities corresponding to the RTS,S/AS01 implementation and evaluation in the context of the MVIP. The Programme is jointly led by the Global Malaria Programme (GMP) and the Immunization, Vaccines & Biologicals (IVB) departments at WHO, collaborating closely with AFRO and country offices, ministries of health in pilot countries, and PATH, as well as coordinating relevant activities with the vaccine manufacturer, GlaxoSmithKline Biologicals.

Purpose of the MVIP Framework for Policy Decision

During their April 2017 meetings, MPAC and SAGE endorsed the establishment of a joint working group to develop a MVIP Framework for Policy Decision for RTS,S/AS01. Through the Framework, MPAC and SAGE will be able to consider, align on, and document in advance, how data collected through the MVIP might be used to answer the key outstanding questions on feasibility, impact, and safety of RTS,S/AS01 to inform WHO policy on broader use of the vaccine. The Framework will consider the use and relative weight of data collected through the pilot (1) at the pilot end, when final results are available; (2) during the course of the MVIP, when emerging data might suggest earlier broader

introduction; and (3) after approximately 30 months of pilot introduction, when the vaccine could be expanded to the comparator areas of the pilot if data indicate a positive benefit-risk profile.

The Framework serves several important functions: it will prompt WHO advisory groups and policy makers to consider the data being collected at this early stage to assure the data to be collected are sufficient to support a policy decision; it will enable MPAC and SAGE to refine their understanding of the relative contribution of the collected data (feasibility, safety, impact) to a future policy recommendation; and it will document the expected use of the data in anticipation of changes in MPAC and SAGE membership between the time the MPAC/SAGE recommendations were made (2015) and when MVIP data are available.

Purpose of the MVIP Framework for Policy Decision Working Group

The development of the MVIP Framework for Policy Decision on RTS,S/AS01 will be a collaborative process among representatives from advisory bodies involved in malaria vaccine policy decision making. The role of the MVIP Framework for Policy Decision Working Group (Working Group) is to deliberate on the use of the data collected through the MVIP in the context of the SAGE/MPAC recommendations on pilot introduction, and to make recommendations to the PAG. The deliberations will be recorded, as will recommendations, and shared with the MVIP Programme Advisory Group for consideration, then SAGE and MPAC for their endorsement and advice to WHO leadership (including the ADGs of FWC and HTM and the RD of AFRO, and the Directors of IVB, GMP and AFRO) and the MVIP Programme Coordination. Specific responsibilities of the Working Group include:

- Consider the JTEG, SAGE/MPAC and WHO recommendations around the use of data on feasibility, safety and impact and discuss and recommend the relative contribution of the collected data to a future policy decision
- Consider and discuss specific questions on the use of the data for policy decision and consider whether there are other important questions that should be considered
- Discuss any unintentional consequences that might come from particular decisions around the use of the data (e.g. undue delay in vaccine availability; expansion too early; impact on supply from the manufacturer)
- Determine most appropriate means to translate the above considerations into a framework, set of recommendations to WHO advisory bodies, or key considerations for WHO advisory bodies
- Discuss how the Framework for Policy Decision should be made available and/or utilized
- Provide regular updates to their respective WHO advisory bodies on the Framework for Policy Decision progress and Working Group deliberations
- Participate in the presentation of the Framework for Policy Decision for review and endorsement of their respective advisory bodies

The Working Group has no executive, regulatory or decision-making functions. The Framework and guidance provided by the Working Group will be non-binding on WHO and the Working Group will not directly analyze or review MVIP data.

Working Group Membership

The Working Group will have representation from the WHO advisory bodies that will monitor MVIP progress and/or make recommendations on future use of the malaria vaccine based on MVIP data:

- Malaria Policy Advisory Committee (MPAC) – up to 3 members
- Strategic Advisory Group of Experts (SAGE) on Immunization – up to 3 members
- MVIP Programme Advisory Group (PAG) – up to 3 members
- Immunization & vaccines related implementation research advisory committee (IVIR-AC) –1
- Modelling groups that generate estimates to inform policy decisions – 1 member

Framework for Policy Decision Working Group members will be selected based on recommendations from the chairs of the respective advisory groups. Members will serve in their personal capacities for their scientific and technical knowledge and experience, as well as their commitment and willingness to volunteer the necessary time and effort. Members must respect the impartiality and independence required of WHO, as it also applies to their membership on their respective advisory bodies. When traveling for Working Group activities, members will be reimbursed for travel costs and accommodation according to WHO standard procedures.

Members should be free of any real, potential or perceived conflict of interest. In performing their work, they may not seek or accept instructions from any Government or from any authority external to the Organization, with respect to the matters to be discussed by the Working Group. Members are required to complete a declaration of interest form prior to their appointment and each meeting and their participation is subject to the evaluation of completed forms by the WHO Secretariat.

Working Group Meetings and Operations

The Working Group is expected to once in 2018 and once in 2019. Teleconferences will be called as needed until the Framework is finalized, in 2019. Additional meetings may be called if required.

Information and documentation to which members may gain access in performing MVIP related activities should be considered as confidential and proprietary to WHO and parties collaborating with WHO. Working Group members shall not purport to speak on behalf of, or represent, the MVIP or WHO to any third party. All proposed members will be required to sign an appropriate confidentiality undertaking and provisions on ownership.

WHO, as the secretariat, will provide technical and administrative support to the Working Group to ensure effective delivery on its Terms of Reference.

Presentation of Working Group's Deliberations and Recommendations

The Framework, together with a report of the deliberations and any accompanying recommendations generated by the Working Group will be presented to the MVIP Programme Advisory Group to consider prior to presentation to MPAC and SAGE for their consideration and advice to WHO.

WHO will retain control over the conduct of the MVIP and any subsequent recommendations, decisions, or actions by WHO regarding any proposals, policy issues, or other matters considered by the Working Group. WHO retains full control over the publication of reports from the Working Group meetings, including whether to publish them.

Annex 2: FPD Working Group membership and convenings

A. Working Group Members

Immunization and vaccines related implementation research advisory committee (IVIR-AC)

Quique Bassat, ISGlobal Institute for Global Health Hospital Clinic, Universitat de Barcelona

Malaria Policy Advisory Committee (MPAC)

Gabriel Carrasquilla, Asesorias e Investigaciones en Epidemiologia Salud Y Medio Ambiente (ASIEALAUD), Colombia

Umberto D'Alessandro, Medical Research Council Unit, The Gambia and LSHTM United Kingdom

Modelling groups (SwissTPH and Imperial College)

Melissa Penny, Swiss Tropical and Public Health Institute, Switzerland

MVIP Programme Advisory Group (PAG)

Eusebio Macete, Centro de Investigaçao da Manhiça (CISM), Mozambique

Kim Mulholland, London School of Hygiene and Tropical Medicine, United Kingdom/MCRI, Australia

Peter Smith, London School of Hygiene and Tropical Medicine (LSHTM), United Kingdom - **Chair**

Strategic Advisory Group of Experts (SAGE) on Immunization

Terry Nolan, Murdoch Children's Research Institute, Australia

Fred Were, University of Nairobi, Kenya (also PAG member)

B. Working Group convenings

The Working Group has been convened three times: an initial teleconference on 17 July 2018, a face-to-face meeting in Geneva on 3 to 4 December 2018, and a teleconference on 11 February 2019.

Members completed a declaration of interest form prior to each meeting, which the WHO secretariat evaluated and determined there to be no conflicts.

Annex 3: Questions presented to FPD Working Group

Discussion during the Working Group's meeting on 3-4 December 2018 was structured around the below key questions to consider in the context of RTS,S/AS01.

Key questions A – policy recommendation for broader use across sub-Saharan Africa: *The Joint Technical Expert Group on Malaria Vaccines (JTEG) noted in its report (Sept 2015): It would be appropriate for WHO to recommend countrywide introduction if concerns about safety have been resolved, and if favourable implementation data become available, including high coverage of the fourth dose*.
1. What would be considered "resolved" safety concerns? (a) Meningitis: what level of increased risk would need to be ruled out (8:1; …2:1, other?)? (b) Cerebral malaria: what level of increased risk would need to be ruled out? (c) Sex-specific mortality: what level of increased risk would need to be ruled out? (d) What if safety signal(s) get confirmed but a favourable benefit risk profile persist?
2. What would be considered "high coverage of the fourth dose"? (a) Can a threshold of coverage be defined above which sufficient impact would be predicted? (b) If a threshold for predicting impact cannot be defined, a recommendation might rely on trial data (~90% 4 dose coverage) prior modelling data (72% 4 dose coverage) or impact findings from the pilot, (impact on severe malaria or mortality).
3. What would be considered "favourable" implementation data, and what would be required for an early policy recommendation? (a) No or little adverse effect on coverage of other vaccines? Or timing of other vaccines? (b) Continued use of ITNs (or if reduced use, impact data still positive)? (c) No change in health seeking behaviour for fever? (d) Cost effectiveness?
4. What criteria, if met, would likely lead to a recommendation <u>not</u> to implement the vaccine
5. What is role of data to measure impact on all-cause mortality? (a) MPAC states not required for policy recommendation; severe malaria is marker of mortality.
Key questions B – expansion within the three MVIP countries: *The WHO Research Ethics Review Committee emphasizes that if the RTS,S/AS01 vaccine is seen as beneficial, it should be offered in the comparator areas as soon as possible (i.e. when comparator areas are no longer required for assessment of safety or impact, approximately 30 months after vaccinations begin)?*
1. What criteria should be met before expansion of RTS,S/AS01 into pilot comparator areas can be considered?
2. **What about expansion beyond the pilot areas in the three MVIP countries? Would this necessarily be tied to a policy recommendation for broader use across Sub-Saharan Africa?**
Key questions C - conflicting or delayed data: The MVIP takes place in Ghana, Malawi and Kenya. Current target start dates are close together, all expected in Q1 2019. Safety endpoints are powered based on pooled data from all three countries; impact endpoints are powered based on each country.
1. How would conflicting data from different countries be considered?
2. How would data be considered if data from one of the 3 countries was delayed?

Annex 4: Expected timing of availability of pilot implementation evidence

Based on current assumptions across the three MVIP countries' related to the expected rate of accumulating events malaria prevalence and vaccine introduction timings, the Working Group received a summary of the expected timing of availability of evidence around 24 months after the start of vaccine introduction in the first country.

Based on the assumption that the mortality rate is 8.5/1000/year, and the size of each cluster is as described in the protocol with an assumed annual birth cohort of 4000, it is expected that enough events will have accrued by month 24 to have about 90% power to exclude the female:male mortality ratio being 20% higher in the RTSS arm than in the control arm (if there is no interaction by sex) (using the method for power calculation for interaction described by Cheung et al.,Tropical Medicine and International Health 13:247d In, 2008).

Using a similar method, comparing between arms the differences in rates in vaccine-eligible and non-eligible age groups within clusters, and assuming rates of 0.4/1000/year for meningitis, and 2/1000/year cerebral malaria, there is about 80% power to rule out a 3-fold or greater increased rate of meningitis associated with introduction of RTSS vaccine (if RTSS does not increase the risk of meningitis); and about 90% power to rule out a 2-fold or greater increase in risk of cerebral malaria (if there is no effect (increase or decrease) on cerebral malaria incidence), by month 24. There is over 80% power to detect a 30% reduction in severe malaria by month 24 by country, or a 10% reduction in mortality by month 24 across all countries combined.

Updated calculations will be done when preliminary data on actual event rates are available, four to five months after vaccinations start. These estimates will be included in the MVIP Statistical Analysis Plan, under development, as will case definitions and indicators.

Annex 5: Prior vaccine and malaria intervention policy decisions and considerations

A) Standards applied for other vaccine policy recommendations

The Working Group reviewed prior SAGE policy decisions on other vaccines to inform questions pertinent to RTS,S/AS01 with attention to the type and quality of data available at the time of a recommendation. Rotavirus vaccines, pneumococcal conjugate vaccines, and dengue vaccine case studies were the most relevant examples for this exercise. Specifically the group focused on the following issues in prior policy decisions:

- Assessment of safety signals for risk-benefit assessment
- Availability of mortality impact data
- Consideration of disparate efficacy or impact results across study sites/countries
- Availability of feasibility and cost-effectiveness data

As illustrated by the case studies below, global policies for vaccine use evolve after initial licensure, prequalification, and SAGE recommendations, as additional information, including mortality data, are generated over time.

Pneumococcal conjugate vaccine (PCV)

WHO's initial recommendation for PCV use in 2003 was informed by evidence on efficacy, effectiveness and safety from industrialized settings, but the recommendation did not extend to resource-poor countries. The WHO recommendation for use broadly in national immunization programs was made in 2007 based on review of efficacy, safety and limited mortality impact data from a secondary analysis of one study in the Gambia (16% reduction in all-cause mortality).

Like malaria, pneumonia and pneumococcal disease account for a large proportion of child mortality globally. The 7-valent pneumococcal conjugate vaccine (PCV7) was first licensed in the United States in 2000, and included serotypes covering 65–80% of the serotypes associated with invasive pneumococcal disease among children in the United States and Western Europe. However, serotype coverage was thought to be less compatible for other parts of the world, and the first WHO position paper (2003) [12] did not recommend routine use of PCV in developing countries due to lack of evidence of efficacy and feasibility in those settings. The WHO position at that time was as follows *"Large-scale childhood immunization using the conjugate vaccine has been highly effective in reducing the burden of invasive pneumococcal disease among infants and young children in the United States… Hence, where control of invasive pneumococcal disease in childhood is a public health priority and the vaccine serotypes are shown to match the most important local serotypes, the conjugate vaccine merits consideration for inclusion in national childhood immunization programmes"*. In 2003, the future recommendations for routine use of pneumococcal vaccines in developing countries was deemed to be dependent largely on the demonstration of protective efficacy against pneumonia. At that time, more information was noted to be required by SAGE to assess the impact of conjugate vaccines on the incidence and mortality of pneumonia among infants and other high-risk groups in developing countries.

The first WHO recommendation for introduction of PCV in national immunization programmes was made in 2007 [13], noting priority in countries with high prevalence of child mortality: "*WHO considers that pneumococcal conjugate vaccine should be a priority for inclusion in national childhood immunization programmes. Countries with mortality among children aged <5 years of >50 deaths/1000 births or with more than 50,000 children's deaths annually should make the introduction of PCV-7 a high priority for their immunization programmes*". This recommendation was based on Phase 3 trial vaccine efficacy and safety data for PCV-9 from developing settings. Vaccine impact data were available from industrialized settings that had introduced vaccine previously and were accruing post-marketing data.

At the time of the 2007 recommendation data were available from a Gambian randomized clinical trial (RCT) showing that the efficacy of 3 doses of PCV-9 against vaccine-type invasive pneumococcal disease was 77% (95% CI, 51–90%), and efficacy against invasive disease regardless of pneumococcal serotype was 50% (95% CI,21–69%). Another RCT in South Africa found 83% (95%CI, 39–97%) protective efficacy against vaccine-type invasive pneumococcal disease in HIV-negative children and 65% (95% CI, 24–86%) efficacy in HIV-positive children. The efficacy of conjugated pneumococcal vaccine against pneumonia has also been documented in developing countries. In the PCV-9 studies mentioned above, efficacy was 35% (95% CI, 26–43%) in the Gambia and 20% (95% CI, 2–35%) in South Africa using WHO's standards for radiologically confirmed pneumonia.

At the time of the 2007 recommendation, mortality data were available from the Gambian clinical trial of 9-valent PCV described above which showed a 16% (95%CI, 3–28%) reduction in all-cause child mortality. All-cause mortality was not a primary endpoint in any of the PCV trials. However, in the Gambia trial, the baseline mortality rates were high enough to perform a secondary analysis. Despite the reduction in overall mortality, the Gambian study showed little or no protection against clinically diagnosed pneumonia.

Rotavirus vaccine

WHO initial recommendation in 2007 to introduce rotavirus vaccine if data suggest significant public health impact was based on clinical efficacy data from the United States, Europe, and Latin America; and did not recommend global inclusion of rotavirus vaccines into national immunization programmes given the lack of data from other regions. In 2009, this recommendation was extended to all regions based on the available efficacy data from African and Asian countries.

As with malaria and pneumonia, diarrhea is one of the leading causes of death in children worldwide. Rotavirus is the causative agent for a significant proportion of severe diarrhea in children under five years of age, and especially under one year of age. WHO policy recommendations for rotavirus vaccination have evolved with accrual of evidence since the initial publication of guidance in 2007. At that time, WHO recommended [14] inclusion of rotavirus vaccination in national immunization programs in regions and countries where vaccine efficacy data were available to suggest significant public health impact and where appropriate infrastructure and financing mechanisms were available to sustain vaccine utilization. 'Significant public health impact' and 'appropriate infrastructure' were not explicitly defined. Clinical efficacy data for Rotarix (RV1) and Rotateq (RV5) were available primarily from the United States, Europe, and Latin America. WHO did not recommend global inclusion

of rotavirus vaccines into national immunization programmes given the lack of data from other regions. In 2007 no increased risk of intussusception in vaccinated groups with either RV1 or RV5 was observed. Given the concern about risk of intussusception from experience with Rotashield where it had been pulled from the market in 2000, WHO also recommended that rotavirus vaccine introduction should be accompanied by careful post-marketing national surveillance to evaluate impact and any potential association between rotavirus vaccines and intussusception in the concerned age group [14].

A revision of the 2007 policy was published in 2009 [15] extending the recommendation for routine rotavirus vaccine introduction globally: "WHO recommends that rotavirus vaccine for infants should be included in all national immunization programmes. In countries where diarrhoeal deaths account for ≥10% of mortality among children aged <5 years, the introduction of the vaccine is strongly recommended". This recommendation was based on new efficacy data available from trials in African (Malawi, South Africa, Kenya, Ghana, Mali) and Asian (Bangladesh, Viet Nam) countries representing multiple mortality strata. In a large RCT of RV1 in Malawi (high mortality rate among children aged <5 years) and South Africa (intermediate mortality rate among children aged <5 years) after 1 year of follow up, the efficacy against severe rotavirus gastroenteritis (RVGE) was 61% (95% CI, 44–73%) in the combined study populations, 77% (95% CI, 56–88%) in South Africa and 50% (95% CI, 19–68%) in Malawi). Despite lower efficacy in Malawi, the number of episodes of severe RVGE prevented by vaccination was higher (3.9/100 vaccinees) than in South Africa (2.5/100 vaccinees) because of the higher incidence of severe RVGE in young infants in Malawi. Initial Phase 3 efficacy results were also available for RV5 in Africa and Asia. The RCT was designed to separately analyse the combined results for the sites in three countries in Africa (Ghana, Kenya and Mali) and the combined results for the sites in two countries in Asia (Bangladesh and Viet Nam). The efficacy of a 3-dose regimen of the vaccine against severe RVGE during the first year of follow-up was 64% in Africa (95% CI, 40–79%). When results are reviewed separately by country, vaccine efficacy at 1 year varied greatly: Ghana 65% (95%CI 35.5–81.9), Kenya 83% (95%CI 25.5–98.2), Mali 1% (95%CI -431.7–81.6) [16]. Upon subsequent review of the Mali results, it was determined that children enrolled in the study were infrequently being brought to medical attention when they became ill and instead were being taken to traditional healers so that very few cases of RVGE were identified. In the second year of the study sensitization of participants was increased, leading to an increase of reported cases and a higher point estimate for vaccine efficacy (19.2% (95%CI -23.1–47.3)) [17]. Despite the variation in findings across sites, the pooled efficacy was considered and cited in the global policy recommendation.

At the time of the 2009 recommendation, post-marketing safety monitoring data were available and showed no increased risk of intussusception in the US, Australia, and Latin America. Data available were sufficient to rule out the level of risk of intussusception that had been seen with Rotashield (attributable risk of 1 case per 10,000 individuals vaccinated). Clinical trials had no been powered to rule out a smaller risk of intussusception. No evidence of mortality impact due to rotavirus vaccine was not available or required for this policy recommendation [15].

A 2013 position paper broadened the policy recommendation for global use of rotavirus vaccines [18]. At the time of this decision, limited evidence of mortality impact had become available from observational studies in Brazil and Mexico. In Brazil, vaccination resulted in 22-28% reduction in diarrhoea-related deaths in children ≤2 years. In Mexico, there was a relative reduction in the rate of diarrhoea-related deaths among infants <11 months of age (41%;95% CI: 36%–47%) and among children aged 12-23 months (29%; 95% CI: 17%–39%). However, secondary analysis of mortality impact was not consistent across trials and study designs were not intended to look at mortality

impact. Although the Brazil and Mexico observational data were considered, the WHO evidence-to-recommendation tables at the time of the 2013 position paper were as follows:

- We are not certain about the effect of use of RV1 on all-cause death in low mortality countries
- We are not certain about the effect of use of RV1 on all-cause death in high mortality countries
- We are not certain whether the use of RV5 in low mortality countries has any effect on all-cause death
- We are not certain whether the use of RV5 in high mortality countries has any effect on all-cause death

In 2013, extensive clinical data supported the safety of both RV1 and RV5 and the benefits of rotavirus vaccination for children. The 2013 WHO position paper noted that the benefits of vaccination far outweigh any currently known risk associated with use of either rotavirus vaccine despite the fact that the RCTs conducted lacked power to rule out very small relative risks of association. No increased risk of intussusception was detected with either RV1 or RV5 in 2 RCTs, each of which including approximately 60 000–70 000 infants and designed to detect a risk similar to that seen with Rotashield (attributable risk 1 per 10 000). Following clinical trials, post-marketing surveillance intussusception data has accrued indicated attributable risk of 1-2 per 100,00 at the time of the 2013 position paper; intussusception surveillance data continues to accrue and attributable risk varies by setting but has remained in the range of 1-5 per 100,000 children [18]. The SAGE recommended that country-specific plans for rotavirus vaccine introduction consider not only potential public health impact and risk, but also cost-effectiveness, affordability, and financial and operational impact on the immunization delivery system.

The FPD Working Group discussed the utility of comparing relative and attributable risk of intussusception in relation to impact on rotavirus hospitalizations and deaths averted as a potential threshold that could be applied when considering RTS,S/AS01 meningitis and cerebral malaria risk. Table 1 provides reference data from the Mexican and Brazilian studies described above as well as from Australia and the USA.

Table 1. Risk–benefit estimates of rotavirus disease and intussusception outcomes by country (*adapted from Table 2, Rha et al. Expert Reviews Vaccines 2014* [19])

Country	Outcome	Rotavirus outcomes averted	Intussusception outcomes caused	Rotavirus outcome averted: intussusception outcome caused	Ref
Mexico	Hospitalizations Deaths	11,551 663	41 2	282:1 331:1	[20]
Brazil	Hospitalizations Deaths	69,572 640	55 3	1265:1 213:1	[20]
Australia	Hospitalizations Deaths	6,528 NR	14 NR	466:1 NR	[21]
USA	Hospitalizations Deaths	53,444 14	35-166 0.1-0.5	322-1530:1 28-134:1	[22]

Estimates based on one vaccinated birth cohort to age 5 years. NR: Not reported

Dengue vaccine

In 2016, WHO recommended that countries should consider introduction of the dengue vaccine CYD-TDV in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease. The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination. In 2017, SAGE considered newly available safety data which showed an increased risk of hospitalized and severe dengue in seronegative individuals after year 3 to 66 months of follow-up, and in 2018 recommended that countries using the vaccine for dengue control should implement pre-vaccination screening so that only seropositive individuals are vaccinated.

Dengue is a mosquito-borne illness that causes both asymptomatic infection and in some cases can cause severe hemorrhagic disease and death. Four viral serotypes exist; infection leads to development of temporary protective immunity to the infecting serotype. After an initial infection, as immunity wanes, individuals are at risk for severe disease [23]. In contrast to malaria, there is no specific treatment for clinical dengue disease. CYD-TDV (Dengvaxia®) is a live attenuated (recombinant) tetravalent vaccine, licensed in December 2015 for individuals 9 to 45 years of age in geographic settings with high burden of disease and dengue seroprevalence 70% or greater. It is recommended as a 3 dose series with doses 6 months apart. As of June 2018, CYD-TDV has been approved for licensure by regulatory authorities in 20 countries.

In July 2016, WHO published the first position paper on dengue vaccine [23] with a recommendation as follows "*Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease… The vaccine is not recommended when seroprevalence is below 50% in the age group targeted for vaccination… Use of CYD-TDV in populations in which seroprevalence is low in the age group considered for vaccination is not recommended because of low efficacy and potential longer-term risks of severe dengue in vaccinated seronegative individuals*".

This WHO position was informed by clinical trial and safety data, mathematical modelling and cost-effectiveness analyses which suggested that the public health benefits of vaccination could be maximized if dengue seropositivity was high in the age group targeted for vaccination. Data on CYD-TDV was available from two parallel Phase 3 randomized clinical trials, known as CYD14 and CYD15. CYD14 was conducted at sites in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand, and Viet Nam), with 10 275 participants aged 2–14 years at first vaccination. CYD15 was conducted at sites in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico (USA)), with 20 869 participants aged 9–16 years at first vaccination. Vaccine efficacy against virologically-confirmed dengue illness was assessed during the active phase of surveillance (25 months post-enrolment). Per protocol vaccine efficacy against virologically-confirmed symptomatic dengue illness of any serotype was 56.5% (95% CI 43.8%–66.4%) in CYD14, and 60.8% (95% CI 52.0%–68.0%) in CYD15 (from one month post dose 3 for 12 months). Vaccine efficacy varied by country, with efficacy ranging from 31.3% (95% CI 1.3%–51.9%) in Mexico to 79.0% (95% CI 52.3%–91.5%) in Malaysia.

The lower limit of the licensed indication at 9 years of age was chosen due to a safety concern identified in the Phase 3 clinical trials. During hospital-based surveillance, a signal emerged in the 2–5

year age group (age group only included in CYD14). While the cumulative relative risk of hospitalized dengue illness between vaccine and placebo arms in the 2–5 year age group during the entire trial period to date was not statistically significant (1.3 (95% CI 0.8–2.1)), a statistically significant RR of 7.5 (95%CI 1.3-313.8) was observed among 2-5 year olds only in the period in year 3 after dose 1. There were 15 hospitalized dengue cases in vaccinated children versus 1 in unvaccinated children [23]. Several hypotheses have been suggested to explain the results, including that in seronegative children, of whom there is a higher percentage in the younger age groups, the vaccine may act as a silent natural infection that primes seronegative vaccinees to experience a secondary-like infection upon their first exposure to dengue virus. At the time of the April 2016 SAGE meeting and July 2016 WHO position, this increased risk had not been observed in those aged 9 years and older. At that time, the SAGE noted the limited safety data in seronegative populations and recommended post-marketing safety surveillance to monitor hospitalized and severe dengue illness in vaccinated persons.

Feasibility data were available nor cited as a requirement for the policy recommendation despite challenges associated with implementation of the 3-dose vaccination schedule in the target population of older children and the multiple new visits required to meet the schedule.

A revision to the SAGE recommendation occurred following the April 2018 SAGE meeting due to new safety data from November 2017 showing that while overall population level benefit was favourable, there was an increased risk of hospitalized and severe dengue in seronegative individuals after year 3 to 66 months of follow-up [24]. In areas of 70% dengue seroprevalence, over a 5-year follow-up, for every 4 severe cases prevented in seropositives there would be 1 excess severe case in seronegatives per 1000 vaccinees; for every 7 hospitalizations prevented in seropositive vaccinees, there would be 1 excess hospitalization in seronegative vaccinees. The SAGE considered the safety data as well as feasibility of individual pre-vaccination screening, and recommended that countries using the vaccine for dengue control should implement pre-vaccination screening so that only seropositive individuals are vaccinated.

Neither the original policy recommendation for use nor the recent revision considered mortality impact as mortality impact data were not available.

B) Standards applied for malaria intervention policy recommendations

In contrast to the process for SAGE vaccine policy decisions published in position papers, malaria intervention policy decisions have not followed a consistent procedure or format for publication. Currently recommended malaria prevention tools include long lasting insecticidal nets (LLINs), Intermittent Preventive Treatment in infants (IPTi), Intermittent Preventive Treatment in pregnancy (IPTp), indoor residual spraying (IRS), and in areas with highly seasonal malaria, seasonal malaria chemoprevention (SMC). Increased rollout of malaria control methods had led to over 50% reduced malaria mortality in sub-Saharan Africa since 2000 [2], but ongoing gaps in access to preventive, diagnostic and treatment measures continue to exist.

Insecticide Treated-Nets (ITNs)

ITNs and specifically, LLINs have been shown to cause a reduction in both malaria disease and childhood mortality in randomised controlled trials. 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 [25]. The impact of ITNs is based not only on

individual-level protection but also on community-level transmission reduction [26]. However, ITN use and protection wanes over time in the absence of new distributions and it is therefore important that countries maintain distribution of replacement nets at least every 3 years [27], including in areas implementing malaria vaccination.

Early support for vector control activities began after WHO hosted a convention in 1992 to increase attention on malaria prevention measures with acknowledgement of ITNs as the most promising strategy. At this point, data were available to show that use of pyrethroids were safe, effective to decrease mosquito bites and repel and kill mosqutoes, effectiveness could be optimized based on the quantity of pyrethroid used, and cost-effective [25]. At the time of the convention, data from a study in the Gambia were also available showing a 42% reduction in all-cause mortality among children 1–59 months after implementation of ITNs [28]. Subsequently in 1993, WHO reported on Implementation of the Global Malaria Control Strategy and noted that "Impregnated bednets have proved their efficacy in reducing morbidity and mortality in certain areas, but more research is needed…. efficacy under local conditions … sustainability" [29]. In this period, before the large malaria policy and funding initiatives had been established, there was no mechanism in place to incentivize ITN production and roll-out. Four additional RCTs with mortality impact endpoints were published in 1995 [30], 1996 [31, 32], and 1997 [33]. These additional data contributed to the basis for the recommendation for additional scale up of ITNs [34].

Table 2. Insecticide-treated net data for policy recommendation

Data Available at Time of Policy Statement:	Data Unavailable at Time of Policy Statement:
• Pyrethroids safe • ITN's decrease mosquito bites, and repel and kill mosqutoes • Cost-effectiveness of ITN's • **Impact on overall mortality** (42% in The Gambia, 1991)—more data was requested	• Feasibility • Impact on resistance

Drug-based malaria prevention tools (IPTp, ITPi, SMC)

Key drug-based malaria preventive tools include IPTp to prevent malaria in pregancy, IPTi to prevent malaria in the first year of life (which has not been widely adopted) and, SMC, limited to areas with highly seasonal malaria. All of these rely on inexpensive, well-tolerated antimalarial drugs.

IPTp is the distribution of a complete dose of an antimalarial medicine to pregnant women at different intervals during pregnancy, usually during ANC visits, regardless of disease status. The original WHO policy recommendation (2004) on IPTp was: "*All pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening...IPT-SP doses should not be given more frequently than monthly. Currently, the most effective drug for IPT is sulfadoxine-pyrimethamine (SP) because of its safety for use during pregnancy, efficacy in reproductive-age women and feasibility for use in programmes as it can be delivered as a single-dose treatment under observation by the health worker*."

At the time of the initial (2004) recommendation, there were two major topics addressed by the Technical Expert Group (TEG) regarding IPTp that needed further information: SP use in IPTp in areas with high SP resistance, and the impact of IPTp in the presence of high coverage of other interventions [35]. Data of SP efficacy in high resistance areas was available for children, but there was not data

available on in vivo protective efficacy in pregnant women [35]. The TEG also requested further studies to determine: the optimal dose and dose interval, effect of seasonal malaria transmission on SP effectiveness, impact (and validation of results) of IPTp on low birth weight, maternal anaemia, and peripheral and placental parasitemia, and whether SP should be replaced with another antimalarial (superiority RCT, dose/schedule for other antimalarials, effectiveness, etc). No thresholds for parasite prevalence were established regarding when to halt or initiate IPTp use. No recommendations were made on IPTp use outside of Africa.

In 2012, following a subsequent evidence review on dose-dependent efficacy of SP and the impact of IPTp in regions with high prevalence of sulphadoxine pyrimethamine (SP)-resistant parasites, WHO made the following updated recommendation: "*The [Evidence Review Group] (ERG) advises that an update to the WHO policy on IPTp is needed and recommends that all pregnant women in areas of stable (high or moderate) malaria transmission should receive SP at each scheduled ANC visit. IPTp-SP doses should be administered as early as possible during the 2nd trimester of gestation, with each dose given at least 1 month apart from any other and continuing up to the time of delivery [36].*"

The updated policy recommendation concluded that IPTp was effective even in areas with high SP resistance, but recommended that SP should not be used as a monotherapy in malaria treatment outside of IPTp to avoid resistance.[2] The dose-dependent recommendation was based on the results of a meta-analysis that looked at 2 dose versus 3 dose regimens of SP in 7 RCT's (6281 pregnancies) [36]. The analysis showed a reduction in risk of low birth weight of 21% (95 CI: 8-32) for a three dose regimen versus a two dose regimen. The update also cited new cost-effectiveness data showing IPTp to be cost effectiveagainst in high malaria transmission areas for prevention of neonatal mortality and maternal malaria.

The recommendation called for further data on: IPTp-SP use outside of Africa; information on effectiveness at different transmission levels; programmatic effectiveness of IPTp service delivery at ANC visits and barriers to uptake [36]. There was insufficient evidence available for WHO to make a policy recommendation on what level of malaria transmission should serve as the threshold for halting IPTp. A subsequent 2013 draft recommendation suggested halting IPTp-SP when *P. falciparum* prevalence stayed below 5% in children under-15 for three years [37]. However, this threshold has yet to be formally included in WHO policy, and the 2014 WHO policy brief requested more information before selecting a threshold below which IPTp use should be halted [38].

Table 4. Intermittent Preventive Treatment in Pregnancy (IPTp) data for policy recommendation

	Data Available at Time of Policy Decision:	**Data Unavailable at Time of Policy Decision:**
2004	• **1 RCT**, Shulman C., 1999: **maternal anaemia** & **birthweight** • At least two SP doses needed to be beneficial • In HIV+ women, monthly dose of SP needed • Cost-effectiveness data • No signs of additional risk or benefit from a third dose of SP	• Feasibility, efficacy and safety of alternative antimalarials for IPTp • Efficacy in areas with high SP resistance • Impact of IPTp in areas with high coverage of other malaria interventions

2012 update	• IPTp still effective in areas with high SP resistance • New dose-dependent results, based on a meta-analysis of 2-dose vs. 3-dose regimens (7 RCT's, 6281 pregnancies): 21% reduction in low birth weight (95 CI: 8%-32%) with three doses • IPTp shown to be cost-effective for preventing maternal malaria and neonatal mortality in areas with high malaria transmission	• IPTp impact outside of Africa • Effectiveness of IPTp at different transmission levels • Programmatic effectiveness of IPTp delivery at ANC visits • Level of malaria transmission where IPTp should be implemented or halted

IPTi is a malaria prevention intervention that involves the distribution of SP through EPI programs alongside routine vaccines. WHO's current policy recommendation (2010) on IPTi is: "*The co-administration of SP-IPTi with DTP2, DTP3 and measles immunization to infants, through routine EPI in countries in sub-Saharan Africa, in areas with moderate-to-high malaria transmission (Annual Entomological Inoculation Rates >10), and where parasite resistance to SP is not high –defined as a prevalence of the pfdhps 540 mutation of <50%*" [39]. At the time of the policy recommendation, the available evidence showed that initial concerns around severe skin reactions seen in some of the early studies were not observed in larger trials or the IPTi Consortium's analysis. A pooled analysis of the six original trials showed 30% efficacy (19.8%-39.4%) against clinical malaria, 21.3% (8.3%-32.5%) against anaemia, and an all-cause decline in hospital admissions of 23% (10.0%-34.0%). There was one additional study presented for consideration whose results were published after the pooled analysis that showed IPTi efficacy of 6.7% (-45.9% –22.0%) against clinical malaria. The pooled analysis showed no signs of a rebound effect, though further observation was recommended following reports of increasing anaemia, high density parasitemia and severe malaria-associated anaemia in the SP arms of three of the RCT's. Implementation study results showed SP to be cost-effective and help increase EPI coverage.

At the time of the policy recommendation, it was unknown what parasite SP resistance threshold made IPTi ineffective. Additionally, there was uncertainty on the impact of IPTi on severe malaria incidence and malaria mortality, and there was a noted need for evidence for IPTi use in areas with low malaria transmission rates.

Table 5. Intermittent Preventive Treatment in infants (IPTi) data for policy recommendation

Data Available at Time of Policy Decision:	Data Unavailable at Time of Policy Decision:
• **6 RCT**'s: 30% efficacy (95 CI: 19.8-39.4) against **clinical malaria**, 21.3% (95 CI: 8.3-32.5) against **anaemia**, 23% (95 CI: 10.0-34.0) against **all-cause hospital admissions** • No signs of rebound (call for further data) • No **serological interactions** with response to EPI vaccines • **Operational experience** from pilot implementation • Low cost, and helped increase coverage of EPI vaccines • Initial safety concern of severe skin reaction resolved when not observed in large IPTi Consortium studies	• Threshold of SP resistance where IPTi becomes ineffective / not cost-effective • Efficacy on severe malaria incidence and malaria mortality • IPTi impact in areas with low malaria transmission

SMC, also known as Intermittent Preventive Treatment in children (IPTc), is the provision of antimalarial treatment courses to children under five in the Sahel region of Africa, where there are large seasonal variations in malaria transmission rates between the rainy and dry seasons. The current WHO policy on SMC (2012) is: "*SMC is recommended in areas of highly seasonal malaria transmission across the Sahel sub-region. A complete treatment course of amodiaquine plus sulfadoxine-pyrimethamine (AQ+SP) should be given to children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season (provided both drugs retain sufficient antimalarial efficacy)*" [40].

The 2012 policy recommendation was based on evidence available from 8 RCT's (7 sets of results had been published) that looked at monthly and two monthly dose regimens across a cumulative 900,000 treatment courses [41]. Efficacy from these studies looked at: uncomplicated malaria, severe malaria, moderate anaemia and all-cause mortality. Pooled results showed that monthly and bimonthly SMC regimens (any antimalarial) had an efficacy of 78% (95 CI: 69 – 84) against uncomplicated malaria, and this immunity lasted for approximately 4 weeks following each dose. Monthly SMC regiments (any antimalarial) showed efficacy of 61% (95 CI: 15 – 82) against severe malaria, and 20% (95 CI: -5 – 38) against severe anaemia. There were not many reported deaths across the eight studies, making evaluations of impact on all-cause mortality unreliable, but the pooled analysis showed an efficacy of 18% (95 CI: -69 – 61) against all-cause mortality. No serious adverse events were attributed to SMC across the eight studies. There was no association between efficacy and the SP dose (half or whole tablet).

Cost-analysis data was also considered, and showed SMC to be highly cost-effective in areas with attack rates greater than 0.2 clinical attacks per transmission during the rainy season, and cost-

effective at rates from 0.1 to 0.2 clinical attacks per transmission. SMC was not cost-effective at attack rates below 0.1 clinical attacks per transmission season.

This 2012 WHO recommendation was made without evidence on efficacy of alternative dose regiments, safety risks of repeated AQ doses (specifically neutropenia and hepatotoxicity), impact in other age groups, impact on malaria transmission, and without defined thresholds for initiating, altering or stopping SMC in a particular area. Due to the lack of data to answer these questions, the WHO policy also contains the caveat: "*While there are several potential approaches to implementing SMC, there is presently insufficient evidence to recommend a standard deployment strategy and individual approaches best suited to local conditions should be used*."

Table 6. Seasonal Malaria Chemoprevention (SMC) data for policy recommendation

Data Available at Time of Policy Decision:	Call for further data at Time of Policy Decision:
• **8 RCT's**, 900k treatment courses • 78% efficacy (95 CI: 69-84) against **uncomplicated malaria**; protection lasted about 4 weeks • 61% (95 CI: 15-82) against **severe malaria**, 20% (95 CI: -5.0-38.0) against **severe anaemia**, 18% (95 CI: -69 -61) mortality • No AESI reported • No association observed between SP dose and efficacy • Highly **cost-effective** at attack rates greater than 0.2 clinical attacks per transmission season, cost-effective at attack rates of 0.1-0.2	• Efficacy of alternative dose regimens • Safety risk of repeat AQ doses (neutropenia and hepatotoxicity) • Impact in different age groups • Impact on malaria transmission • Data for starting and stopping thresholds of malaria transmission

Impact of RTS,S/AS01 on utilization of other malaria interventions will be assessed during the household surveys by measuring and comparing prevalence estimates in vaccination and comparator areas. Communication will be a key component of any RTS,S/AS01 introduction plan to maintain use of other malaria control tools, including emphasis on the partial protection of the vaccine and the need to continue sleeping under and an ITN and the need to seek diagnosis and treatment for fever early.

C) Operational feasibility: Expected MVIP coverage based on Immunization coverage trajectories over time following new vaccine introductions

Definition of "high" coverage

The JTEG has recommended that "high" immunization coverage be documented in order to recommend continued implementation. However, as the SAGE has previously recognised (SAGE, April 2018), the relatively low coverage levels of MCV2 provided to children aged 15–18 months in MVIP countries could indicate challenges in reaching children in the second year of life with the fourth dose of RTS,S/AS01.

The WHO recommendation acknowledged that receiving all four doses of the vaccine ensures optimal benefit of the vaccine and avoids an age-shift in timing of severe disease that was observed in the

Phase 3 trial among children randomized to receive only 3 vaccine doses. However, subsequent long-term follow up data from the MAL-076 study are reassuring, showing no excess risk of severe malaria among those who receive only 3 doses and modelling estimates based on Phase 3 data predict that the added benefit of a fourth dose may be small compared to that of the first three doses. Nonetheless, given uncertainty around the added benefit of a fourth dose, efforts at maximizing coverage of the full four dose series during the Programme is desirable.

Considering experience with introduction of other childhood vaccines, the definition of "high" coverage is challenging, and would be expected to differ for the third and fourth doses of RTS,S/AS01. Coverage is expected to be lower for the fourth dose of RTS,S/AS01 compared to the third dose because of healthcare visits during the second year of life are less well established than those in infancy. Examples from other vaccine introductions were reviewed to determine realistic goals for coverage based on the strength of the immunization system to support the additional vaccine introduction and new immunization schedule.

Documentation of achieving high coverage is not typically a prerequisite for a WHO policy recommendation for vaccine introduction, unless there is an epidemiological rationale. For example, with vaccines that induce population-level protection ("herd immunity"), suboptimal childhood vaccination coverage can lead to an age shift in disease at the population level, but this principal does not apply to malaria vaccination as the RTS,S/AS01 vaccine is expected to provide individual protection only and not expected to have an effect on malaria transmission.

Strength of routine immunization in the pilot countries

After responding to call for expressions of interest, the pilot countries were selected for participation in the pilot implementations based on standardized criteria, including demonstration of a strong EPI programme. Coverage levels for diphtheria-tetanus-pertussis (DTP) and measles-containing vaccine (MCV) are considered indicators of health system performance. Vaccines given in the second year of life, such as MCV2 and meningococcal A vaccine, were assessed as relevant by the Working Group when considering potential RTS,S/AS01 coverage. The additional visits to be introduced for RTS,S/AS01 can be leveraged as opportunities to reach children at critical time points for well child exams, including weight monitoring, and to provide vitamin A and deworming recommended at two years of age. Based on the WHO recommendations, the EPI Programmes defined the most appropriate target age for children to receive each dose of RTS,S/AS01 given the existing routine immunization schedule.

Expected coverage trajectory over time following new vaccine introduction

Vaccine coverage rates for second year of life vaccines are generally suboptimal in Africa. As of 2016, WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) average MCV2 coverage was 74% with many countries having introduced more than 5 years ago. Coverage for vaccines administered at the same or similar times points as RTS,S/AS01: MCV1, MCV2 and Meningococcal serotype A (MenA) (introduced in Ghana only) vary greatly among pilot countries (Table 7).

Table 7. Immunization programme performance in MVIP countries: 2017 vaccine coverage estimates*

	Ghana	Kenya	Malawi
DTP-HepB-Hib, first dose, at 6 weeks	99%	93%	93%
DTP-HepB-Hib, third dose, at 14 weeks	99%	82%	88%
Measles-containing vaccine (MCV1) 1st dose, 9 months	95%	89%	83%
Measles-containing vaccine (MCV2) 2nd dose, 18 months	83%	35%	67%
Meningococcal conjugate serotype A vaccine, 18 months	82%**	NA	NA

2nd year of life

*according to WHO/UNICEF coverage estimates, as of 15 July 2018

**Country reported estimate, first full year after introduction

Vaccine coverage trends increase over time following introduction. The trajectory in coverage for first year of life vaccines has been increasing since the start of the EPI program. Since the 1980's trends in coverage over time for infant DTP, MCV, and oral polio vaccines have been observed and found to vary considerably by region and country; however, generally, the acceleration in coverage is highest when national coverage levels are between 25-30%, and where there is investment in the immunization system. Coverage levels tends to level off when they are high, e.g. over 80% [42].

In the pilot countries, increasing trends have been observed in average WUENIC estimates [43] for vaccines given during the first year of life (third dose pneumococcal vaccine, Haemophilus influenza type b vaccine, second dose rotavirus vaccine) during the first three years after introduction (Figure 1a). When MCV2 as a second year of life (2YOL) vaccine is considered, increasing trends are also observed though the highest coverage achieved has been lower than for vaccines given in the first year of life (Figure 1b).

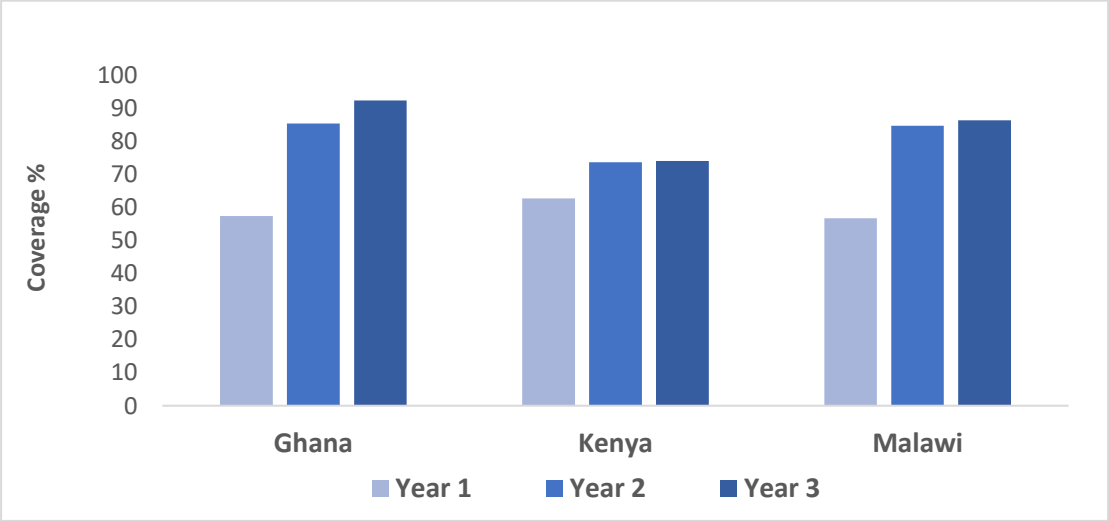


Figure 1a. Average WHO/UNICEF (as of 15 July 2018) estimated first year of life vaccine coverage in Ghana, Kenya, and Malawi during first 3 years following introduction, including the year of introduction (**third dose pneumococcal vaccine, Haemophilus influenza type b vaccine, and second dose rotavirus vaccine**)

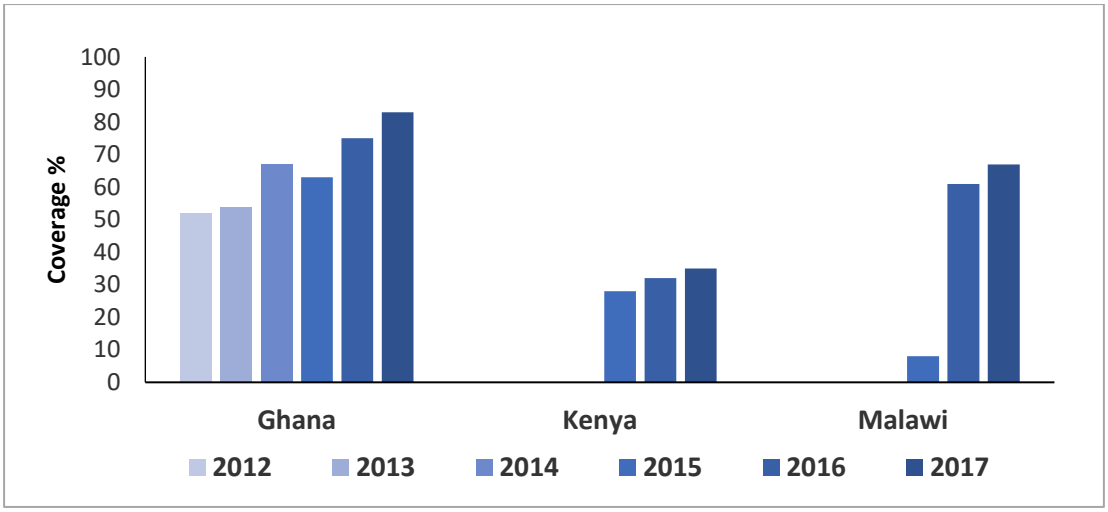


Figure 1b. **Second dose measles-containing vaccine** WHO/UNICEF estimated coverage (as of 15 July 2018) in Ghana, Kenya and Malawi, 2012-2017. The first year shown for each country is the year of introduction.

A preliminary analysis performed by CDC using the WHO/UNICEF coverage data (2016) [43] of the time needed to attain various MCV2 coverage levels showed that among 22 countries in AFRO who have introduced MCV2, 17 have achieved coverage of at least 60%. Among the 13 countries that had reported at least five years of data, attaining 60% coverage took an average of 1.4 years. Attaining 70% and 80% coverage took 2 and 3.9 years respectively (Table 8).

Table 8. Average time to reach target MCV2 coverage in years, as of 2016

	Average time (years) to reach MCV2 target coverage, as of 2016*			
	60%	**70%**	**80%**	**90%**
WHO African Region	1.4	**2**	**3.9**	5
Number of countries (%)**	13 (59)	11 (50)	7 (32)	4 (18)

* Among total 22 countries in AFRO who have introduced MCV2 as of 2016, 17 have achieved coverage of at least 60%.

** Excludes countries who didn't report for >5 years

Note: This reflects first time countries hit the selected target coverage. Many countries hit 70% or 80% one year and then the next year (or few years) they were back down in the 60% range.

The meningococcal serotype A conjugate vaccine (MenA) is another example of a 2YOL vaccine that has recently been introduced in multiple countries in the meningitis belt, including in Ghana. The MenA coverage trajectory experience may be informative for potential coverage expected for RTS,S/AS01 and the impact on other routine EPI vaccines. MenA vaccination campaigns in Africa since 2010 have led to dramatic reductions in meningococcal meningitis and community acceptance of vaccination was observed to be high [44]. Burkina Faso introduced MenA into the routine EPI in March 2017 at age 15-18 months, concomitantly with MCV2. A coverage survey was recently conducted one year after introduction in Burkina Faso to examine MCV2 coverage in pre- and post-MACV introduction cohorts to assess changes regionally and nationally, with the hypothesis that introduction of MenA, highly desirable by endemic communities, might lead to an improvement of MCV2 coverage, available to children at the same vaccination visit. Results of the survey showed that after one year of introduction, MenA coverage reached 58% (95%CI 56-61), much lower than the 96% coverage that has been achieved during the mass vaccination campaign conducted in Burkina Faso in 2010 [45].

MCV2 coverage did increase significantly by about 5% compared to pre-MenA introduction coverage (Table 9). Given the methodology of the survey, the increase in MCV2 coverage cannot be attributed to the introduction of MenA into the routine EPI schedule. While MACV introduction may have contributed, it cannot be separated from the expected modest increase in coverage during the first few years post-introduction. The introduction of RTS,S/AS01 coinciding with other 2YOL vaccines might present a similar opportunity for improvement of other immunization or coverage.

Table 9. Measles-containing vaccine dose 1 (MCV1), MCV2, and meningococcal serotype A conjugate vaccine (MenA) coverage before and after MenA introduction in routine childhood immunization, Burkina Faso, 2018*

% Coverage (95% CI)	Pre MenA Introduction Age Group (30-41 months)	Post-MenA Introduction Age Group (18-26 months)	Change in Coverage
MCV1	88 (87, 90)	89 (87, 91)	1.0 (-0.8, 2.8)
MCV2	**62 (59, 65)**	**67 (64, 69)**	**4.5 (1.3, 7.7)**
MenA	NA	**58 (56, 61)**	na

*Burkina Faso introduced MenA vaccine into the EPI in March 2017; the coverage survey was conducted 12 months after introduction in March 2018. Data from Zoma, Walldorf et al, manuscript in preparation.

Assessment of coverage during the MVIP evaluation period

Administrative coverage data will be available monthly after the start of RTS,S/AS01 vaccination based on routine reports from vaccination facilities up to the district and national levels. However, administrative coverage data has well-known limitations for over or underestimation [46, 47]; reliability of administrative data depend greatly on completeness and timeliness of reporting and accuracy of population denominator estimates for the age group eligible for vaccination. Administrative coverage estimates may become more reliable over time. Given the limitations to administrative coverage data, household survey data will a more reliable source of RTS,S/AS01 and other vaccine coverage [48] but will not be available as early and will only be available intermittently following the conduct of a coverage survey and subsequent statistical analysis. Representative population-based survey data that would include the fourth RTS,S/AS01 dose will be estimated at the coverage survey planned to occur at 30 months after vaccine introduction with results available approximately 2 months later depending on the time needed for analysis.

The full evaluation period of approximately 50 months may be sufficient for scale up and achievement of "high" coverage for first year of life RTS,S/AS01 doses 1, 2, and 3, with less certainty for the fourth dose considering experience with other 2YOL vaccines. In contrast, evaluation at 18-24 months following the first RTS,S/AS01 fourth dose administration may not allow enough time for the trajectory towards high coverage, especially for the fourth dose. Similar to the trends observed for MCV2, achievement of fourth dose RTS,S/AS01 vaccine coverage comparable to the third dose will likely take several years.

During the course of the evaluation, the immunization program will have the opportunity to strengthen procedures around the new immunization visits and respond to early challenges identified

through the planned post-introduction evaluation and through the Health Care Utilization Qualitative Longitudinal evaluation (HUS). The HUS will inform interpretation of coverage estimates, and will explore contextual and behavioural factors that might impede or facilitate RTS,S/AS01 uptake in terms of: delivery and integration, community reception and acceptability, and vaccine uptake and consequences.

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Annex 2: Malaria vaccine targets and pipeline

1. Malaria vaccine targets

The pre-erythrocytic stages (stages 1 – 3 in Figure 1) encompass the injection of the sporozoite stage of the parasite by the bite of an infected female anopheline mosquito, and the rapid homing of the sporozoite into the liver cells within a matter of minutes to a few hours. Blood stage (erythrocytic, anti- disease vaccines) target stages 4-6, and transmission blocking vaccines stages 7-9.

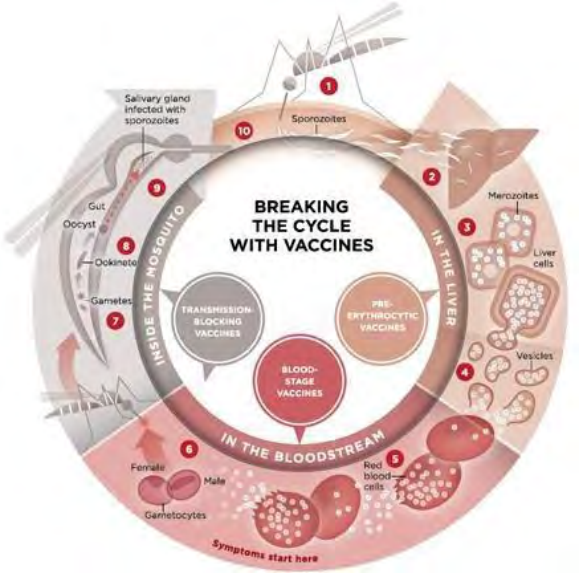

Fig. 1 Malaria life cycle and associated vaccine targets (Figure by PATH Malaria Vaccine Initiative)[1]

Numerous antigens that are unique to either the merozoite (e.g. the merozoite surface antigens) or to the infected erythrocyte (e.g. erythrocyte-associated surface antigens) are potential erythrocytic-stage vaccine antigens, and such vaccines would either prevent the invasion of the erythrocyte by the merozoite, or would target the infected erythrocyte for destruction by the host's immune system. The net effect of such erythrocyte-stage immune responses could be to limit or ameliorate the blood-stage manifestations of the malaria parasite infection. Small subsets of infected erythrocytes undergo a developmental switch into the sexual stage of the organism, termed gametocytes. Gametocytes develop into extracelluar gametes in the midgut of the mosquito vector when taken in a blood meal from an infected person to undergo fertilisation and continue development in the mosquito. Although most gametocytes remain within the host erythrocyte until they are taken up during a blood meal ingested by a female anopheline mosquito, some of the infected erythrocytes rupture in the host's reticuloendothelial system and present gametocyte-specific antigens to the host's immune system. Vaccines targeting gametocyte stages of the parasite, or targeting gametes and the post fertilization stage – the zygotes and subsequent ookinetes, which are found only in the mosquito midgut after fertilization occurs, may provide transmission-blocking immune responses that could interrupt transmission of the parasite from an infected person to an uninfected person by preventing development of a mature sporozoite in the mosquito. Combination vaccines containing antigens

expressed at different stages of the parasite's life-cycle may induce an immune response with a broad biological effect.

2. Malaria vaccine pipeline

Through a series of ongoing consultations, WHO is currently revising the preferred product characteristics (PPC) for malaria vaccines. PPCs are are technical documents describing WHO preferred attributes of products for licensure, policy, and programmatic implementation in lower middle income country settings. They address several product characteristics including indication, target population, safety and efficacy, formulation and presentation, dose regimen, co-administration, route of administration, product stability and storage, and access and affordability. These preferences are shaped by the unmet public health needs in priority disease areas as well as the realities of the disease epidemiology and delivery systems in the target geographies.[2]

Many *P. falciparum* malaria-vaccine projects are in clinical stages of evaluation (Figure 2). However, only RTS,S/AS01 (a pre-erythrocytic stage vaccine) has completed pivotal phase III evaluation, reached the regulatory review stage, and has been introduced in sub-national pilot implementation through EPI programmes.

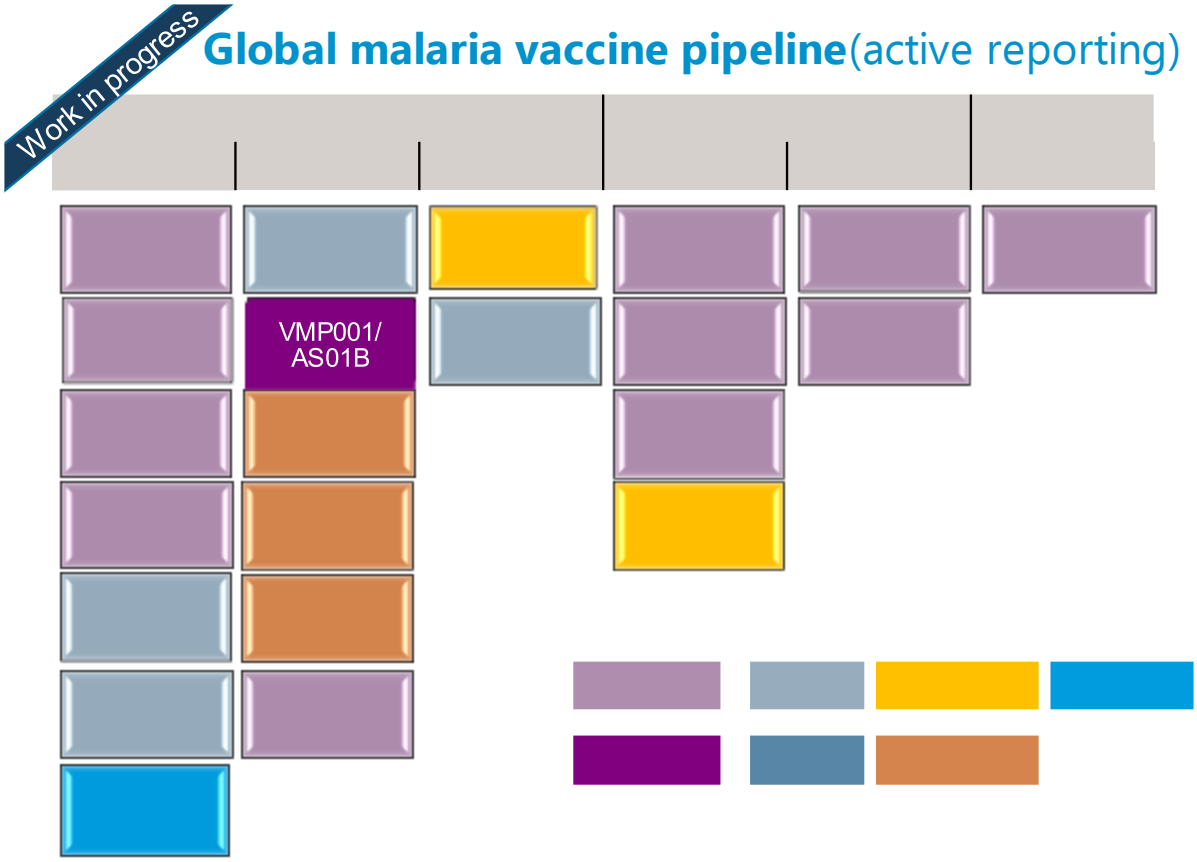

Fig. 2 Global malaria vaccine pipeline August 2021[3]

A recent WHO review meeting summarized progress in malaria vaccine development.[4] Experimental challenge trials (controlled human malaria infection [CHMI]) have proven to be a valuable tool to inform vaccine formulation, dose, route, schedule and development programmes, and have enabled a less risky approach to investment by providing early indications of efficacy. CHMI with sporozoites delivered by infected mosquitos or direct venous inoculation (DVI) can be used to assess pre-erythrocytic vaccine candidates. Blood stage challenge is applicable for blood- or sexual- (but not pre-erythrocytic-) stage candidates.

One pre-erythrocytic vaccine, **RTS,S/AS01,** has completed clinical development and is now in pilot implementation. Additionally, two pre-erythrocytic vaccine candidates have reached late-stage clinical development: PfSPZ, and R21/MM. The RTS,S/AS01 vaccine is based on the *P. falciparum* sporozoite antigen CSP, and was developed after a series of clinical trials demonstrated that simpler CSP-based vaccines provided inadequate clinical efficacy. RTS,S uses a delivery system based on the hepatitis B–malaria antigen fusion protein. Because RTS,S formulated on aluminium-containing adjuvants alone afforded no protection in human-challenge studies, other adjuvants were explored. The formulation designated as RTS,S/AS01 appeared to provide the greatest protection.[5]

PfSPZ. Sanaria corporation has developed a pre-erythrocytic radiation attenuated product consisting of aseptic, purified, vialed, cryopreserved *P. falciparum* sporozoites (PfSPZ). These sporozoites are available as fully infectious (for intravenous CHMI) or for immunization (radiation- and genetically-attenuated sporozoites for immunisation).[6] PfSPZ is produced through mosquito salivary gland dissection; it requires administration by direct venous inoculation, and must be stored in liquid nitrogen. In a CHMI trial in malaria-naïve US adults, three doses of $9x10^5$ PfSPZ administered through DVI induced >90% protection against CHMI after three weeks, and was 70% at 24 weeks using a challenge strain homologous to that used for immunisation.[7] Efficacy against heterologous strains was reduced. Other CHMI trials in non-immune populations have yielded similar results.

In a Phase 1 field trial in Malian adults who received five doses of 2.7×10^6 PfSPZ at months 0, 1, 2, 3 and 5, protective efficacy was 29% against *P. falciparum* infection as determined by thick blood smear during the transmission season.[8] In malaria-experienced adults in Burkina Faso (n=80) who received three doses of 2.7×10^6 PfSPZ at 8-week intervals prior to the transmission season, protective efficacy against *P. falciparum* infection as determined by thick blood smear was 38% during the six months following the third dose.[9] In both CHMI and field trials, PfSPZ has shown favourable safety and tolerability profiles. No PfSPZ vaccine efficacy has been shown against malaria in young children Published data on efficacy in field trials in African children are not yet available. A Phase 3 trial is currently planned in Equatorial Guinea as part of a Bioko Island malaria elimination project.[10] PfSPZ is also being developed for prevention of malaria in travellers and the military.

R21. The R21 anti-sporozoite subunit candidate vaccine, developed at Oxford University, is an RTS,S-like vaccine targeting the same circumsporozoite protein antigen, but with enhanced efficacy related to different immunogenic properties.[11] The R21 particle is formed from a single CS-hepatitis B

surface antigen (HBsAg) fusion protein, hence 100% of the molecules in each particle include the CS antigen, compared with 20% in RTS, S/AS01 which also includes free HBsAg. This difference could mean that R21 exposes more CS protein (CSP) epitopes to the immune system than RTS,S/AS01. The Matrix-M adjuvant was selected instead of AS01 based on ease of access and demonstrated potent immunogenicity. Unpublished phase 1 trials showed that a low dose formulation (10 µg R21/Matrix-M) had similar immunogenicity to 50 mg of RTS,S/AS01, and favourable safety. In a CHMI trial, a 3-dose schedule of 10 µg R21/Matrix-M induced 82% sterile protection against CHMI after3 weeks (NCT02572388, NCT02925403, unpublished).

In a phase 2b trial in children aged 5–17 months in a highly seasonal area of Burkina Faso, low dose (5 µg) R21 was given with two different doses of Matrix-M (25 or 50 µg); the control group received rabies vaccine.[12] The doses were administered at 4-week intervals before the malaria season, with a fourth dose 1 year later, again before the malaria season. One hundred and fifty children comprised each of the three groups (n=150 in each). R21/MM had a favourable safety profile and was well tolerated. At six months following the last dose (end of transmission season), protective efficacy against clinical malaria was 74% (95% CI 63–82) in the 5 µg R21 / 25 µg MM group, and 77% (95% CI 67–84) in the 5 µg R21 / 50 µg MM group. Of note, in the same site in Burkina Faso in the RTS,S / AS01 phase 3 trial, the vaccine efficacy at 6 months follow-up was similar - 72% (95% CI 60-80). At 1 year, R21/MM vaccine efficacy remained high, though few cases occurred in the second six months (dry season). Participants vaccinated with R21/MM showed high titres of malaria-specific anti-Asn-Ala-Asn-Pro (NANP) antibodies 28 days after the third vaccination, which were almost doubled with the higher adjuvant dose; titres waned but were boosted to levels similar to peak titres after the primary series of vaccinations with a fourth (booster dose) 1 year later.
Follow-up of this phase 2 is continuing; a phase 3 trial across five African sites of differing malaria transmission and seasonality was initiated at the 2 highly seasonal sites in 2021.

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Annex 3: Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced

Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced

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Background:

The RTS,S/AS01 malaria vaccine was introduced in pilot schemes in Malawi, Ghana and western Kenya in 2019, to evaluate safety, and effectiveness before the vaccine could be recommended more widely.

The evaluation, planned over 4 years, aims to assess the feasibility of achieving high uptake of the vaccine, and to measure the effect that introducing the malaria vaccine has in reducing child deaths and hospital admissions with severe malaria, in areas with year-round malaria transmission. The evaluation also addresses three safety signals that were observed in the phase 3 trial but whose significance was unclear: an unexplained excess of meningitis cases in RTS,S/AS01 recipients, an excess in cerebral malaria cases among RTS,S/AS01 recipients, and an excess of deaths among girls who received RTS,S/AS01.

It was anticipated that sufficient data to assess the safety signals and the initial impact on the incidence of hospital admission with severe malaria was likely to be available after the first 2 years of the evaluation. The primary analysis of these outcomes would be done at that time. These results, if favourable, would be sufficient to support a recommendation for wider use of the vaccine. Information which would follow later would include uptake of the fourth dose and the impact of vaccine introduction on all-cause mortality.

Evaluation design:

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 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. A total of 158 areas were randomized (66 districts in Ghana; 46 sub-counties in western Kenya; and 46 groups of immunization clinics and their associated catchment areas, in Malawi). Each area had a total population of about 100,000 and an expected birth cohort of about 4,000 per year. The areas where introduction was delayed serve as comparison areas for the purpose of the evaluation. Household surveys were conducted throughout the implementation and comparison regions in each country, before vaccine introduction, to assess at baseline the coverage of EPI vaccines, use of insecticide-treated bednets and malaria prevalence in children, and information about care-seeking for children who are unwell (with reported fever).

The vaccine schedule involves four doses, at 6,7,9 and 24 months of age in Ghana and Kenya and at 5,6,7 and 22 months in Malawi. The RTS,S/AS01 vaccine is delivered by national immunization programmes through their routine systems. This has involved adding three vaccination visits to the EPI schedule in Ghana and Kenya and four additional visits in Malawi. In each country the fourth dose is given 15 months after the third dose, three months earlier than in the phase 3 trial.

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 maintained 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.

At the start of the evaluation, the pilot areas in all three countries had high coverage of the routine childhood vaccines in the first year of life. The percentage of children 12-23 months who had received their third dose of DTP-containing vaccine[1] was 95% in Ghana, 95% in Malawi and 92% in Kenya, and 89%, 93% and 90% respectively had received their first dose of measles-containing vaccine. With respect to vaccines in the second year of life, among children 24-35 months of age, the percentage that had received their second dose of measles-containing vaccine was 82% in Ghana. Among children aged 5-48 months 91% slept under an long-lasting insecticide-treated bednet (LLIN) in Malawi, where an LLIN distribution campaign had been completed just prior to the survey, 64% in Ghana, and 87% in Kenya, and the prevalence of recent or current *P.falciparum* infection in this age group, as measured by rapid diagnostic test, was 21% in Ghana, 22% in Malawi and 22% in Kenya.

The evaluation continues until 2023 but by April of 2021 sufficient data had accrued to address the safety signals observed in the phase 3 trial, and to provide evidence of the impact of vaccine introduction on the incidence of hospital admission with severe malaria. This analysis of safety and impact on severe malaria is the primary analysis on which decisions about wider use of the vaccine will be based.

Statistical methods:

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 of estimation takes advantage of the fact that surveillance is maintained for all children between 1 and 59 months of age, including both eligible children, and children who are not eligible for vaccination because they are too young or were too old when the vaccine was introduced. If the vaccine has no effect, the ratio of the number of events in eligible versus non-eligible children should be the same in intervention and comparator areas. The ratio of these ratios, is an estimate of the incidence rate ratio associated with vaccine introduction in the vaccine-eligible age group. Confidence intervals are estimated using standard methods (Annex 1). Events are classified as belonging to vaccine-eligible children, or non-eligible children. To avoid contamination, children who were just too old to be eligible, by up to two months, were excluded from analysis, as the vaccine uptake in this group is unknown. For this reason, the total events in eligible and non-eligible categories is slightly less than the total number of events for that outcome.

By using the data for the non-eligible children in each region there is an adjustment for underlying differences in disease burden or access to hospital between implementation and comparison regions, in so far as these factors will tend to be highly correlated between different age groups. Pre-intervention data on the incidence of the outcomes of interest could serve this purpose but surveillance was established only when the vaccine was introduced and vaccine introduction could not have been delayed in order to obtain such data. A second advantage is that reliance on population denominators, which are challenging to estimate reliably, is avoided when estimating incidence rate ratios.

[1] Vaccine status documented from the home-based record (HBR) or according to caregiver recall, except at baseline in Ghana where vaccine status was determined only from children with an HBR (in Ghana 88% of children 12-23months surveyed had an HBR).

For safety outcomes, the research question[2] was whether the excess of cases of meningitis and cerebral malaria, and the excess mortality in girls, which were unexplained, were causally related to the vaccine. We therefore estimated the number of events required for 90% power to detect rate ratios for these safety signals, if they were of the magnitude observed in vaccinated children the phase 3 trial[3], after allowing for dilution due to vaccine coverage being less than 100%, and allowing for effects of contamination[4]. We also allowed for potential confounding whereby, in the case of meningitis, if RTS,S/AS01 recipients have also received Hib and pneumococcal vaccine, which protect against meningitis, this could to some extent mask a safety signal (in practice this was a small effect due to the fact that vaccine-preventable serotypes were relatively uncommon causes of meningitis). We calculated that the meningitis signal in the phase 3 trial would equate to a rate ratio of 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 later, when data on RTS,S/AS01 coverage from the household surveys was available). We 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. For impact outcomes, we estimated that a total of about 3000 severe malaria cases (eligible and non-eligible groups combined) would be required for 80% power to detect a reduction of 24% and 4000 for 90% power. Based on event rates observed in the first year of the evaluation we 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 was a total of 134 cases of meningitis, and 572 of cerebral malaria, and by March 31 2021, 4280 deaths with cause of death. Deaths that occurred in April 2021 were excluded as verbal autopsies were not complete.

Results:

Vaccine delivery and uptake:

In Malawi the first child was vaccinated on April 23 2019, in Ghana on April 30 2019, and in Kenya on September 13 2019. By April 30 2021, a total of 652,673 children had received their first dose, 226,498 in Malawi, 238,318 in Ghana and 187,857 in Kenya, representing 76% of the estimated target population of eligible children over that period in Malawi, 70% in Ghana and 82% in Kenya. A total of 494,745 children had received their third dose (173,552 in Malawi, 200,398 in Ghana and 120,795 in Kenya), respectively 64%, 67% and 69% of the estimated target number. When

[2] SAGE/MPAC (2015) Evidence-to-recommendations table on the use of malaria vaccines, 2015. Available at: https://www.who.int/immunization/policy/position_papers/malaria_evidence_recommendations_table.pdf WHO (2016) Malaria vaccine: WHO position paper – January 2016. Weekly epidemiological record Jan 2016 no. 4. 91:33–52 http://www.who.int/wer

[3] In the phase 3 trial, 21 cases of meningitis occurred in RTS,S/AS01 recipients, a rate of 1.05/1000, and one case in control children, a rate of 0.1/1000; the rate ratio was 10.5 (95%CI 1.41,78.0). There were 43 cases of cerebral malaria in RTS,S/AS01 recipients and 10 cases in control children, a rate ratio of 2.15 (1.1,4.3). There were 67 deaths in girls who received RTS,S/AS01 and 17 in girls in the control group, a mortality ratio of 2, while in boys there were 45 deaths in RTS,S/AS01 recipients and 29 in boys in the control group, mortality ratio 0.8. The relative mortality ratio (girls:boys) was 2.61 (95%CI 1.29,5.26).

[4] Statistical Analysis Plan for the MVPE. V3.42, July 2021. https://www.clinicaltrials.gov/ProvidedDocs/65/NCT03806465/SAP_001.pdf
Protocol V9.0, April 2020. https://www.clinicaltrials.gov/ProvidedDocs/65/NCT03806465/Prot_ICF_000.pdf

vaccination coverage was assessed in Malawi in a survey conducted in March 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, a 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 of the third dose was 9.7 months and 90% of third doses were received by 13.4 months of age. In Kenya, a survey in May to July 2021, assessing coverage in children due for dose 1 between Dec 2019 and Jan 2021, found 78.6% of children 12-23 months of age had received the first dose and 62.3% the third dose. The median age of the third dose was 9.0 months and 90% of third doses were received by 11.0 months of age.

In each country, uptake of RTS,S/AS01 appeared equitable, with similar coverage across wealth rankings based on household assets, and by gender.

When uptake of RTS,S/AS01 was compared in relation to whether the child had slept under a treated bednet the night before the survey, in Ghana 60% of those not using a net had received three doses of the malaria vaccine compared to 71% among those who did use a net, while in Malawi the corresponding estimates were 55% in those not using a net and 66% among net users, and in Kenya, 51.4% among non-users and 63.2% among net users.

Preliminary results from the surveys in Ghana and Malawi indicate that RTS,S/AS01 introduction did not influence uptake of other childhood vaccines, or use of insecticide-treated bednets, and there was no evidence of changes in care-seeking behaviour associated with receipt of the malaria vaccine.

In each country, coverage of the first dose of RTS,S/AS01 was less than for the first dose of measles-containing vaccine, indicating that there are missed opportunities for RTS,S/AS01 vaccination when children attend for measles vaccine. In Ghana, coverage of the first dose of RTS,S/AS01 was 75.0% compared to 88.3% for the first dose of measles-containing vaccine. The corresponding estimates in Malawi were 72.5% for the first dose of RTS,S/AS01 and 79.7% for the first dose of measles vaccine, and in Kenya, 78.6% for RTSS-1 and 90.9% for measles vaccine.

The first children were eligible for their fourth dose of vaccine in September 2020 in Malawi, in November 2020 in Ghana and in March 2021 in Kenya. By April 2021, a total of 79,523 children had received their fourth dose, 33,509, 35,209 and 10,805 in Malawi, Ghana and Kenya, representing 40%, 40% and 64% of the respective estimated target numbers. Coverage of the 4th dose will be assessed through surveys in 2022.

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, and 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.

In children in implementation areas who were under 48 months of age but were too old, by at least 2 months, when the vaccine was introduced to have been eligible to receive RTS,S/AS01, (again out of those with an HBR), 1.9% of children in Malawi and 2.9% in Ghana had documented receipt of RTS,S/AS01. Older children were not surveyed in Kenya.

By April 2021, the youngest children to be vaccinated at the start of vaccine introduction, who were aged 5 months in Malawi and 6 months in Ghana and Kenya, would have been aged 29 months in Malawi, 30 months in Ghana, and 30 months in Kenya. In Kenya, at the start of vaccine introduction, children up to 11 months of age could be vaccinated with their first dose. Thus the oldest child to have been vaccinated in Kenya at the start of the programme would have been aged 30 months by April 2021. Guidelines in Ghana at the start of vaccine introduction limited administration of the first dose to children 6 and 7 months old, and in Malawi to children aged 5 months. Therefore, the results of the evaluation to April 2021 refer to children aged between 5 and 30 months (Figure 1).

Hospital surveillance:

Across the three countries there was a total of 27,678 admissions to sentinel hospitals in children 1-59 months, during the period from vaccine introduction until the end of April 30th 2021, 13,918 in areas where the vaccine was provided (implementation areas), of which 4,853 were vaccine-eligible based on their date of birth, and 13,760 in comparison areas, 5,141 being eligible by the same criteria. Among vaccine-eligible children, 2,156 of the admissions in implementation areas were for conditions unlikely to be directly affected by the malaria vaccine (patients who did not have malaria or anaemia, and also excluding patients with meningitis), compared to 2,245 admissions in children who were too young to receive the malaria vaccine, or too old when the malaria vaccine was introduced. In comparison areas, the number corresponding number of admissions (excluding malaria, anaemia and meningitis), was in a similar ratio, 2,003 among those who would have been eligible for the malaria vaccine and 2,062 among those who would not have been eligible. The pooled estimate across the three countries of the incidence rate ratio for hospital admission with conditions excluding malaria and anaemia (and meningitis), among vaccine-eligible children, in implementation areas compared to comparison areas, was 1.05 (95% confidence interval 0.95, 1.17), indicating that the implementation and comparison areas were broadly comparable with respect to admission with conditions that were unlikely to be affected directly by the malaria vaccine.

Mortality surveillance:

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 the deaths to March, 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%). In Malawi, it was possible to estimate population denominators using data from the 2018 census and then to compare the rates of mortality with mortality estimates from the census. The population under 5 years of age in each areas in the implementation and comparison regions was estimated using projections from the 2018 census and population estimates for facility catchments provided by the EPI programme. The age structure was estimated based on projected number of births in each area and census estimates of the infant and child survival for each district. The total person time in children aged 1-59 months, during the surveillance period, was 1,681,572 person years, during this time a total of 7359 deaths were reported in this age group, a rate of 4.38/1000 (both sexes combined). This is similar to the national estimate derived from the 2018 census of 5.08[5] (both sexes combined). In Kenya and Ghana recent census data are not available (in Kenya, full results from the 2019 census are not available yet, in Ghana the 2021 census was recently completed).

[5] The national estimate of under-5 mortality, ${}_5q_0$, in Malawi from the 2018 census is 44 per 1000 live births. Subtracting the neonatal mortality of 19.8/1000, and converting to mortality rate per 1000 person years, gives a national mortality rate 1-59 months of 5.08/1000 person years. The weighted average of district estimates from the census gives an estimate of 5.17/100 person years 1-59 months for MVIP areas.

Safety:

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 cerebro-spinal 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 (Figure 4). 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, if it had occurred. Of the patients with probable or confirmed meningitis in vaccine-eligible age groups from implementation areas, 41% (11/27) had received 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*).

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 5). Among these, there were 55 cases of cerebral malaria (positive for *P.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%CI 0.44, 1.35). The incidence rate ratio for admission with other forms of severe malaria excluding cerebral malaria was 0.70 (95%CI 0.54, 0.89). There was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria (relative rate ratio 0.94 (95%CI 0.57, 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 (unresponsive) on the AVPU score. 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).

Of the patients with cerebral malaria in vaccine-eligible age groups from implementation areas, 47% (23/49) had received RTS,S/AS01 vaccine, compared to 53% (2479/4650) of all other admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 1.03, 95%CI 0.56,1.90; the odds ratio among cases meeting the stricter definition requiring an LP, was 1.58, 95%CI 0.66,3.80).

There was therefore no evidence that introduction of the malaria vaccine led to an increase in the incidence of hospital admission with cerebral malaria.

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 (Figure 6). In children who were not eligible to have received the vaccine there were 4218 deaths in implementing regions and 3874 in comparison regions. The mortality ratio in the vaccine-eligible age group (eligible for three doses) between implementing and comparison regions, was 0.93 (95%CI 0.84,1.03), a 7% reduction (95%CI -3%,16%). There was no evidence that the mortality ratio differed between girls and boys, the p-value for this interaction was 0.343. The mortality ratio in girls was 0.98 and in boys 0.90, the relative mortality ratio (girls:boys) was 1.08 (95%CI 0.92,1.28). 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).

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 12-23month olds, coverage of the first dose of RTS,S/AS01 was slightly higher in girls than boys (77.6% in girls and 73.0% in boys in Ghana and 75.1% in girls and 70.1% in boys in Malawi, and 79.0% in girls and 78.2% in boys in Kenya), and similarly for the third dose ().

Impact:

Hospital admission with severe malaria among children eligible to have received three doses of RTS,S/AS01:

Among children eligible to have received all three primary doses of RTS,S/AS01, there was 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 implementing and comparison areas was 0.70 (95%CI 0.54, 0.92), a reduction of 30% (95%CI 8%, 46%), again there was no evidence that effectiveness differed between cerebral malaria and other forms of severe malaria. When cases were excluded if they had impaired consciousness or convulsions but had not had an LP performed to exclude meningitis, and they did not fulfil other criteria for severe malaria (severe anaemia or respiratory distress), there was a total

of 873 severe malaria cases in age groups eligible to have received three doses of malaria vaccine, 324 from implementation areas and 549 from comparison areas. In non-eligible age groups there were 989 cases from implementation areas and 1026 from comparison areas. The incidence rate ratio comparing incidence of admission with severe malaria between implementing and comparison areas was 0.65 (95%CI 0.49, 0.86).

Of the patients with severe malaria in vaccine-eligible age groups from implementation areas, 30% (123/415) had received 3 doses of RTS,S/AS01 vaccine, compared to 47% (1384/2951) of all other admissions in this age group from implementation areas (odds ratio, adjusted for country and age, 0.49, 95%CI 0.39,0.61).

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).

Hospital admissions of patients 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%).

All-cause hospital admission:

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%).

Strengths and limitations:

The evaluation was well powered to detect safety signals observed in the phase 3 trial if they had occurred. Hospital surveillance was strengthened and standardised to optimize detection and diagnosis of meningitis and severe malaria. Where we were able to assess completeness of mortality surveillance, in Malawi, the rates of mortality were similar to estimates from the recent census. Using data from household surveys on coverage and timing of the first dose of RTS,S/AS01 we estimated that the proportion of vaccinated person time in implementation areas would have been at least 60%, and less than 5% in comparison areas, and less than 2% in non-eligible age groups in implementation areas (Figure 3). We estimated that the meningitis signal in the phase 3 trial would then translate to a rate ratio of 3.9, and the cerebral malaria signal would translate to a rate ratio of 1.6. The 95% confidence intervals for the pooled estimates obtained during this evaluation exclude these values (Table 2). The relative mortality ratio between girls and boys in the phase 3 trial (i.e. the ratio of mortality in girls who received RTS,S/AS01 to that in girls in the control group, divided by the corresponding ratio in boys) was 2.6, this would translate to a relative mortality ratio of 1.8 if it occurred in the pilot implementation areas. The estimate of the mortality ratio between implementation and comparison regions, for girls, was similar to that for boys, and the ratio of the effect in girls to that in boys was 1.08, with a narrow confidence interval (95%CI 0.93,1.25) that

excludes a gender interaction such as that observed in the phase 3 trial. There was similarly no evidence of interaction when analysis was limited to eligible children above 18 months of age.

The impact on severe malaria is consistent with impact that would be expected on the basis of the efficacy observed in the phase 3 trial and given the level of uptake of the vaccine in implementation areas[6].

The observed reductions in all-cause hospital admissions, and all cause mortality, were associated with more uncertainty, but the point estimates were consistent with the impact on severe malaria. Severe malaria accounted for about 20% of all admissions to sentinel hospitals in eligible age groups in comparison areas, so a reduction of 30% in severe cases equates to about an expected 6% reduction in all cause admissions, similar to what was observed. If vaccine effectiveness against malaria deaths is similar to that for admission with severe malaria, the point estimate of a reduction of 7% in mortality would be consistent with about 23% of deaths (excluding injuries) being caused by malaria in these populations and age groups.

The use of data for non-eligible age groups aimed to control for underlying differences between intervention and comparator areas. Randomization balance was assessed, for hospital surveillance, in terms of comparability in admissions with conditions unlikely to be affected by the vaccine, which appeared well balanced overall. But imbalance with respect to the outcomes of interest cannot be excluded and may have influenced results. There was variability in point estimates of effects between countries but there was wide uncertainty around these. The analyses were powered only for pooled analysis across the three countries.

Contamination due to the malaria vaccine being received by children in comparison areas, or by children in non-eligible age groups in implementing areas, could have diluted estimates of effects. These effects have been allowed for, using survey estimates of the proportion of children in comparison areas who received the malaria vaccine, and of the proportion of non-eligible children in comparison and implementation areas who received the vaccine. Misclassification of events to clusters or age groups, could have occurred. Efforts were made to verify cluster assignments based on village of residence, but there could have been some misclassifications. Children just outside the age range for eligibility, but who might have received the vaccine, were excluded from the non-eligible group during analysis to reduce bias. Dates of birth were verified from documents where possible but errors in age could have led to misclassification of age group.

However, the fact that the impact observed against severe malaria was consistent with the expected impact, and the consistent point estimates for other impact outcomes, argue against dilution effects having been significantly under-estimated.

Confounding, whereby malaria vaccine uptake is associated with underlying risks of malaria, meningitis or mortality, could influence estimates of effects. However, we found no association between EPI coverage and malaria prevalence during baseline surveys, and with respect to

[6] We estimated, using data for Malawi as an example, the proportion of person time accounted for by children who had received their third dose and among these the proportion of person time within 6 months of the third dose, when the vaccine is most effective, the proportion 6-12 months since the third dose, and the proportion more than 12 months since the third dose. These periods were associated with vaccine efficacies against clinical malaria of 67.6%, 38.9% and 27.9% in the phase 3 trial. The proportions of person time in these periods were estimated using information on age of receipt of RTS,S/AS01 doses in the coverage surveys. These proportions were 0.6, 0.32, 0.08, giving a mean efficacy of 55%. The fraction of person time vaccinated with 3 doses was 45%. The product (0.55x0.45) gives an expected reduction in the incidence of malaria of 25% in Malawi.

meningitis, although children who received the malaria vaccine were more likely to have previously received pneumococcal vaccine and Hib vaccine than children who did not receive the malaria vaccine, which might mask an effect of the malaria vaccine on meningitis risk, we observed that vaccine serotypes of Hib and pneumococcus were relatively uncommon when CSF samples were investigated by PCR .

Vaccination status was assessed from the home-based records where possible, and otherwise from caregiver recall, but caregiver recall of vaccination status appeared unreliable. This was a limitation of the analysis of vaccination status of children who died, as vaccine documentation was available for only 40% of deaths. Vaccine documentation was better for hospital patients. Records were available for 82% of vaccine-eligible hospital patients from implementation areas. And during the household surveys, a high proportion of children had a vaccine record available, over 90% of children in Ghana and over 80% in Malawi and Kenya.

Key points:

- High, equitable coverage of the primary three doses of RTS,S/AS01 was achieved in all three countries. In Malawi, where 86.2% of children 12-23months old had received DTP3, and 72.5% had received their first dose of RTS,S/AS01 and 62.3% received their third dose. In Ghana, where DTP3 coverage was 93.4%, 75% of children had received the first dose of RTS,S/AS01 and 67% three doses. In Kenya, DTP3 coverage was 93.7%, 78.6% of children had received the first dose of RTS,S/AS01 and 62.35 the third dose.
- The evaluation over the first 24 months of the MVPE was well powered to detect effects of RTS,S/AS01 introduction on the incidence of hospital admission with meningitis and with cerebral malaria in pooled analysis of the data from the three MVIP countries. Sufficient events were observed to allow effects of the magnitude observed in the phase 3 trial to be detected if they occurred, with 90% power, after allowing for the level of vaccine coverage.
- There was no evidence that RTS,S/AS01 introduction increased incidence of hospital admission with meningitis. The incidence rate ratio (RTS,S:comparator) was 0.81 (95%CI 0.43,1.55).
- There was no evidence that RTS,S/AS01 introduction was associated with an increase in hospital admission with cerebral malaria. The incidence rate ratio for admission with cerebral malaria was 0.77 (95%CI 0.44,1.35), and 0.96 (0.61,1.52) when a broader definition was used, and 0.66 (95%CI 0.31, 1.43) when a narrower definition was used. There was also no evidence that RTS,S/AS01 introduction was less effective against hospital admission with cerebral malaria than with other forms of severe malaria.
- The evaluation was not powered at this time point to assess impact of vaccine introduction on mortality but the evaluation was well powered to detect gender imbalance in all-cause mortality of the magnitude observed in the phase 3 trial, in children up to about 2yrs of age. 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.
- RTS,S/AS01 introduction was associated with a reduction in incidence of hospital admission with severe malaria, the reduction of 30% was consistent with the reduction that would be expected on the basis of the efficacy observed in the phase 3 trial, given the level of coverage of 3 doses of RTS,S/AS01 achieved in the evaluation areas.

- Continued evaluation will assess the impact of the 4th dose in each country, and impact of vaccine introduction on mortality.

Figures and Tables:

The age distribution of eligible children in the pilot areas in each country is shown in Figure 1. The number of children given their first dose of RTS,S/AS01 in each month, is shown in Figure 2, and the estimated proportion of eligible children who had received their first dose of RTS,S/AS01, by month of age, is shown in Figure 3. Figures 4-6 show the number of cases of meningitis, severe malaria, and the number of deaths, by age, in eligible age groups in each country.

Table 1 shows the rate ratios for the impact outcomes. Table 2 gives a comparison of the rate ratios for the safety outcomes with the rate ratios that would have been expected if the safety signals in the phase 3 trial had occurred during the pilot implementations. Tables 3 and 4 give the baseline characteristics of implementation and comparison areas that were used during randomization. Table 5 summarises results from the household surveys of RTS,S/AS01 coverage.

Statistical methods, and country-specific estimates for each outcome, are given in Annex 1.

Figure 1. Distribution by age of total person years, up to April 30 2021, in children eligible to have received at least one dose of RTS,S/AS01, in each country.

In Malawi, the estimates are based on denominators derived from the 2018 national census (estimates for the population in comparison areas in hospital catchments, are shown). In Ghana and Kenya, exact denominators have not been estimated, the approximate age pattern is shown. In Malawi, the first dose of RTS,S/AS01 was provided for children aged 5 months, starting on April 23 2019. In Ghana, the first dose was provided for children aged 6 and 7 months, starting April 30 2019. In Kenya, the first dose was given to children from 6 to 11 months of age, starting Sep 13 2019.

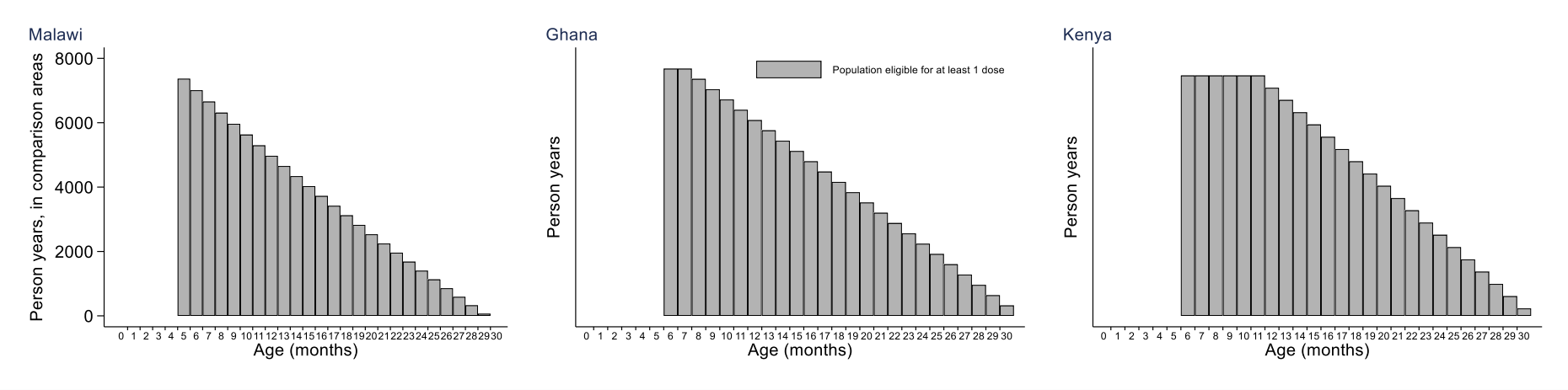


Figure 2: Total Number of first RTSS doses (RTSS-1) administered per month, in each country, up to April 2021.

When the vaccine was first introduced, in Malawi, vaccine administration was limited to children 5 months of age; in Ghana, to children 6 and 7 months of age, and in Kenya, to children 6 to 11 months of age. Vaccine administration started on April 23 2019 in Malawi, and Sep 13 2019 in Kenya, the data for the first month therefore reflects that vaccine was delivered for only part of the month. In Ghana, delivery started on April 30 2019.

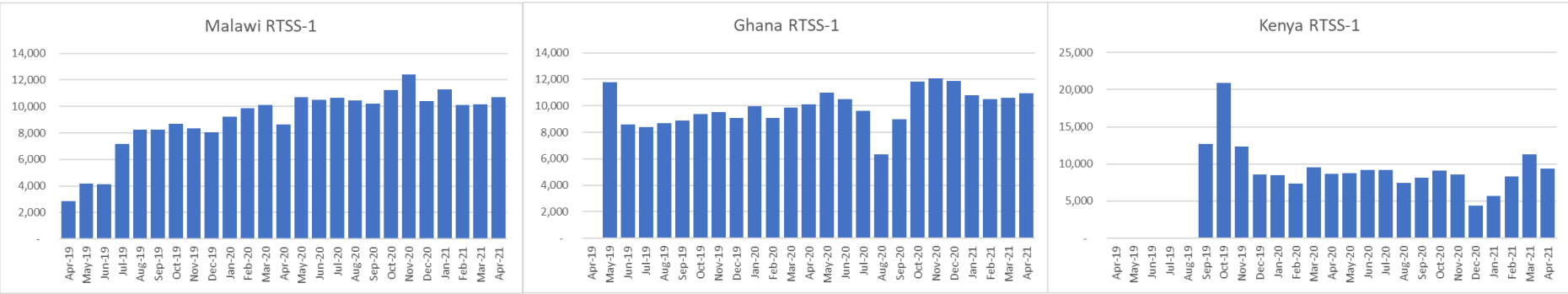


Figure 3. A: Estimated proportion of vaccinated person time, by age, in eligible age groups in implementation areas in Malawi, Ghana and Kenya.

The proportion of children in implementation areas who had received their first dose of RTS,S/AS01 was estimated for each month of age, was estimated from the household surveys in each country. The overall proportion of vaccinated person time, across all ages, was 0.668 (Kenya), 0.690 (Ghana) and 0.611 (Malawi).

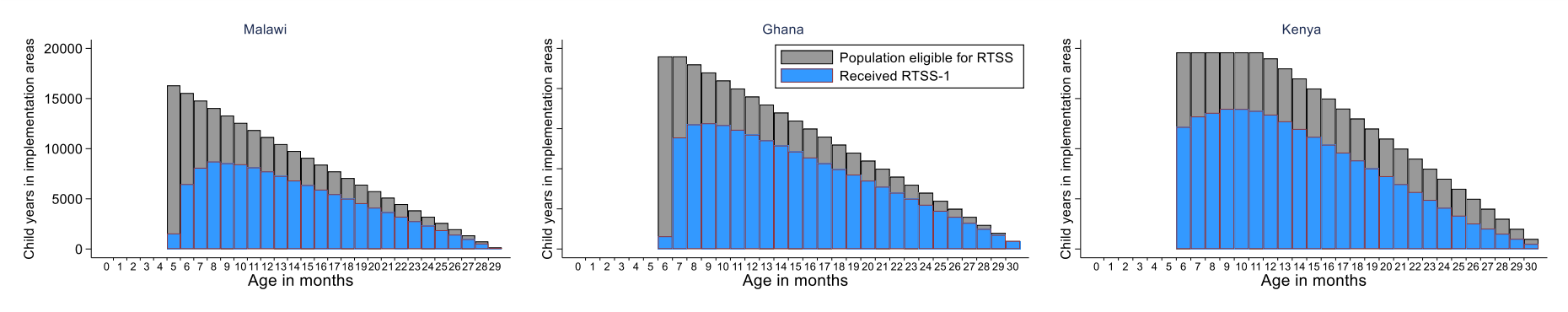


Figure 4. Age distribution of meningitis cases (probable and confirmed cases) admitted to sentinel hospitals from both implementation and comparison areas, up to April 30 2021, in age groups who would have been eligible to receive (at least one dose of) the malaria vaccine, in each country.

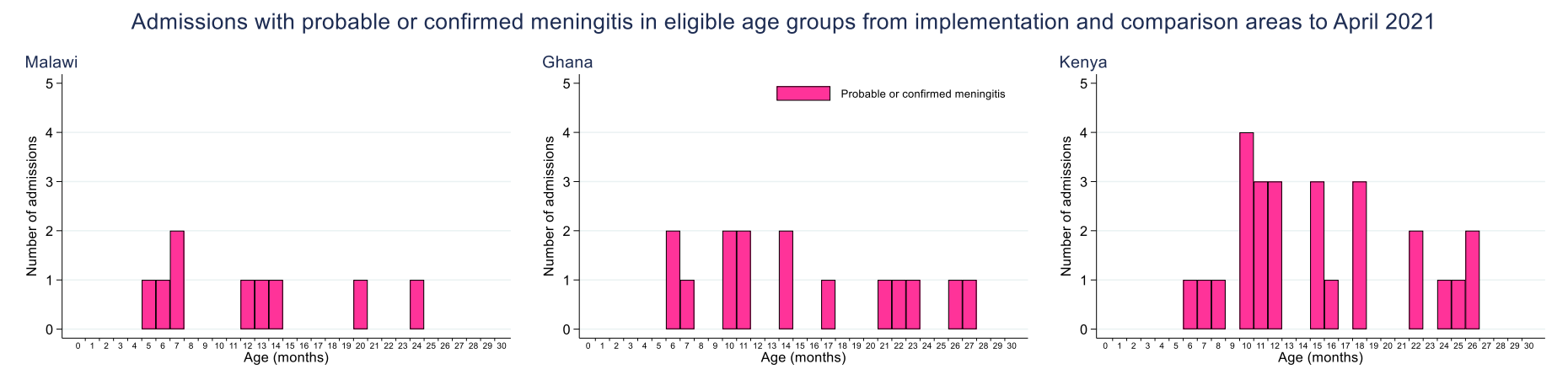


Figure 5. Age distribution of severe malaria cases from comparison areas admitted to sentinel hospitals up to April 30 2021, in age groups who would have been eligible to receive (at least 1 dose) of the malaria vaccine.

The bars indicate the number of severe cases, the number of these that had severe malaria anaemia, and the number that had cerebral malaria. (The figure is not intended to show the degree of overlap between the different forms of severe malaria).

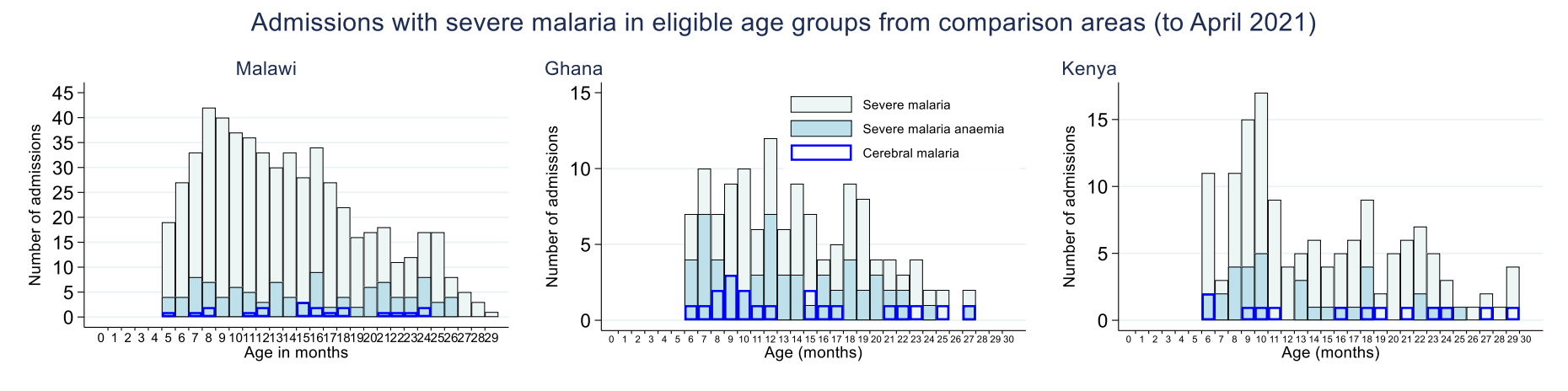


Figure 6: Age distribution of deaths due to any cause except injury, occurring in comparison areas up to March 31 2021, in age groups who would have been eligible to have received at least one dose of RTS,S/AS01, in each country.

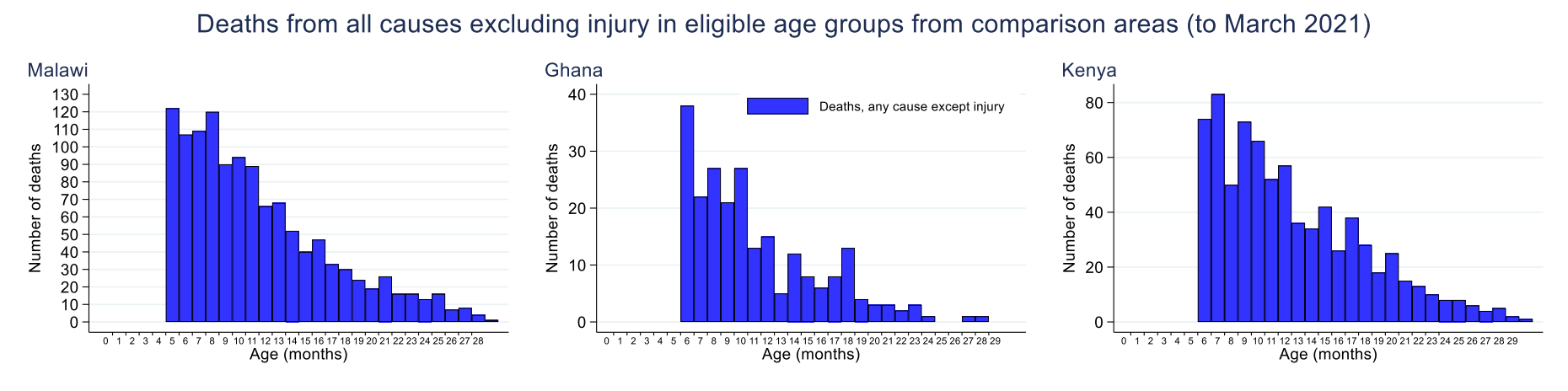


Table 1: Summary of impact outcomes:

Outcome	No. of events in eligible age groups[1]		Rate ratio (95%CI)	% impact[2] (95% confidence interval)
	Implementing	Comparison		
Hospital admission with severe malaria[3]	418	689	0.70 (0.54, 0.92)	30% (8.0%,46%)
Hospital admission with severe malaria[4]	324	549	0.65 (0.49, 0.86)	35% (14%,51%)
Mortality due to all causes excluding injuries[5]	1421	1443	0.93 (0.84,1.03)	7.0% (-3.0%,16%)
Hospital admission for any cause[6]	3340	3678	0.92 (0.83, 1.03)	8.0% (-3.0%,17%)
Hospital admission with a positive malaria test	1119	1606	0.79 (0.68, 0.93)	21% (7.0%,32%)
Hospital admission with severe malaria anaemia	131	153	0.78 (0.55, 1.09)	22% (-9.0%,45%)

1: Number of cases by area are given for the age-eligible population. Rate ratios were estimated by comparing the ratio of events in eligible to non-eligible children in implementation areas, with the corresponding ratio in comparison areas (Annex 1).

2: percentage reduction in incidence associated with introduction of the RTS,S/AS01 vaccine, among the age group of children eligible to have received three doses of the vaccine.

3: Severe malaria definition: *P. falciparum* infection detected by RDT microscopy AND one or more of the following: a) impaired consciousness (Glasgow coma score<11, Blantyre coma score<3, or assessed as P or U on the AVPU score and CSF findings not consistent with probable or confirmed meningitis; b) multiple of atypical convulsions (more than two episodes within 24 hours or prolonged (>15minutes), or focal) and CSF findings not consistent with probable or confirmed meningitis; c) respiratory distress (manifested as chest indrawing or deep breathing); d) severe malaria anaemia (haemoglobin concentration <5g/dL or haematocrit <15%).

4: Severe malaria, defined as above, but excluding cases if they had impaired consciousness or convulsions but had not had an LP performed to exclude meningitis, and they did not fulfil other criteria for severe malaria (severe anaemia or respiratory distress).

5: Death due to any cause excluding injury (InterVA code 12).

6: A stay in hospital/inpatient facility for at least one night, (and patients who were admitted but died before an overnight stay was completed).

Table 2: Comparison with safety signals observed in the phase 3 trial[1]

Outcome	Rate ratio in the phase 3 trial[2] (95%CI)	Rate ratio of the phase 3 trial, adjusted for MVIP coverage[3] (95%CI)	Rate ratio in the MVIP (95%CI)	z	p-value
Meningitis	10.5 (1.41,78.0)	3.92 (1.22,12.6)	0.81 (0.43, 1.55)	2.31	0.0207
Cerebral malaria[4]	2.15 (1.1,4.3)	1.60 (1.05,2.43)	0.77 (0.44, 1.35)	2.06	0.0397
Cerebral malaria[5]		1.60 (1.05,2.43)	0.96 (0.61, 1.52)	1.62	0.1049
Mortality ratio[6]	2.61 (1.29,5.26)	1.83 (1.17,2.85)	1.08 (0.93, 1.25)	2.19	0.0285

1: If the safety signals observed in the phase 3 trial occurred in the MVIP, the magnitude of the effect we would observe would be smaller than in the phase 3 trial, since not all children will have received the vaccine. Any effects would be further diluted if there was contamination due to some children in comparison areas, or children in non-eligible age groups, receiving the vaccine. We used estimates of coverage and timing of malaria vaccine doses from the household surveys in each country to estimate the person time in vaccinated children as a proportion of total person time, and the degree of contamination. These estimates were used to calculate the expected effect in each country, if the safety signals in the phase 3 trial had occurred in the pilot. The average of these effects for each outcome is shown in column 2, and compared with the observed rate ratio from the MVIP (column 3) using a z-test. For each safety outcome, the observed rate ratio in the MVIP was inconsistent with the signal in the phase 3 trial. The hypothesis that the signal observed in the phase 3 trial occurred in the MVIP, given the degree of dilution that was estimated, was rejected ($p<0.05$), except when the broader case definition for cerebral malaria was used (including cases in whom lumbar puncture had not been performed), when the p-value was 0.1049.

2: Rate ratio in the phase 3 trial comparing the combined vaccine groups (R3R and R3R) with the control group, from month 0 to study end.

3: In each country the expected rate ratio for each safety outcome, if the safety signal from the phase 3 were to have occurred in the MVIP, was estimated as $R'=[(Rc+1-c)/(Rd+1-d)]/[(Rf+1-f)/(Rg+1-g)]$, where R is the rate ratio in the phase 3 trial, c is the proportion of vaccinated person time in implementation areas in eligible age groups, d the proportion in comparison areas in eligible age groups, and f and g are the corresponding values in non-eligible groups, for that country. The average across the three countries was calculated as $\exp[\Sigma w_i \log(R_i')]$, where the weights w_i are the normalised weights used to obtain the pooled estimate of the rate ratio (column 3) for that outcome (as detailed in Annex 1), so that the comparison is based on the same relative weightings of the three countries. The estimates used were c=0.611 in Malawi, 0.690 in Ghana and 0.668 in Kenya (Figure 3); the corresponding proportions in comparison areas were d=0.016, 0.056, 0.087, and in non-eligible age groups in implementation areas, f=0.016 in Malawi and 0.027 in Ghana and Kenya. We (conservatively) assumed g=0 in each country.

4: Cerebral malaria, MVIP cases in which lumbar puncture had been performed to exclude cases with probable meningitis.

5: Cerebral malaria, using, for MVIP, a case definition broadened to include cases in which lumbar puncture had not been performed.

6: The mortality ratio, in the phase 3 trial, was defined as the ratio of the mortality rate between vaccine recipients and controls, for girls, relative to that for boys.

Table 3. Baseline characteristics of the malaria vaccine pilot area (variables used for randomisation constraints):

	Ghana		Kenya		Malawi	
	Vaccinating	**Comparison**	**Vaccinating**	**Comparison**	**Vaccinating**	**Comparison**
Number of clusters, N	33	33	23	23	23	23
Surviving infants, N (Total; cluster-level median [min-max])	128624; 3490 [912-7026]	133702; 3700 [1202-8954]	126698; 5296 [3736-8805]	125747; 5275 [2702-10739]	107728; 4536 [2816-6931]	113997; 4831 [3026-8112]
Parasite prevalence, % (cluster-level median [min-max])	22% [12-52]	21% [11-45]	21% [7-43]	19% [5-43]	19% [6-39]	20% [6-46]
Coverage of pentavalent dose 1, % (cluster-level mean [min-max])	99% [61-162]	97% [51-141]	71% [26-126]	74% [55-94]	89% [60-114]	93% [59-135]
Coverage of pentavalent dose 3, % (cluster-level mean [min-max])	96% [61-138]	99% [50-140]	63% [26-113]	66% [51-85]	85% [54-103]	87% [57-151]
Coverage of measles dose 1, % (cluster-level mean [min-max])	93% [67-136]	95% [46-172]	65% [31-120]	66% [52-83]	83% [51-107]	81% [49-122]
Number of hospitals, N	39; 1.45 [0-5]	42; 1.55 [0-5]	30; 1.35 [0-3]	30; 1.30 [0-4]	10; 1.08 [0-2]	10; 1.08 [0-2]
Number of health centers, N (Total; cluster-level median [min-max])	153; 4.22 [2-13]	155; 3.76 [1-15]	90; 3.27 [1-10]	93; 3.43 [0-10]	66; 2.84 [0-6]	66; 2.64 [1-5]
Number of dispensaries, N (Total; cluster-level median [min-max])	799; 21.73 [9-62]	776; 21.14 [6-47]	314; 11.90 [5-32]	320; 12.90 [6-29]	18; 1.60 [0-3]	18; 1.19 [0-3]

Table 4. Baseline characteristics of the malaria vaccine pilot area, restricted to clusters within the pre-defined sentinel hospital areas

	Ghana		Kenya		Malawi	
	Vaccinating	**Comparison**	**Vaccinating**	**Comparison**	**Vaccinating**	**Comparison**
Number of sentinel hospitals	8		6		4	
Number of clusters, N	15	17	16	12	8	9
Surviving infants, N (Total; cluster-level median [min-max])	71992; 4419 [1379-7026]	76097; 3994 [1202-8954]	87824; 5222 [3736-8805]	67836; 5414 [3487-10739]	37908; 4490 [2816-6931]	49039; 5309 [3670-8112]
Parasite prevalence, % (cluster-level median [min-max])	21% [12-52]	19% [11-45]	23% [9-43]	19% [10-43]	15% [6-36]	21% [10-46]
Coverage of pentavalent dose 1, % (cluster-level mean [min-max])	99% [63-162]	93% [51-109]	69% [26-126]	76% [59-94]	86% [63-100]	90% [78-117]
Coverage of pentavalent dose 3, % (cluster-level mean [min-max])	94% [61-137]	95% [50-118]	61% [26-113]	67% [53-82]	84% [56-103]	84% [70-118]
Coverage of measles dose 1, % (cluster-level mean [min-max])	91% [67-136]	91% [46-117]	64% [31-120]	69% [52-83]	82% [51-103]	78% [63-99]
Number of hospitals, N	25; 1.92 [0-5]	26; 1.94 [0-5]	21; 1.36 [0-3]	15; 1.29 [0-2]	3; 1.41 [0-2]	5; 1.19 [0-2]
Number of health centers, N (Total; cluster-level median [min-max])	73; 4.26 [2-13]	82; 4.08 [1-12]	58; 3.11 [1-8]	56; 3.99 [2-10]	24; 3.12 [0-6]	26; 2.74 [2-5]
Number of dispensaries, N (Total; cluster-level median [min-max])	423; 25.74 [10-62]	433; 22.54 [6-47]	214; 12.04 [5-27]	152; 11.68 [6-22]	4; 1.00 [0-1]	7; 1.12 [0-2]

Table 5. RTS,S/AS01 vaccine uptake from household surveys of children aged 12-23 months

	Ghana	Kenya	Malawi
Month of survey	November 2020	May – July 2021	March 2021
Period when children surveyed were due to have received their first dose of RTS,S/AS01	Jun 2019 – May 2020	Dec 2019-Jan 2021	Sep 2019 – Aug 2020
No. with home-based record of vaccination (HBR)/no. surveyed (%)	1082/1179 (91.8%)	1395/1438 (98.0%)	1082/1184 (91.4%)
Coverage of 1st dose by HBR (by HBR or recall)	79.7% (75.2%)	79.5% (78.6%)	74.1% (72.5%)
Coverage of 3rd dose by HBR (by HBR or recall)	71.2% (67.0%)	65.5% (62.3%)	65.2% (62.3%)
median age of receiving dose 3	9.7 months	9.0 months	8.5 months
90th percentile of age at dose 3	13 months	11.0 months	13 months
% received RTSS-1 in comparison areas by HBR	6.1%	10.2%	1.9%
% received RTSS-1 in older age groups in implementation areas, by HBR	1.1%	Not surveyed	1.9%

Annex 1: Calculation of incidence rate ratios

In each country, the log of the rate ratio comparing the incidence in eligible age groups in RTS,S/AS01 implementation areas with that in comparison areas, was estimated as:

$D = \log(R_1) - \log(R_0)$, where R_1 is the ratio of the number of events in eligible age-groups to the number of events in non-eligible age groups, in implementation areas, and R_0 is the corresponding ratio in comparison areas. The variance of D is $V(D) = V(R_1)/R_1^2 + V(R_0)/R_0^2$, where

$$V(R_j) = \left(\frac{m_j}{(m_j-1)n_{j,B}^2}\right)\sum_{i=1}^{m_j}\left(n_{j,i,A} - R_j n_{j,i,B}\right)^2 \qquad j = 0,1$$

Where m_j is the number of clusters in implementation areas (j=1) or comparison areas (j=0), $n_{j,i,A}$ is the number of events in eligible age groups in cluster i in implementation areas (j=1) or comparison areas (j=0), and $n_{j,i,B}$ the corresponding number in non-eligible age groups, and $n_{j,B}$ is the total events in non-eligible groups in implementation (j=1) or comparison (j=0) areas.

The estimates of D for each country, D_1, D_2 and D_3, were combined to give a pooled estimate $\overline{D} = \sum D_i/V(D_i)/\sum 1/V(D_i)$, i=1..3, with variance $V(\overline{D}) = 1/\sum[1/V(D_i)]$. The pooled rate ratio was then calculated as $\exp(\overline{D})$ and the 100(1-α)% confidence interval given by $\exp[\overline{D} +/- t_{\alpha/2,C-6}\sqrt{V(\overline{D})}]$, with df equal to the total number of clusters C less 2x3=6.

Figure A1. Probable or confirmed meningitis: Rate Ratios for the association between the introduction of RTS,S/AS01 and probable or confirmed meningitis in children age-eligible to receive dose 1.

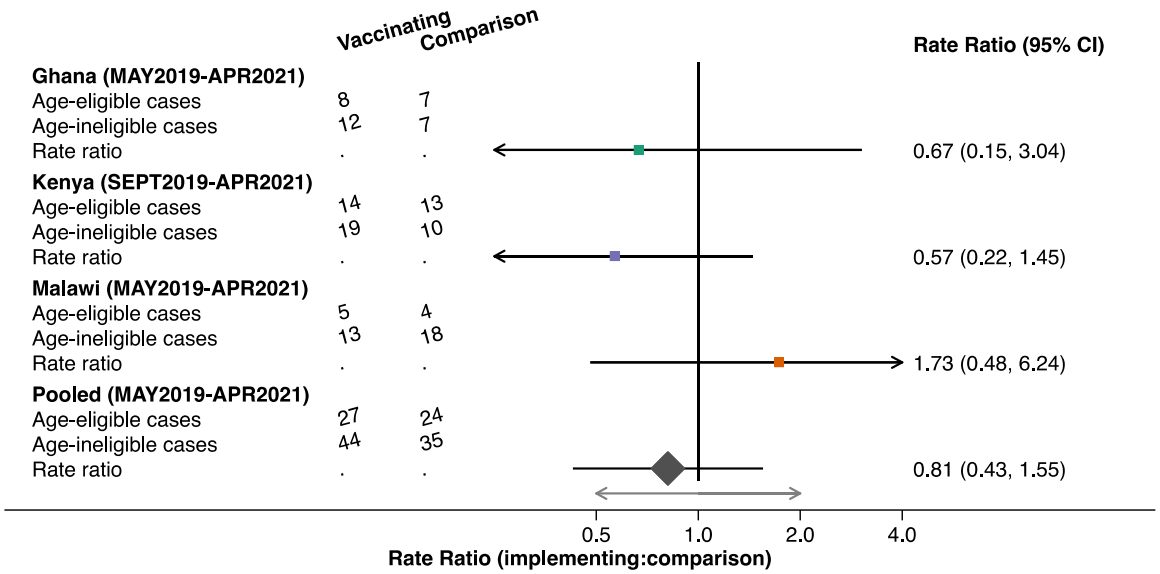


Figure A2. Cerebral malaria: Rate Ratios for the association between the introduction of RTS,S/AS01 and cerebral malaria (including children with malaria and impaired consciousness with unknown meningitis status) in children age-eligible to receive dose 1.

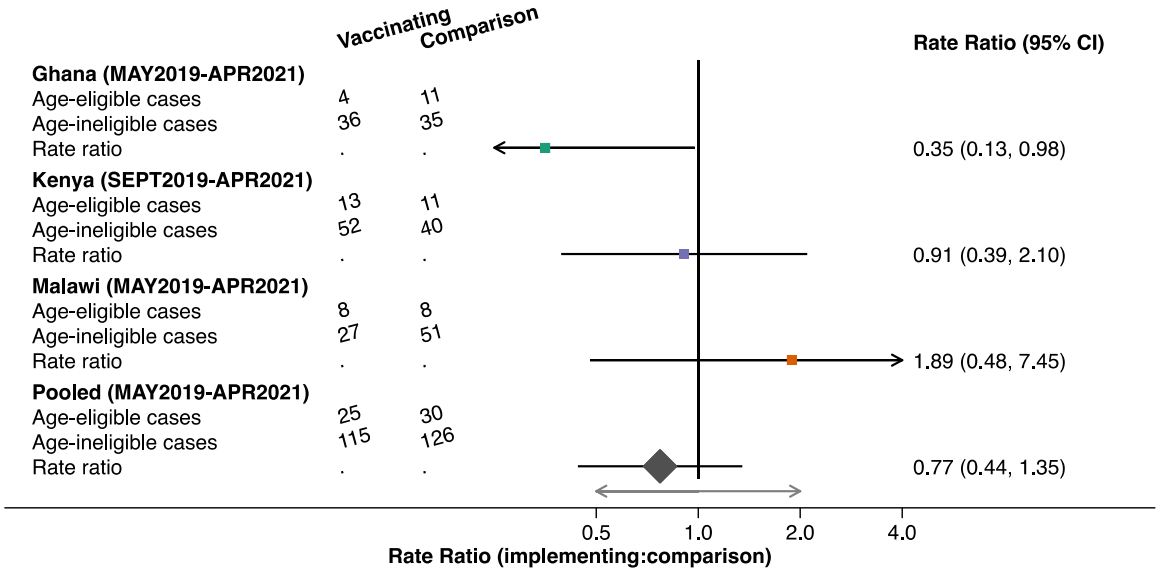


Figure A3. Severe malaria: Rate Ratios for the association between the introduction of RTS,S/AS01 and severe malaria (including children with malaria and impaired consciousness or convulsions with unknown meningitis status) in children age-eligible to have received dose 3.

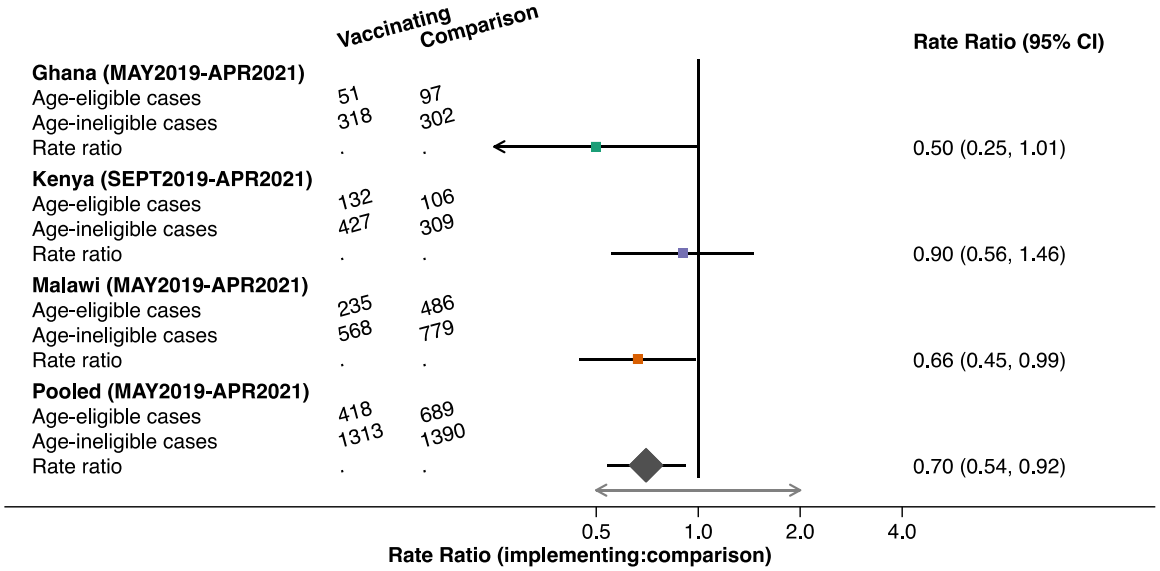
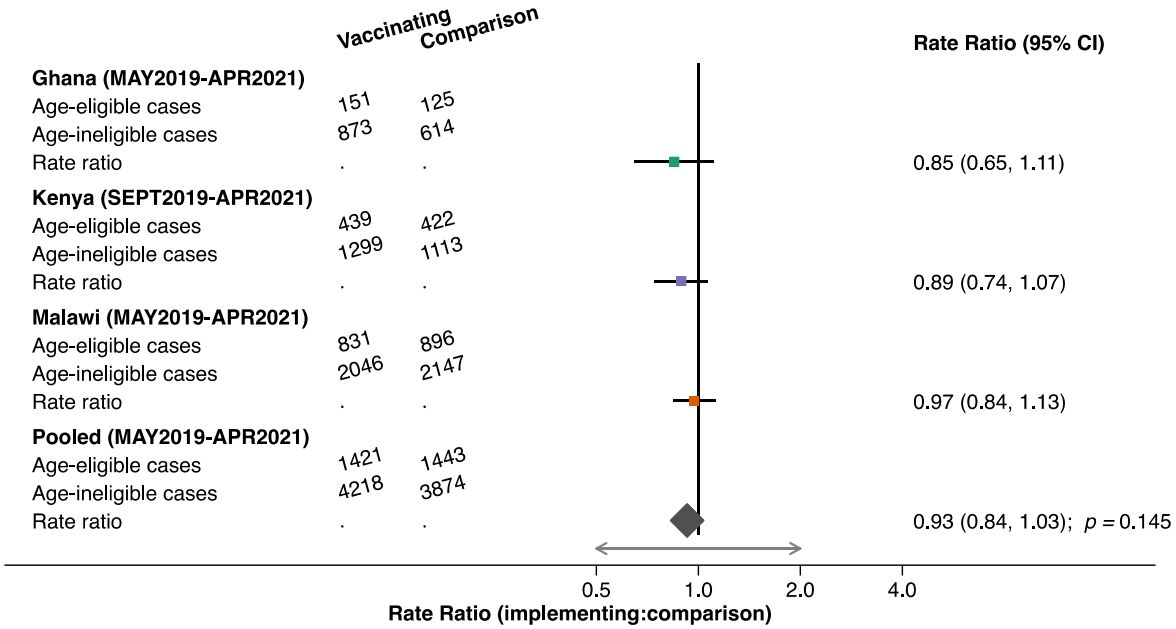


Figure A4. Mortality excluding accidents and trauma (impact population): Rate Ratios for the association between the introduction of RTS,S/AS01 and death (excluding those due to accidents or trauma) in children age-eligible to have received dose 3.



ORIGINAL ARTICLE

Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention

D. Chandramohan, I. Zongo, I. Sagara, M. Cairns, R.-S. Yerbanga, M. Diarra, F. Nikièma, A. Tapily, F. Sompougdou, D. Issiaka, C. Zoungrana, K. Sanogo, A. Haro, M. Kaya, A.-A. Sienou, S. Traore, A. Mahamar, I. Thera, K. Diarra, A. Dolo, I. Kuepfer, P. Snell, P. Milligan, C. Ockenhouse, O. Ofori-Anyinam, H. Tinto, A. Djimde, J.-B. Ouédraogo, A. Dicko, and B. Greenwood

ABSTRACT

BACKGROUND

Malaria control remains a challenge in many parts of the Sahel and sub-Sahel regions of Africa.

METHODS

We conducted an individually randomized, controlled trial to assess whether seasonal vaccination with RTS,S/AS01$_E$ was noninferior to chemoprevention in preventing uncomplicated malaria and whether the two interventions combined were superior to either one alone in preventing uncomplicated malaria and severe malaria-related outcomes.

RESULTS

We randomly assigned 6861 children 5 to 17 months of age to receive sulfadoxine–pyrimethamine and amodiaquine (2287 children [chemoprevention-alone group]), RTS,S/AS01$_E$ (2288 children [vaccine-alone group]), or chemoprevention and RTS,S/AS01$_E$ (2286 children [combination group]). Of these, 1965, 1988, and 1967 children in the three groups, respectively, received the first dose of the assigned intervention and were followed for 3 years. Febrile seizure developed in 5 children the day after receipt of the vaccine, but the children recovered and had no sequelae. There were 305 events of uncomplicated clinical malaria per 1000 person-years at risk in the chemoprevention-alone group, 278 events per 1000 person-years in the vaccine-alone group, and 113 events per 1000 person-years in the combination group. The hazard ratio for the protective efficacy of RTS,S/AS01$_E$ as compared with chemoprevention was 0.92 (95% confidence interval [CI], 0.84 to 1.01), which excluded the prespecified noninferiority margin of 1.20. The protective efficacy of the combination as compared with chemoprevention alone was 62.8% (95% CI, 58.4 to 66.8) against clinical malaria, 70.5% (95% CI, 41.9 to 85.0) against hospital admission with severe malaria according to the World Health Organization definition, and 72.9% (95% CI, 2.9 to 92.4) against death from malaria. The protective efficacy of the combination as compared with the vaccine alone against these outcomes was 59.6% (95% CI, 54.7 to 64.0), 70.6% (95% CI, 42.3 to 85.0), and 75.3% (95% CI, 12.5 to 93.0), respectively.

CONCLUSIONS

Administration of RTS,S/AS01$_E$ was noninferior to chemoprevention in preventing uncomplicated malaria. The combination of these interventions resulted in a substantially lower incidence of uncomplicated malaria, severe malaria, and death from malaria than either intervention alone. (Funded by the Joint Global Health Trials and PATH; ClinicalTrials.gov number, NCT03143218.)

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This article was published on August 25, 2021, at NEJM.org.

DOI: 10.1056/NEJMoa2026330

In many parts of the Sahel and sub-Sahel regions of Africa, malaria transmission is high during a few months of the year.[1] Seasonal malaria chemoprevention, which involves monthly administration of sulfadoxine–pyrimethamine and amodiaquine to young children during the transmission season, is highly effective in preventing malaria.[2] However, despite widespread deployment of seasonal chemoprevention and access to effective diagnosis and treatment, the burden of malaria remains very high in many parts of the Sahel and sub-Sahel regions. Of the 10 African countries classified by the World Health Organization (WHO) as "high burden to high impact" and targeted for enhanced malaria control, 6 are within this region.[3]

In a multicountry, phase 3 trial involving young children,[4] the malaria vaccine RTS,S/AS01$_E$, a viruslike particle expressing the *Plasmodium falciparum* circumsporozoite protein and hepatitis B surface antigen, administered with the adjuvant AS01$_E$, reduced the incidence of malaria,[5] and it is currently being evaluated in a large pilot implementation program in Ghana, Kenya, and Malawi.[6] The protective efficacy of RTS,S/AS01$_E$ is higher during the first few months after vaccination[4,7,8] but then wanes, although not completely.[9] Therefore, we have suggested that RTS,S/AS01$_E$ could be used as a seasonal vaccine in areas in which malaria transmission is highly seasonal, with an annual booster dose administered to vaccine-primed children just before the peak of the transmission season.[10] In this article, we describe the results of a double-blind, randomized, controlled trial involving young children in Burkina Faso and Mali that investigated whether seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine after priming was noninferior to chemoprevention in preventing clinical malaria and whether a combination of the RTS,S/AS01$_E$ vaccine and chemoprevention was superior to either intervention alone.

Methods

Trial Oversight

The trial protocol[11] (available with the full text of this article at NEJM.org) was approved by the ethics committees of the London School of Hygiene and Tropical Medicine; the Ministry of Health of Burkina Faso; the University of Sciences, Techniques, and Technologies of Bamako; and the national regulatory authorities of Burkina Faso and Mali. A data and safety monitoring board reviewed serious adverse events, approved the statistical analysis plan, and archived the locked databases before unblinding. A steering committee provided scientific advice and monitored the progress of the trial. The trial was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and all applicable local regulations. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol. GlaxoSmithKline (GSK) Biologicals donated the RTS,S/AS01$_E$ and Havrix vaccines. Dispersible sulfadoxine–pyrimethamine and amodiaquine and matching placebos were donated by Guilin Pharmaceutical.

Trial Sites and Population

The trial was conducted in Bougouni district and neighboring areas in Mali and in Houndé district in Burkina Faso.[12] Information regarding the trial sites is provided in the Supplementary Methods section and Figure S1 in the Supplementary Appendix, available at NEJM.org.

Enrollment and Randomization

All households with children who would be 5 to 17 months of age on April 1, 2017, within the trial areas were enumerated from February through March 2017. Inclusion and exclusion criteria are listed in the Supplementary Appendix. After written informed consent had been obtained from parents or guardians, an independent statistician randomly assigned eligible children to receive chemoprevention (chemoprevention-alone group), the RTS,S/AS01$_E$ vaccine (vaccine-alone group), or chemoprevention plus RTS,S/AS01$_E$ (combination group). The randomization list used permuted blocks after sorting according to age, sex, area of residence, and previous receipt of chemoprevention. Tablet computers with the randomization list were accessible only to the chief pharmacists. All other investigators and trial staff were unaware of treatment assignments until the locked database for analysis had been archived with the data and safety monitoring board in June 2020. All participating children were given an identity card containing their photograph and a quick response (QR) code that included the child's trial identification number, name, and date of birth. At the time of vaccination or administration of chemoprevention, these cards were scanned to

ensure that the correct intervention was administered.

INTERVENTIONS

All the participating children were given a long-lasting insecticide-treated bed net at the time of enrollment. Children in the vaccine-alone group and the combination group received three doses of RTS,S/AS01$_E$ in April, May, and June 2017, followed by a fourth and fifth dose in June 2018 and June 2019 (Fig. S2). Syringes containing vaccines were prepared by a chief pharmacist and masked with tape to conceal the contents from the administrator, caretakers, and children. The pharmacist and the vaccine administrators had no further role in the trial.

Children in the chemoprevention-alone group and the combination group received four courses of sulfadoxine–pyrimethamine and amodiaquine at monthly intervals each year; children in the vaccine-alone group received four courses of sulfadoxine–pyrimethamine and amodiaquine placebos on that same schedule. Children 12 months of age or older in the chemoprevention-alone group and the combination group received 500 mg of sulfadoxine, 25 mg of pyrimethamine, and 150 mg of amodiaquine on day 1, and an additional 150-mg dose of amodiaquine on days 2 and 3; infants received 250 mg of sulfadoxine, 12.5 mg of pyrimethamine, and 75 mg of amodiaquine on day 1 and 75 mg of amodiaquine on days 2 and 3. The trial drugs were prepared by a pharmacist, who had no further role in the trial, and were placed in resealable envelopes labeled with the QR code. Administration of each dose of sulfadoxine–pyrimethamine and amodiaquine or placebo was directly observed by trial staff at distribution points in trial villages. Children in the chemoprevention-alone group also received three doses of inactivated rabies vaccine (Rabipur)[13] in 2017 and a dose of hepatitis A vaccine (Havrix)[14] in 2018 and 2019.

OUTCOMES

The primary outcome was uncomplicated clinical malaria, defined as a measured temperature of at least 37.5°C or a history of fever within the previous 48 hours and *P. falciparum* parasitemia (parasite density ≥5000 per cubic millimeter) in children who presented to a trial health facility. Prespecified secondary outcomes were hospital admission with malaria, death from malaria, and malaria parasitemia or anemia at the end of the malaria transmission season (see the Supplementary Methods section of the Supplementary Appendix).

SURVEILLANCE

Trial staff based at trial health facilities tested children with suspected malaria with the use of a rapid diagnostic test. Children who were positive were treated with artemether–lumefantrine, and a blood film was obtained for subsequent microscopic examination. Blood films were read by two independent microscopists according to a standardized algorithm.[15] Discrepant readings were resolved by a third reader. The quality of the blood film readings in each country was confirmed by an external reference laboratory (see the Supplementary Methods section in the Supplementary Appendix and Table S1 and Fig. S3).

Each week, 24 randomly selected children in each country were visited at home (8 children per trial group), and a blood film was obtained. Children were also evaluated during a cross-sectional survey conducted 1 month after the last course of chemoprevention at the end of each malaria transmission season to measure hemoglobin level and to obtain a blood film. At the end of the 2018 and the 2019 transmission seasons, 200 randomly selected school-age children who were 6 to 12 years of age (and therefore too old to receive chemoprevention), resided in the trial areas, and were in good health were tested for malaria by means of microscopic examination. If a child was identified as having clinical malaria at a home visit or in a cross-sectional survey, the child was treated with artemether–lumefantrine.

To determine the curative efficacy of the chemoprevention regimen, further informed consent was obtained, and children with asymptomatic malaria parasitemia at the time of the final cross-sectional survey were treated with the same doses of sulfadoxine–pyrimethamine and amodiaquine as those used for the chemoprevention intervention. Blood films were obtained for microscopic analysis on days 1, 2, 4, 7, 14, and 28 after treatment.

Serious adverse events were reported within 72 hours after identification. Deaths that occurred outside a health care facility were assessed by means of verbal autopsy.[16] Assignment of the causes of hospital admissions or deaths that occurred inside or outside the hospital was performed by two physicians who were unaware of the trial-

group assignments. A third independent physician reviewed cases for which there was a disagreement, and a consensus was reached.

STATISTICAL ANALYSIS

The rationale for the trial's sample size is described in the statistical analysis plan, available with the protocol. For the noninferiority comparison, we determined that 2000 children per group would provide 80% power to exclude, at the 2.5% significance level, a difference in the hazard ratio for clinical malaria between the vaccine-alone group and the chemoprevention-alone group of 20% (favoring vaccine alone) over the 3-year trial period. For the superiority comparisons, assuming that the difference in the hazard ratio between the combination group and the vaccine-alone group or the chemoprevention-alone group would be 30% (favoring the combination), we calculated that this sample size would provide close to 100% power to exclude a minimum difference in the hazard ratios of 0% and would give the trial 90% power to exclude a minimum difference in the hazard ratios of 15%.

The primary analysis was performed in the modified intention-to-treat population, which included all eligible children whose parents or guardians provided consent and who received a first dose of trial vaccine or placebo in April 2017. The per-protocol population for each trial year included all children who received all doses of the vaccine and attended all four chemoprevention visits in that year. Secondary outcomes were assessed only in the modified intention-to-treat population. Person-time at risk was calculated from the date of first vaccination until the date of death, the date of permanent emigration, the date consent was withdrawn, the date last seen for children lost to follow-up or who temporarily traveled out of the trial area, or the end of the trial (March 31, 2020).

The hazard ratio for the primary outcome was estimated with the use of Cox regression models, adjusted for trial center, with a robust standard error to account for potential clustering of recurrent episodes of malaria. Protective efficacy (the percent difference in the total number of events over the trial period) was estimated as $(1-\text{hazard ratio}) \times 100$. Effect modification according to trial center and year, prespecified in the statistical analysis plan, was assessed with the use of the Wald test for the interaction term without adjustment for multiple comparisons. Two-sided 90%, 95%, and 99% confidence intervals for the hazard ratio for the comparison of RTS,S/AS01$_E$ alone with chemoprevention alone were calculated and compared with the prespecified noninferiority margin of 1.20. To preserve the type I error rate at 5%, a closed testing procedure was used: the Wald test of the null hypothesis of equal hazard ratios comparing all three groups was performed. If the null hypothesis was rejected at the 5% significance level, pairwise comparisons were performed, also with a 5% significance level. Incidence rate differences and prevalence ratios were calculated with the use of published methods.[17,18] An analysis was conducted to explore patterns of missingness in the outcome data and to assess sensitivity to missing outcome data (Table S8). Full details of the conduct of the trial are provided in the protocol.

RESULTS

VACCINE COVERAGE

From April through May 2017, a total of 5920 children received the first dose of the trial vaccine or placebo (1965 in the chemoprevention-alone group, 1988 in the vaccine-alone group, and 1967 in the combination group), and the data from these children were used in the calculation of the hazard ratios. On March 31, 2020, a total of 1716 children (87.3%) in the chemoprevention-alone group, 1734 (87.2%) in the vaccine-alone group, and 1740 (88.5%) in the combination group had completed follow-up (Fig. 1). Country-specific information, including the reasons for and timing of losses to follow-up, is provided in Figures S4 through S7. The baseline characteristics and the use of insecticide-treated bed nets were well balanced between groups (Tables S2 through S4). Children who did not receive a first dose of vaccine or vaccine placebo were of similar ages and sexes and had similar (though slightly lower) coverage of other childhood vaccines as children who were vaccinated (Table S5). In the first year of the trial, 93.4% of children received all three doses of vaccine; among children who were still in follow-up, 95.1% received a booster dose in year 2 and 94.7% received a booster dose in year 3 (Table S6). All four chemoprevention visits were attended by 82.8% of the children in year 1, 84.1% in year 2, and 87.7% in year 3 (Table S7).

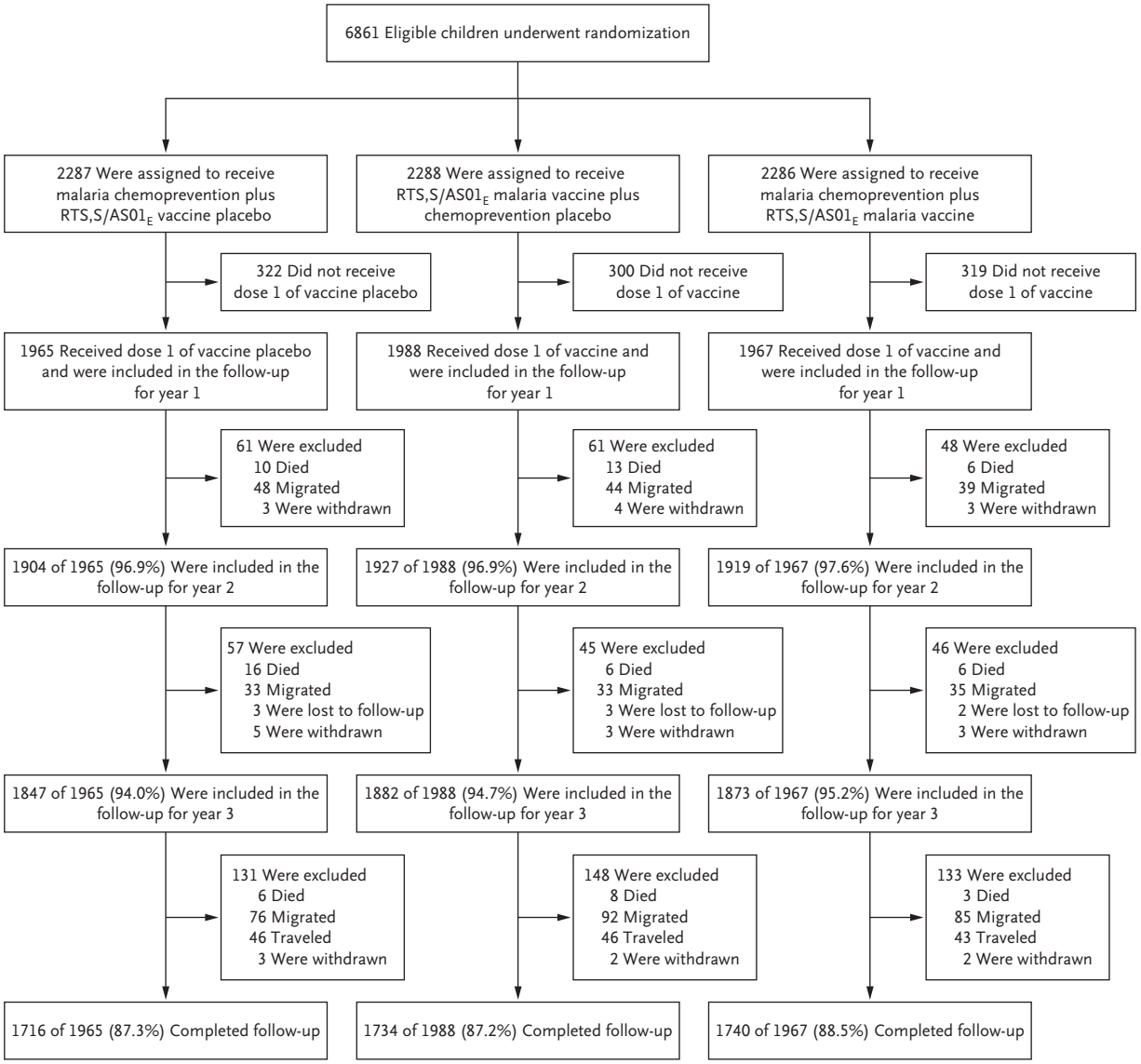


Figure 1. Randomization and Follow-up.

Children in the vaccine-alone and combination groups who did not attend the first intervention visit (vaccine dose 1) were considered to have not participated in the trial. Of the children who attended the first visit in 2017, a total of 1790 of 1965 (91.1%) in the chemoprevention-alone group, 1840 of 1988 (92.6%) in the vaccine-alone group, and 1815 of 1967 (92.3%) in the combination group attended the first visit to receive chemoprevention or chemoprevention placebo. Children who did not have an outcome of interest that was observed through passive case detection but who remained in the trial (i.e., did not die or migrate and were not withdrawn during the trial period) were considered to be included in the trial follow-up in each year. The number of children remaining in follow-up at the end of the trial was confirmed by an exit census of all children in March 2020. Table S8 in the Supplementary Appendix shows the characteristics of children whose data were censored during the trial period as compared with those who remained in the trial. Children who traveled were considered to be those who temporarily traveled away from the trial area at the time of the exit census in March 2020 but had not permanently migrated; for these children, the last documented contact date was used to calculate person-time at risk.

EFFICACY

There were 3825 events of clinical malaria among the children. In the modified intention-to-treat analysis, the incidence of clinical malaria was 278.2 events per 1000 person-years at risk in the vaccine-alone group and 304.8 events per 1000 person-years in the chemoprevention-alone group (hazard ratio, 0.92) (Table 1). The 90%,

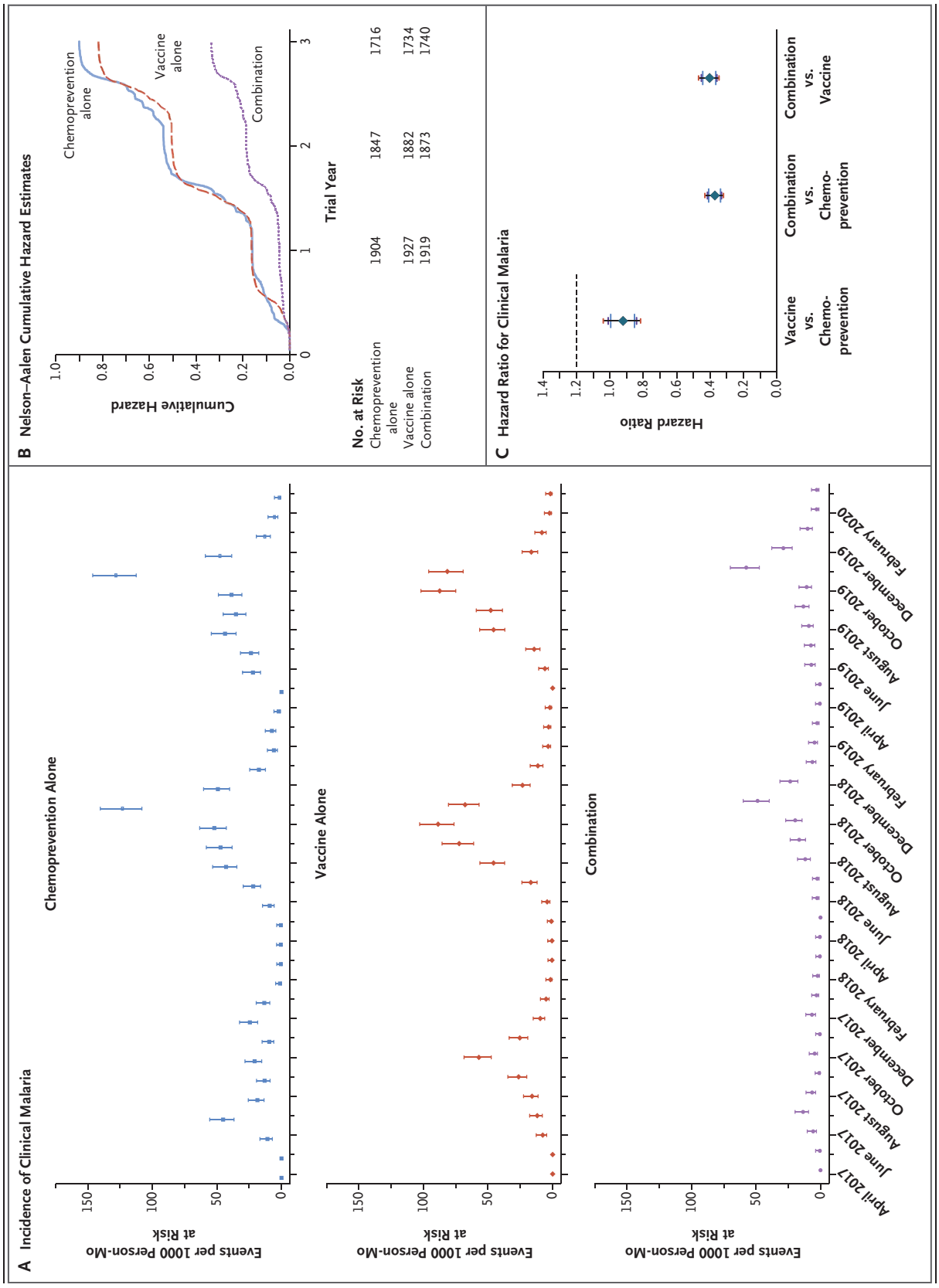
Table 1. Incidence of Uncomplicated Clinical Malaria (Modified Intention-to-Treat Population).*

Variable	Person-yr at Risk	Events	Incidence (95% CI)	Protective Efficacy, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Protective Efficacy, Combination vs. Vaccine Alone (95% CI)
		no.	*no. of events/1000 person-yr at risk*		
Burkina Faso and Mali					
Chemoprevention alone	5449.9	1661	304.8 (290.5 to 319.8)	Reference	
Vaccine alone	5535.7	1540	278.2 (264.6 to 292.4)	7.9 (–1.0 to 16.0)	Reference
Combination	5508.0	624	113.3 (104.7 to 122.5)	62.8 (58.4 to 66.8)	59.6 (54.7 to 64.0)
Burkina Faso					
Chemoprevention alone	2602.9	1028	394.9 (371.5 to 419.8)	Reference	
Vaccine alone	2550.9	998	391.2 (367.7 to 416.3)	1.1 (–10.1 to 11.1)	Reference
Combination	2602.3	401	154.1 (139.7 to 169.9)	61.1 (55.4 to 66.1)	60.7 (55.0 to 65.7)
Mali					
Chemoprevention alone	2847.0	633	222.3 (205.7 to 240.4)	Reference	
Vaccine alone	2984.8	542	181.6 (166.9 to 197.5)	18.6 (3.4 to 31.3)	Reference
Combination	2905.7	223	76.7 (67.3 to 87.5)	65.6 (57.9 to 71.9)	57.8 (47.9 to 65.8)
Year 1					
Chemoprevention alone	1794.3	309	172.2 (154.0 to 192.5)	Reference	
Vaccine alone	1816.8	318	175.0 (156.8 to 195.4)	–1.7 (–21.4 to 14.8)	Reference
Combination	1802.3	88	48.8 (39.6 to 60.2)	71.7 (63.8 to 77.8)	72.1 (64.4 to 78.2)
Year 2					
Chemoprevention alone	1868.5	705	377.3 (350.5 to 406.2)	Reference	
Vaccine alone	1903.4	647	339.9 (314.7 to 367.1)	10.1 (–1.9 to 20.6)	Reference
Combination	1894.4	264	139.4 (123.5 to 157.2)	63.2 (56.8 to 68.6)	59.1 (51.9 to 65.1)
Year 3					
Chemoprevention alone	1787.1	647	362.0 (335.2 to 391.0)	Reference	
Vaccine alone	1815.5	575	316.7 (291.9 to 343.7)	12.7 (0.9 to 23.1)	Reference
Combination	1811.3	272	150.2 (133.3 to 169.1)	58.6 (51.5 to 64.6)	52.6 (44.2 to 59.7)

* The modified intention-to-treat population included all eligible children whose parents or guardians provided consent and who received a first dose of trial vaccine or vaccine placebo. Children received chemoprevention (chemoprevention-alone group), RTS,S/AS01$_E$ (vaccine-alone group), or chemoprevention and RTS,S/AS01$_E$ (combination group). The protective efficacy was calculated as (1 – hazard ratio) × 100. CI denotes confidence interval.

Figure 2 (facing page). Primary Outcome.

Children received chemoprevention alone, the RTS,S/AS01$_E$ vaccine alone, or a combination of chemoprevention and RTS,S/AS01$_E$. Panel A shows the incidence of uncomplicated clinical malaria (the primary outcome) in each of the three groups. The I bars indicate 95% confidence intervals. Panel B shows the Nelson–Aalen cumulative hazard estimates for each group and the number of children remaining at risk at the end of each trial year. Panel C shows pairwise hazard ratios for uncomplicated clinical malaria. The I bars show 90%, 95%, and 99% confidence intervals: the blue bars represent the 90% confidence intervals (narrowest confidence intervals), the purple bars the 95% confidence intervals, and the red bars the 99% confidence intervals (widest confidence intervals). The dotted line shows the prespecified noninferiority margin of 1.20 for the comparison of vaccine alone with chemoprevention alone.



95%, and 99% confidence intervals for the hazard ratios all excluded the prespecified noninferiority margin of 1.20 (99% confidence interval [CI], 0.82 to 1.04) (Fig. 2).

The incidence of clinical malaria in the combination group was 113 events per 1000 person-years at risk, indicating a protective efficacy of 62.8% (95% CI, 58.4 to 66.8) as compared with chemoprevention alone and an efficacy of 59.6% (95% CI, 54.7 to 64.0) as compared with vaccine alone. The protective efficacy was similar in the two countries but differed over time, being highest in the first year of the trial and slightly lower in years 2 and 3 (Table 1 and Fig. 2B). Results of per-protocol analyses were similar to those of the modified intention-to-treat analyses (Table S9), and the protective efficacy against secondary outcomes (clinical malaria with any parasite density or malaria diagnosed with the use of a rapid diagnostic test) was similar to that against the primary outcome. The incidence of non-falciparum malaria was lower in the two groups that received chemoprevention than in the vaccine-alone group (Table S10).

As compared with chemoprevention alone or vaccine alone, the combined intervention provided a high level of protection against the following prespecified secondary outcomes: hospitalization for malaria, hospitalization meeting WHO criteria for severe malaria, severe malarial anemia, and blood transfusion (Table 2). The protective efficacy of the combination as compared with chemoprevention alone was 62.8% (95% CI, 58.4 to 66.8) against clinical malaria, 70.5% (95% CI, 41.9 to 85.0) against hospital admission with severe malaria, and 72.9% (95% CI, 2.91 to 92.4) against death from malaria. The protective efficacy of the combination as compared with the vaccine alone against these outcomes was 59.6% (95% CI, 54.7 to 64.0), 70.6% (95% CI, 42.3 to 85.0), and 75.3% (95% CI, 12.5 to 93.0), respectively.

The incidences of death from any cause, excluding external causes and surgery, and deaths attributable to malaria were also markedly lower in the combination group than in either single-intervention group. As compared with chemoprevention alone, the combination intervention resulted in an incidence of clinical malaria that was lower by 190.8 events per 1000 person-years at risk (Table S11). In addition, there were 4.8 fewer events of WHO-defined severe malaria, 3.8 fewer hospital admissions for severe malarial anemia, 2.8 fewer blood transfusions, and 1.5 fewer deaths from malaria per 1000 person-years at risk (Table S12).

The prevalence of malaria parasitemia at weekly surveys was consistently approximately 50% lower in the combination group than in the chemoprevention-alone or vaccine-alone groups (Table 3). At the end of each malaria transmission season, the prevalence of *P. falciparum* parasitemia and anemia (hemoglobin level, <7 g per deciliter) was lower in the combination group than in the two other groups (Table 3). The prevalence of *P. falciparum* gametocytemia was also consistently lower in the combination group than in the chemoprevention-alone or vaccine-alone groups (Table S13). Among school-age children living in the trial areas who did not receive a trial intervention, the prevalence of parasitemia was high in each year (>60% in Burkina Faso and >17% in Mali) (Table 3). Among children with asymptomatic parasitemia, the curative efficacy of sulfadoxine–pyrimethamine and amodiaquine after 28 days was 99.1% (95% CI, 93.9 to 99.9) in Burkina Faso and 95.2% (95% CI, 82.7 to 98.8) in Mali (Table S14).

SAFETY

Febrile seizures developed in five children, all of whom had received RTS,S/AS01$_E$, the day after vaccination (three children in the vaccine-alone group and in two in the combination group). Three events occurred after a priming dose, and two occurred after a booster dose. These children recovered and had no sequelae. There were no other serious adverse events that were identified by the investigator as being related to vaccination. Eight cases of clinically suspected meningitis (four in the chemoprevention-alone group, three in the vaccine-alone group, and one in the combination group) were investigated with the use of lumbar puncture, but none showed proven meningitis. The distributions of the causes of hospital admissions and the causes of death are shown in Tables S15 through S17. There was no evidence of higher mortality or a greater number of hospital admissions among girls who received RTS,S/AS01$_E$ than among boys who received RTS,S/AS01$_E$ (Tables S18 and S19).

Table 2. Incidence of Secondary Severe Outcomes According to Trial Group (Modified Intention-to-Treat Population).*

Outcome and Group	Events	Incidence (95% CI)	Protective Efficacy, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Protective Efficacy, Combination vs. Vaccine Alone (95% CI)
	no.	*no. of events/1000 person-yr at risk*		
Hospitalizations				
Any reason, excluding external causes and surgery				
Chemoprevention alone	60	11.0 (8.6 to 14.2)	Reference	
Vaccine alone	73	13.2 (10.5 to 16.6)	–22.3 (–74.4 to 14.3)	Reference
Combination	49	8.9 (6.7 to 11.8)	18.7 (–19.4 to 44.7)	33.5 (3.0 to 54.5)
All cases of malaria				
Chemoprevention alone	49	9.0 (6.8 to 11.9)	Reference	
Vaccine alone	54	9.8 (7.5 to 12.7)	–11.0 (–65.8 to 25.7)	Reference
Combination	28	5.1 (3.5 to 7.4)	43.2 (7.7 to 65.0)	48.8 (17.1 to 68.4)
Severe malaria†				
Chemoprevention alone	37	6.8 (4.9 to 9.4)	Reference	
Vaccine alone	37	6.7 (4.8 to 9.2)	–0.4 (–60.2 to 37.1)	Reference
Combination	11	2.0 (1.1 to 3.6)	70.5 (41.9 to 85.0)	70.6 (42.3 to 85.0)
Cerebral malaria†				
Chemoprevention alone	0	0	Reference	
Vaccine alone	4	0.7 (0.3 to 1.9)	—	Reference
Combination	1	0.2 (0.0 to 1.3)	—	74.6 (–128.0 to 97.2)
Severe malarial anemia†				
Chemoprevention alone	31	5.7 (4.0 to 8.1)	Reference	
Vaccine alone	25	4.5 (3.1 to 6.7)	18.4 (–39.3 to 52.2)	Reference
Combination	10	1.8 (1.0 to 3.4)	67.9 (34.1 to 84.3)	60.6 (18.3 to 81.0)
Blood transfusion				
Chemoprevention alone	23	4.2 (2.8 to 6.4)	Reference	
Vaccine alone	21	3.8 (2.5 to 5.8)	8.3 (–67.6 to 49.8)	Reference
Combination	8	1.5 (0.7 to 2.9)	65.4 (22.9 to 84.5)	62.3 (14.1 to 83.4)
Deaths				
All, including external causes and surgery				
Chemoprevention alone	32	5.9 (4.2 to 8.3)	Reference	
Vaccine alone	27	4.9 (3.3 to 7.1)	15.9 (–40.3 to 49.6)	Reference
Combination	15	2.7 (1.6 to 4.5)	53.4 (14.0 to 74.8)	44.6 (–4.1 to 70.5)
All, excluding external causes and surgery				
Chemoprevention alone	25	4.6 (3.1 to 6.8)	Reference	
Vaccine alone	22	4.0 (2.6 to 6.0)	12.1 (–55.7 to 50.4)	Reference
Combination	12	2.2 (1.2 to 3.8)	52.3 (5.0 to 76.0)	45.7 (–9.6 to 73.1)
Malaria				
Chemoprevention alone	11	2.0 (1.1 to 3.6)	Reference	
Vaccine alone	12	2.2 (1.2 to 3.8)	–9.5 (–148.3 to 51.7)	Reference
Combination	3	0.5 (0.2 to 1.7)	72.9 (2.9 to 92.4)	75.3 (12.5 to 93.0)

* Confidence intervals for the hazard ratios for secondary outcomes were not adjusted for multiplicity, and inferences drawn from these intervals may not be reproducible.
† Cases of severe malaria, cerebral malaria, and severe malarial anemia were classified according to World Health Organization definitions.

Table 3. Prevalence of Outcomes at Weekly Surveys and at Surveys Conducted at the End of Each Malaria Transmission Season.*

Variable	Children	Prevalence Ratio, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Prevalence Ratio, Combination vs. Vaccine Alone (95% CI)
	no./total no. (%)		
***Plasmodium falciparum* infection at weekly surveys**			
2017			
Chemoprevention	17/637 (2.7)	Reference	
Vaccine alone	36/627 (5.7)	2.20 (1.26–3.85)	Reference
Combination	8/648 (1.2)	0.47 (0.21–1.08)	0.21 (0.10–0.46)
2018			
Chemoprevention	46/666 (6.9)	Reference	
Vaccine alone	39/677 (5.8)	0.81 (0.55–1.21)	Reference
Combination	23/685 (3.4)	0.48 (0.30–0.78)	0.59 (0.36–0.97)
2019			
Chemoprevention	26/491 (5.3)	Reference	
Vaccine alone	34/505 (6.7)	1.25 (0.77–2.04)	Reference
Combination	11/518 (2.1)	0.39 (0.19–0.77)	0.31 (0.16–0.60)
***P. falciparum* infection at end-of-season surveys**			
2017			
Chemoprevention	29/1708 (1.7)	Reference	
Vaccine alone	100/1741 (5.7)	3.46 (2.30–5.19)	Reference
Combination	13/1718 (0.8)	0.45 (0.24–0.87)	0.13 (0.07–0.23)
2018			
Chemoprevention	225/1651 (13.6)	Reference	
Vaccine alone	210/1717 (12.2)	0.92 (0.78–1.08)	Reference
Combination	111/1695 (6.6)	0.48 (0.39–0.59)	0.52 (0.42–0.65)
2019			
Chemoprevention	219/1619 (13.5)	Reference	
Vaccine alone	213/1649 (12.9)	0.98 (0.83–1.17)	Reference
Combination	92/1641 (5.6)	0.42 (0.33–0.53)	0.43 (0.34–0.54)
Hemoglobin level <7 g/dl at end-of-season surveys			
2017			
Chemoprevention	21/1710 (1.2)	Reference	
Vaccine alone	28/1742 (1.6)	1.33 (0.76–2.33)	Reference
Combination	18/1719 (1.0)	0.86 (0.46–1.61)	0.65 (0.36–1.17)
2018			
Chemoprevention	38/1655 (2.3)	Reference	
Vaccine alone	40/1717 (2.3)	1.03 (0.67–1.59)	Reference
Combination	12/1695 (0.7)	0.31 (0.16–0.59)	0.30 (0.16–0.57)

Table 3. (Continued.)

Variable	Children	Prevalence Ratio, Vaccine Alone or Combination vs. Chemoprevention (95% CI)	Prevalence Ratio, Combination vs. Vaccine Alone (95% CI)
	no./total no. (%)		
2019			
Chemoprevention	8/1619 (0.5)	Reference	
Vaccine alone	9/1650 (0.5)	1.11 (0.43–2.86)	Reference
Combination	4/1642 (0.2)	0.49 (0.15–1.63)	0.45 (0.14–1.45)
***P. falciparum* parasitemia in school-age children**			
2018			
Burkina Faso			
Any parasite density	123/200 (61.5)		
Parasite density ≥5000/mm^3	20/200 (10.0)		
Mali			
Any parasite density	34/200 (17.0)		
Parasite density ≥5000/mm^3	9/200 (4.5)		
2019			
Burkina Faso			
Any parasite density	123/200 (61.5)		
Parasite density ≥5000/mm^3	19/200 (9.5)		
Mali			
Any parasite density	45/200 (22.5)		
Parasite density ≥5000/mm^3	18/200 (9.0)		

* Samples for blood slides were obtained from a randomly selected subgroup of children each week throughout the trial period for the weekly surveys. Surveys were also performed every year at the end of each malaria transmission season; samples were obtained for blood slides from all children 1 month after receipt of the last course of chemoprevention or placebo. Confidence intervals for the prevalence ratios were not adjusted for multiplicity, and inferences drawn from these intervals may not be reproducible.

DISCUSSION

The results of this trial show that seasonal vaccination with the RTS,S/AS01$_E$ malaria vaccine was noninferior to four annual courses of chemoprevention with sulfadoxine–pyrimethamine and amodiaquine in protecting against uncomplicated clinical malaria over a period of 3 years. A combination of RTS,S/AS01$_E$ and chemoprevention was superior to RTS,S/AS01$_E$ and to chemoprevention alone with respect to reducing the incidence of uncomplicated clinical malaria, hospital admissions with severe malaria, and deaths from malaria. There was some evidence that efficacy of the combination intervention against clinical malaria was higher in the first year of the trial than in the subsequent 2 years, but substantial efficacy was seen in each year of the trial.

Chemoprevention alone was more protective than RTS,S/AS01$_E$ alone during the 4 months when it was administered, but RTS,S/AS01$_E$ alone provided protection outside this period, and was thus not inferior over the whole year. The addition of a fifth course of chemoprevention might have improved efficacy in both the chemoprevention-alone and combination groups[19] and might have reduced the incidence of malaria in the combination group to very low levels, despite the high level of malaria transmission in the trial areas, particularly in Burkina Faso.

The RTS,S/AS01$_E$ vaccine priming and booster regimen was not associated with any new con-

cerning pattern of side effects. Febrile seizures developed in five children who received RTS,S/AS01$_E$, a finding consistent with previous trials of RTS,S/AS01$_E$,[4] but all children recovered and had no sequelae. No cases of meningitis were detected, and no imbalance in death according to sex was seen among children who received RTS,S/AS01$_E$ (meningitis and death were previously reported as safety concerns among children who received this vaccine).[4,20]

Among children who had undergone randomization, 14% in the vaccine-alone and combination groups did not attend the first visit and were considered to have not participated in the trial. This could have introduced a bias in favor of RTS,S/AS01$_E$ because no comparable restriction was applied to children in the chemoprevention-alone group. However, results of the per-protocol analysis and an analysis that was restricted to children who attended the first scheduled visit to receive chemoprevention or placebo were similar to those of the analysis in the modified intention-to-treat population. Strengths of the trial were the large size, high statistical power, high retention rate, the careful assessment of the causes of hospital admissions and deaths, and the consistency of the efficacy estimates against different outcomes and between the two countries.

The drugs currently used for chemoprevention (sulfadoxine–pyrimethamine and amodiaquine) remain effective in the trial areas, as shown by the results of our in vivo study involving asymptomatic children. However, if resistance to these drugs increases without an available alternative chemoprevention regimen, seasonal vaccination with RTS,S/AS01$_E$ could provide a potential alternative. The combination of seasonal chemoprevention (which when used alone has a high level of efficacy against uncomplicated and severe malaria[2]) with seasonal vaccination with RTS,S/AS01$_E$ provides a promising approach to the prevention of malaria in the large areas of Africa with seasonal malaria and where malaria is currently poorly controlled. Further research will be required to determine how best to deliver the combination of chemoprevention and seasonal malaria vaccination in areas of high malaria burden in the Sahel and sub-Sahel regions. In addition, there may be other epidemiologic situations in which a combination of chemoprevention and vaccination could improve on current methods of malaria control.

Supported by grants from the U.K. Joint Global Health Trials (the Department of Health and Social Care, the Department for International Development, the Global Challenges Research Fund, the Medical Research Council, and the Wellcome Trust) (MR/P006876/1) and PATH Malaria Vaccine Initiative (18269). Dr. Cairns was supported by a grant (MR/R010161/1) jointly funded by the U.K. Medical Research Council (MRC); the U.K. Foreign, Commonwealth, and Development Office; and the EDCTP2 program, supported by the European Union.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the members of the trial steering committee (Feiko ter Kuile [chair], Kwadwo Koram, Mahamadou Thera, Joaniter Nankabirwa, and Morven Roberts) and the members of the data and safety monitoring board (Blaise Genton [chair], Sheick Coulibaly, Umberto D'Alessandro, Francesca Little, and Malcolm Molyneux) for their oversight and support; Alice Greenwood for reviewing the hospital records and verbal autopsies and for validating the causes of hospital admissions and deaths that were assigned by the trial team before the database was locked; Simon Correa and Mamadou Ndiath at the MRC Unit the Gambia at the London School of Hygiene and Tropical Medicine for performing quality control of malaria blood film readings; Karen Slater for supporting the trial in many ways; GlaxoSmithKline Biologicals for donating the RTS,S/AS01$_E$ and Havrix vaccines; Lode Schuerman for input regarding the trial design; Birkhäuser (Switzerland) for supplying identity cards and labels; Guilin Pharmaceutical for supplying the chemoprevention drugs; the staff of the Ministry of Health of Mali and the Ministry of Health of Burkina Faso for their assistance with trial operations; all the caretakers and children for their participation; and the late Ogobara Doumbo for help in setting up the trial.

APPENDIX

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Healthcare Utilization Study (HUS) R2 Report: Cross-Country Findings from the Primary Child Caregiver Cohort Sample

Version: 16 July 2021

Cover photo: PATH

July 2021

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About This Report

HUS Background and Research Partners

This document is part of a collection of interim reports on selected findings from the Healthcare Utilization Study (HUS) for the Malaria Vaccine Implementation Programme (MVIP). The HUS is a multi-country, qualitative study designed to provide explanatory insight on the delivery and uptake of the world's first malaria vaccine, RTS,S/AS01 (RTS,S). Following more than 30 years of clinical development and study[a], two World Health Organization (WHO) advisory groups—the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Group (MPAG)—jointly called for pilot implementation of the vaccine in three to five settings in sub-Saharan Africa to further evaluate the vaccine before recommending it for wider use[b]. The MVIP was subsequently created to introduce RTS,S in selected sites in Ghana, Kenya, and Malawi through routine immunization programmes led by ministries of health (MOHs). This phased introduction of RTS,S is accompanied by independent evaluations that focus on the feasibility of administering the recommended 4 doses of the vaccine in children, the vaccine's potential role in reducing childhood deaths, and its safety in the context of routine use. The MVIP is being coordinated by the WHO, in collaboration with PATH, GSK, and the ministries of health from Ghana, Kenya, and Malawi.

The HUS is among MVIP evaluations focused on understanding the feasibility of providing the 4-dose schedule—a schedule that requires new vaccination visits, including for the fourth dose at 24 months of age. Annex 1 shows the RTS,S delivery schedule and eligibility guidance for each country.

Applying a qualitative panel design, the HUS is collecting data from primary child caregivers, health sector personnel, and other community members at three critical points in the vaccine's 24-month delivery cycle. The study is being conducted by a consortium of research partners led by the University of Health and Allied Sciences (UHAS) in Ghana, the Liverpool School of Tropical Medicine (LSTM) in Kenya, and the Malawi-Liverpool Wellcome Trust in Malawi. PATH is leading the overall study.

Steps were taken to ensure that participants answered interview questions freely and truthfully. Prior to obtaining informed consent, interviewers presented themselves to prospective participants following recruitment scripts, specifying their affiliation with a research institution (see script in Annex 2). In the course of the interview, participants were also encouraged to speak openly and truthfully and reminded, as needed, of our commitment to confidentiality and privacy. Additionally, recognizing that repeated interviews with caregivers in the cohort could influence their attitudes and replies, the final round of data collection will include conducting similar interviews in a different, cross-sectional sample of child caregivers.

[a] Kaslow, D. et al. (2018). Vaccine candidates for poor nations are going to waste. *Nature, 564*(7736), 337-339. doi:http://dx.doi.org/10.1038/d41586-018-07758-3

[b] World Health Organization. (2016). Malaria vaccine: WHO position paper. *Weekly Epidemiological Record, 4*(91), 33-52.

Round 2 Reports

As of this report date, two data collection rounds for the HUS have been completed and the final round is underway. A report of preliminary findings from round 1 (R1) was completed in June 2020.[c] The complete packet of R2 reports includes this document (#2 below) along with a background document summarizing HUS methods and study status (#1 below), and three country-specific reports (#3-5 below).

1. Methods and Study Status: Background for HUS R2 Reports
2. Cross-Country Findings from the Primary Child Caregiver Cohort Sample
3. Key findings through Round 2: Ghana
4. Key findings through Round 2: Kenya
5. Key findings through Round 2: Malawi

Country-specific reports provide contextual details pertinent to the RTS,S introductions and uptake and present findings from interviews with health workers and other health personnel. This report presents high-level cross-country findings from R2 interviews with primary child caregivers (PCGs), whose children should have received RTS,S dose 3 at the time of R2 interviews. Primary focuses are:

1. The uptake of RTS,S through dose 3, including factors that facilitate or threaten receipt of all three doses.
2. The impact of RTS,S uptake on malaria treatment seeking and other prevention behaviors.
3. PCG perceptions about RTS,S, sources of RTS,S information, and new/or persistent questions and concerns about RTS,S.

Changes in themes and patterns compared to R1 findings are highlighted throughout.

Ethical Approvals

The HUS has been approved by PATH's Research Ethics Committee (REC), the Ghana Health Service's (GHS) Ethics Review Committee, the University of Malawi College of Medicine's Research and Ethics Committee, the Liverpool School of Tropical Medicine (LSTM) Research Ethics Committee, the Kenya Medical Research Institute's (KEMRI) Scientific and Ethics Unit, the London School of Hygiene & Tropical Medicine's (LSHTM) Observational/Interventions Research Ethics Committee, and the US Centers for Disease Control and Prevention's Center for Global Health (CDC). Written informed consent is sought from every study participant.

[c] Malaria Vaccine Implementation Programme Healthcare Utilization Study: Preliminary Findings From Round 1 Data Collection, 21 June 2020

Key Takeaways from R2 Findings from PCG Interviews

RTS,S uptake

- Uptake of the RTS,S vaccine through the third dose is generally strong.
    - Instances of children who have not received any RTS,S doses are typically due to early barriers, including PCG concerns about the vaccine's safety or confusion about eligibility which caused the PCGs to refuse or delay initial doses until they were no longer eligible.
    - Instances of children who have received fewer than the expected three doses of RTS,S are typically due to service access barriers or to the PCGs' personal circumstances.
- Most caregivers expressed their intent to take their children to receive dose 4, many enthusiastically.

Attitudes and fears about RTS,S

- Positive attitudes and trust in RTS,S among PCGs have increased substantially since R1 interviews, driven mainly by PCGs perceiving 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 immunization (AEFI) are "normal" and similar to other vaccines.
- Fewer threats to RTS,S uptake – e.g., rumors, fears about safety – are evident in R2 compared to R1 data; programmatic barriers (e.g., service access) are more frequently reported in R2.

Malaria treatment seeking and other prevention in the context of RTS,S

- Many of the RTS,S-eligible children have had malaria since receiving RTS,S doses, but this has generally not diminished the PCGs' enthusiasm for RTS,S. PCGs perceive malaria to be less frequent or severe because of the vaccine.
- RTS,S uptake does not seem to interfere with or change existing malaria treatment or prevention behaviors at the time of R2.

RTS,S information and unanswered questions about RTS,S

- While caregivers have greater knowledge of RTS,S and understanding of the 4-dose schedule, confusion and questions persist around the level and duration of protection conferred by the vaccine.

Primary Child Caregiver (PCG) Interviews

Timing of PCG interviews within the RTS,S delivery schedule

Data from multiple study groups are being collected for the HUS, including from primary child caregivers (PCGs), health providers who administer vaccines, sub-national and national health managers and leaders, and various community members (e.g., male household heads, female elders, community leaders). Three data collection rounds were planned to occur at three critical times in the 24-month delivery cycle (Table 1). Interviews in cohort samples of PCGs and health providers planned for each of three rounds of data collection.

Table 1. HUS fieldwork timing linked to RTS,S introduction.

Round 1		Round 2	Round 3
Lead up to initial RTS,S delivery	**Soon after dose 1 (5-6 months old)**	**In-between doses 3 & 4 (≈17 months old)**	**Soon after dose 4 (22-24 months old)**
Ethnographic immersion and data collection in all study groups		Data collection focused on PCGs and health providers Ethnographic immersion	Data collection in all study groups Ethnographic immersion

In order to capture initial reactions to RTS,S introduction and uptake of dose 1 in 5-6 month old children, R1 interviews were conducted soon after the initial launch of RTS,S in April 2019 in Ghana and Malawi and in September 2019 in Kenya. To assess experiences and changes in attitudes mid-way through the vaccine's two-year schedule, R2 interviews were planned to be completed by all individuals in the cohort after dose 3 was administered to RTS,S-eligible children, but before the child was eligible to receive dose 4. The COVID-19 pandemic required a suspension of research activities delaying R2 start-up by six months, which was initially planned to begin in April 2021. R2 interviews commences in September 2020 and were completed in all three countries by December 2020. Although most of the RTS,S-eligible children were still not eligible for dose 4, due to COVID-19 delays five of the PCGs interviewed in R2 had children old enough to receive dose 4. RTS,S uptake analyses presented below focus on PCG adherence through dose 3.

R2 PCG Sample

As described in the background documents to this report,[d] nine community sites per country (27 total) were selected for inclusion the study, with a minimum target sample of five PCGs per community completing all three interviews (R1-R3). To accommodate loss to follow-up (LTFU) and drop-outs, we initially sampled seven individuals per site, for a total of 63 PCGs per country. Twenty-five PCGs (13%) from R1 were LTFU in R2. The PCG sample sizes for R1 and R2 are summarized in Table 2.

[d] HUS Methods and Study Status: Background for HUS R2 Reports

Table 2. PCG cohort sample in R2 by country.

Country	R1 Sample	R2 Sample			
		LTFU	Continued	Replaced	Total
Ghana	62	9	53	0	53
Kenya	63	10	53	10	63
Malawi	63	6	57	0	57
Total	**188**	**25**	**163**	**10**	**173**

Note: LTFU = lost to follow-up; Continued = interviewed in R1 and R2; Replaced = newly recruited in R2.

The most common reason for LTFU was migration out of the study community, though at least one PCG (in Ghana) declined to continue with the study. Research teams in Ghana and Malawi – where LTFUs were generally evenly distributed across community sites – opted to not recruit replacement PCGs for the LTFUs. In Kenya, where LTFUs were concentrated in specific communities, the team opted to replace the lost individuals with newly recruited PCGs to ensure the sample in each community was adequate in round 3. With the exception for one community in Ghana (C3), where only four PCGs were interviewed in R2, all the other community sites retained the minimum target sample of five PCGs in each HUS community.

R2 Interview Focus

Table 3 shows that R2 interviews explored the same topics as in R1, adapting questions to reflect their follow-on nature and building specifically on what the PCGs recounted in R1. The questions and probing specifically explored changes in PCG sentiments and behaviors since the R1 interviews or since her child received initial RTS,S doses.

Table 3. PCG interview topics in R1 and R2.

Round 1 Topics	Round 2 Topics
• PCG sociodemographic and background information • Vaccination history of the RTS,S-eligible child based on review of the child health card • Malaria perceptions • Treatment seeking for malaria in the RTS,S-eligible child • Exposure to RTS,S messages in popular and professional sectors, probing for influences of messages on RTS,S uptake • Questions and concerns about RTS,S • Experiences at the last vaccination visit	• Verification and updates (original cohort); PCG sociodemographic and background information (replacements) • Updates on vaccinations received based on review of the child health card. • Malaria perceptions in the context of RTS,S • Treatment seeking for malaria in the RTS,S-eligible child in the context of RTS,S provision • Exposure to RTS,S messages in popular and professional sectors, probing for changes in PCG understanding and acceptance of RTS,S • Questions and concerns about RTS,S • Experiences at the last vaccination visit • COVID-19 perceptions and impact on service utilization

In R2 we also added questions regarding COVID-19, focused specifically on understanding if and how the pandemic affected the PCGs access to and utilization of child health services and taking their child for scheduled vaccines.

Findings

PCG characteristics and gender of the RTS,S-eligible child

All but two PCGs were female, and most were between 19-34 years old, married or cohabitating, had completed primary school or more, and had more than one child (Table 4). All but six individuals were the mothers of the RTS,S-eligible children. Within and across countries, the proportion of males and females among RTS,S-eligible children was nearly equal (Table 5).

Table 4. Description of primary child caregiver cohort characteristics that remain in the cohort (including replacements).

Characteristic		N (%)		
		Ghana	Kenya	Malawi
Sex	Female	53 (100.0)	62 (98.4)	56 (98.3)
	Missing	-	1 (1.6)	1 (1.8)
Age (years)	15–18	3 (5.7)	3 (4.8)	4 (7.0)
	19–24	14 (26.4)	13 (20.6)	26 (45.6)
	25–29	14 (26.4)	16 (25.4)	6 (10.5)
	30–34	14 (26.4)	17 (27.0)	11 (19.3)
	35–40	4 (7.6)	9 (14.3)	8 (14.0)
	40+	4 (7.6)	5 (7.9)	1 (1.8)
	Missing		-	1 (1.8)
Marital status	Married or cohabiting	42 (79.3)	58 (92.1)	46 (80.7)
	Divorced, widowed, or unmarried	11 (20.8)	5 (7.9)	11 (19.3)
Education	None	5 (9.4)	-	3 (5.3)
	Primary	12 (22.6)	43 (68.2)	42 (73.7)
	Secondary	26 (49.1)	16 (25.4)	8 (14.0)
	Post-secondary	10 (18.9)	4 (6.4)	-
	Missing	-	-	4 (7.0)
Number of children	1	9 (20.8)	10 (15.9)	20 (35.1)
	2	16 (30.2)	8 (12.7)	14 (24.6)
	3+	26 (49.1)	45 (71.4)	23 (40.4)
		2 (3.8)	-	-
Relation to child	Mother	52 (98.1)	59 (93.7)	56 (98.3)
	Grandparent or other	1 (1.9)	4 (6.4)	1 (1.8)

Table 5. Gender of RTS,S-eligible children that remain in the cohort (including replacements).

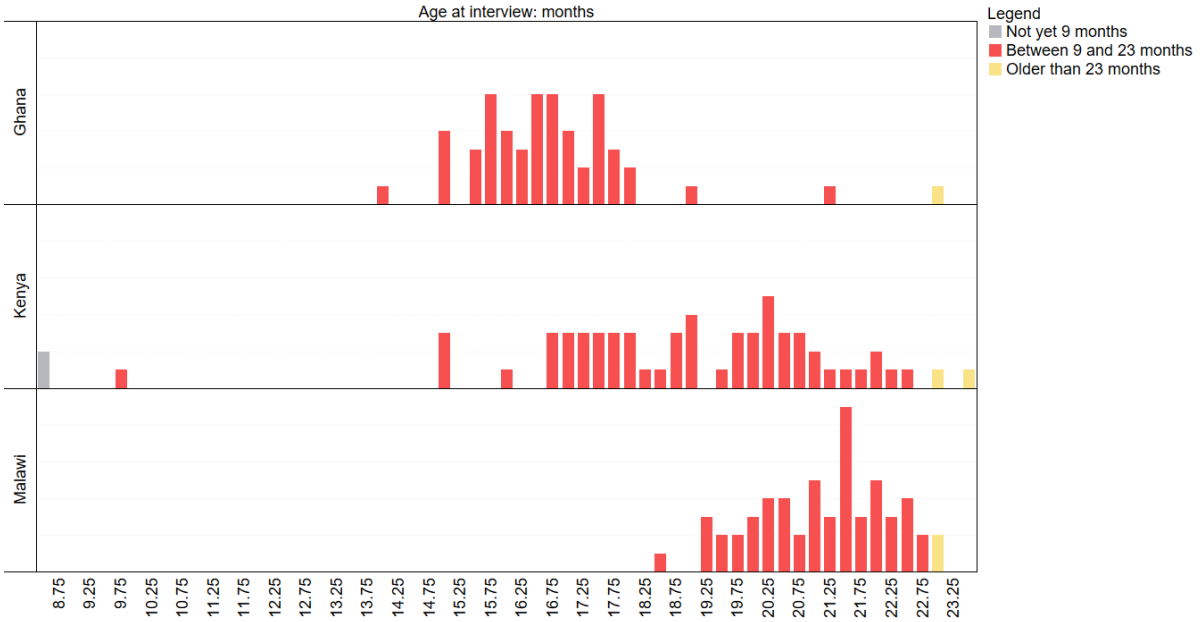
	N (%)		
	Ghana	Kenya	Malawi
Female	24 (45.3)	31 (49.2)	30 (52.6)
Male	29 (54.7)	32 (50.8)	27 (47.4)
Total	**53**	**63**	**57**

Age of RTS,S-eligible child at time of R2 interview

As we were anticipating a range of child ages between the third and fourth RTS,S doses (≈10-23 months) represented in R2 data, it was specified that the mid-point age was ≈17 months as the target. Despite delays in R2 data collection due to COVID-19, in addition to the long period between doses 3 and 4, many children were still between 9 and 23 months old at the time of R2 interviews, indicated by the red bars in Figure 1. Five children were just

over the 23-month mark, indicated by yellow bars in Figure 1. Only two children (whose mothers were newly recruited in R2) were not yet eligible for the third dose of RTS,S at the time of R2 interviews, indicated by the grey bar in Figure 1.

Figure 1. Ages of RTS,S-eligible children at the time of R2 interviews (n=173).



Note: Children indicated in grey are below the nine-month mark and potentially "not [officially] eligible" for RTS,S dose 3; children shown in yellow just exceeded the exact 23-month mark by one or two weeks at time of interview and thus may be fourth-dose eligible; those in red are between the nine-month and 23-month eligibility markers.

The distinct differences in interview timing may be explained, in part, by the fact that the Ghana research team was the first and Malawi's team the last to resume R2 fieldwork. The wide range of ages of children in Kenya in R2, including replacement PCGs, reflect a similarly large age spread from R1.

RTS,S doses received at time of R2 interview

Uptake Patterns

To understand RTS,S-eligible children's vaccination history and RTS,S uptake specifically through dose 3, data were abstracted from the children's vaccination cards. When vaccination cards were not available, PCGs were asked to recall vaccines their children had received. Data were collected on:

1. **Vaccinations/doses other than RTS,S**, including: their Bacille Calmette-Guérin (BCG) vaccine, which is scheduled at birth; the first dose of pentavalent vaccine[e] (Penta-1) scheduled at six weeks; the second dose of pentavalent vaccine scheduled at 10 weeks (Penta-2); and the third dose of pentavalent vaccine scheduled at 14 weeks (Penta-3). Data were also captured for the measles 9-month dose (not shown in the graph).

[e] Vaccine used to immunize against diphtheria, pertussis, tetanus, hepatitis B, and Haemophilus influenzae type b

2. **RTS,S doses**, including:
    a. Dose 1 which children are eligible to receive beginning at 5 months in Malawi and 6 months in Kenya and Ghana.
    b. Dose 2 which children are eligible to receive a month after the receipt of dose 1 in all three countries.
    c. Dose 3 which children are eligible to receive beginning at 7 months in Malawi and 9 months in Kenya and Ghana (in Malawi a child is eligible a month after the receipt of dose 2; in Kenya and Ghana, two months after the receipt of dose 2).
    d. If child is late, maintain 4 weeks apart between doses 2 and 3.

For the three countries combined, Figure 2 shows the children's receipt of RTS,S dose 1, dose 2, and dose 3, as well as other vaccines in the immunization schedule. The figure includes data collected from all PCGs, including returning, LTFU, and replacement PCGs. For LTFU cases, vaccination status of the child is shown through R1 (e.g., through RTS,S dose 1) and then marked in blue as LTFU for RTS,S doses 2 and 3. One participant did not have a vaccination card available in either R1 or R2; this cases is treated as missing and marked in yellow in the Figure 2.

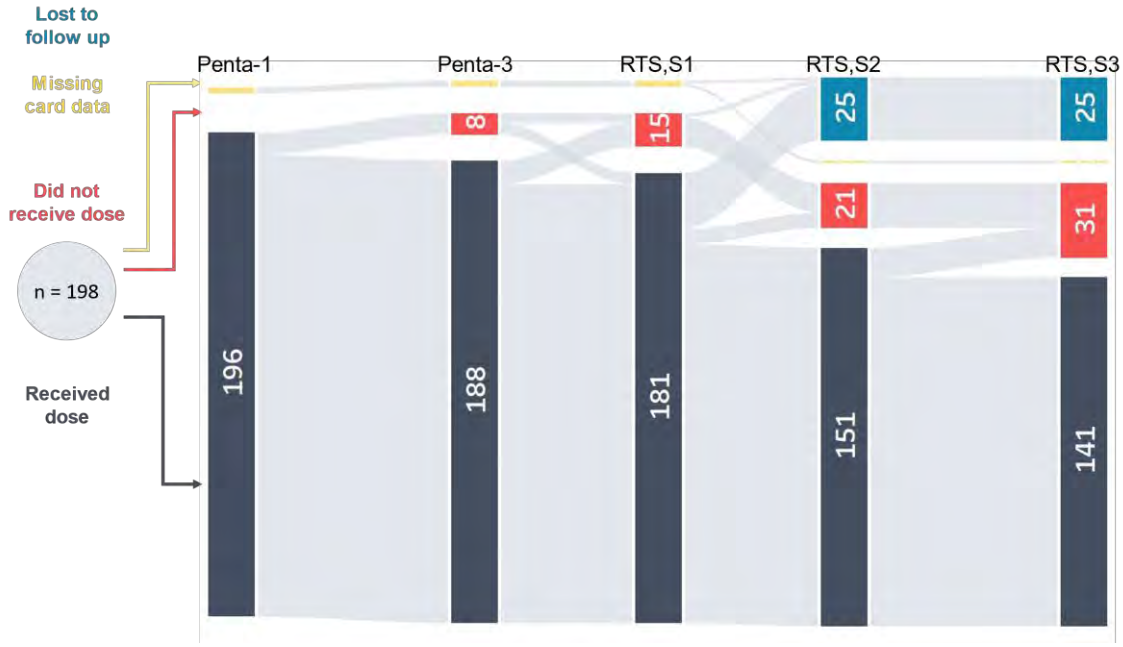
Among the remaining 172 participants, uptake of RTS,S doses is generally high with 141 children having received all three doses recommended at the time of interview. Of these 141 children, four had additionally completed the entire vaccination series and received all four RTS,S doses. Thirty-one children had not yet received at least three doses at the time of the R2 interview, of whom 10 had received doses 1 and 2, eight had received only dose 1, and 13 had yet to receive any RTS,S doses. Crucially, eight participants were missing a vaccine card in R2. Information provided from their vaccine cards in R1 was used to record their children's vaccine receipt. As a result, some of these children may have since received further doses of RTS,S that are not documented here.

Three RTS,S adherence categories as of R2 interviews were derived from the children's vaccination history data:

1. Fully adherent: children who have received three or more doses of RTS,S at the time of interview, as expected based upon eligibility.
2. Partially adherent: children who have received one or two doses of RTS,S but have yet to receive a third dose at time of interview. These children may have yet to receive dose 3 or the PCG has defaulted or delayed.
3. Non-adherent: children who have yet to receive any doses of RTS,S at the time of interview.

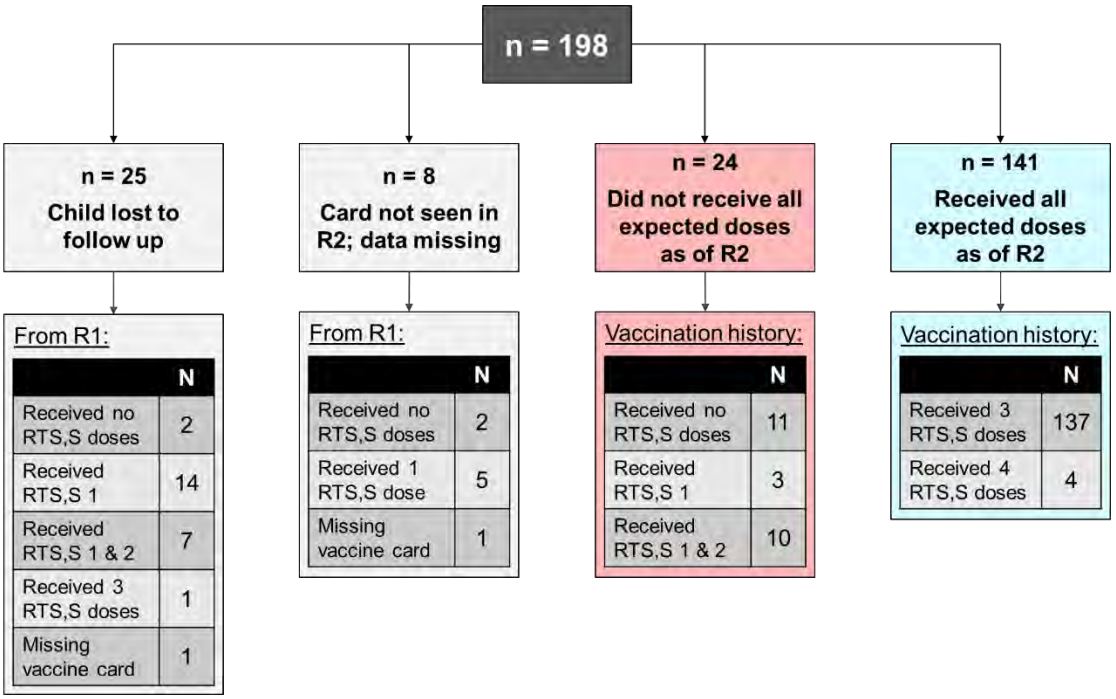
These three adherence categories are explored in further depth in Figure 3. Twenty-four non-adherent (n=11) or partially adherent (n=13) cases were observed in R2. Data were missing on eight cases due to missing vaccination cards; among these eight cases, two were categorized as non-adherent and five as partially adherent based on vaccination history data collected in R1. As noted above, data on one individual was missing in both R1 and R2.

Figure 2. Receipt of preceding vaccines and RTS,S dose 1 to dose 3 in primary child caregiver cohort.



Note: Each bar represents the frequency with which children either received (dark grey) or did not receive (red) a given antigen. Individuals missing a vaccination card are shown in yellow and LTFU in R2 are shown in blue. The light grey curves between the bars represent the path of individuals through the vaccination process. Receipt of doses is only included in the graphic if data were abstracted from vaccination card; data from PCG recall are not included.

Figure 3. Receipt of RTS,S doses in primary caregiver cohort, by uptake category.



Note: Receipt of doses is only included in this graphic if it is recorded on the vaccination card (no recall). Among the PCGs who were not LTFU, 8 did not have a vaccination card available for view in R2; the existing data from R1 is used to record any available information on their vaccination histories. Recall of any additional doses is explored in further detail below.

It is important to note that, as in R1, children in R2 who had not yet received dose 3 may have received it after the interview was conducted. More accurate uptake findings will be available from the final, R3 interviews.

Reasons for non- or partial adherence

PCGs categorized as non- or partially adherent were asked why their child had not received the expected RTS,S doses. Tables 6 - 8 group PCG responses by primary issues identified and summarize variable explanations given by the PCGs. Table 6 presents findings on the non-adherent cases, Table 7 the partially adherent cases, and Table 8 captures responses from eight individuals missing vaccination cards.

Table 6. Reasons given by PCGs for their children not receiving any RTS,S doses.

Primary Issue	Variable Explanations Given
Information gap (n = 3)	Three PCGs exhibited significant gaps in information about RTS,S and weak connections to the health system. Despite their children not receiving any doses, all three expressed trusts in vaccines generally, were enthusiastic about a malaria vaccine, and open to their children receiving the vaccine. One PCG, for instance, believed that her child had received three malaria vaccinations (R1) and as a concluding thought to the R2 interview asked: *"How many [malaria] vaccines does he have left"?* (C25_047). Another, who took her child to a private clinic for vaccinations, had very little information about RTS,S in both R1 and R2 interviews, asking as her final question: *"Given that the book says she hasn't received the malaria vaccine, where can I go to get it?"* (C18_004).
Injection-related adverse events following infection (AEFI) experience (n = 3)	Three of the caregivers described initially hesitating to accept RTS,S due to fears of the injection, recounting their own or a close relative's bad experience with an injection. For instance, one individual explains that her sister's child died soon after being vaccinated, causing her fears and her husband to forbid taking the child for vaccination (C5_006). All three of these caregivers ended up overcoming their initial hesitations and wanting their children to receive RTS,S, but were no longer eligible to receive the vaccination by that point. For example, one PCG decided to not allow the child to receive RTS,S when it was introduced because of prior AEFIs, but had a change of heart after hearing many positive messages and testimonials about it from others who took it (C11_004).
Early concerns, early rumors (n = 2)	Two PCGs delayed taking RTS,S due to early concerns and rumors about RTS,S. In one instance, the PCG was confused about "*this new vaccine*", wondering *"what disease is it for?*" (C2_006). She also was confused about the phased introduction of RTS,S and further discouraged by her husband's skepticism of the value of vaccines. Similarly, another of these individuals describes early skepticism in R1 induced by rumors about RTS,S being experimental on African children. In the R2 interview, both caregivers explained that they have changed their mind and now sees that the malaria vaccine is beneficial. Similar to other mothers who initially rejected the vaccine and are whose children are now ineligible, they are open to their children receiving the vaccine and hope that eligibility criteria will be broadened to include older children (C2_007).
Access to care (n = 2)	Two PCGs describe barriers to care as the main reasons for their children not receiving RTS,S. Though under-informed about RTS,S, one of these caregivers expresses significant trust in vaccines and a keen interested in her child receiving RTS.S. She has tried multiple times to have her child vaccinated without success due to health worker strikes and coming at the wrong time. As a closing thought to the R2 interview she says she wants to know: "when is it [malaria vaccine] coming?" (C11_005).
Perceived as received (n = 1)	In one case, the mother perceived that the child had received RTS,S doses, even though the child health card does not have any record of RTS,S. It was not clear whether the issue is a documentation error or, if not, why the vaccine was not received.

Overall, PCGs in the non-adherent category were accepting of RTS,S, but delays in receiving dose 1 – due to initial hesitancy or had limited awareness / access to RTS,S – led to their children becoming ineligible (too old) to start the schedule.

Table 7 summarizes issues related to initial hesitancy or low demand for the vaccine were less prevalent among the PCGs partially adherent category. Instead issues of access or supply-side barriers took precedence, such as facility stock outs, health worker strikes, or having been turned away. When personal circumstances interfered with the PCGs' ability to take their children for later doses, challenges were often framed as competing household responsibilities or personal circumstance (illness, work) rather than as doubts or fears about RTS,S. In this sense, drop-out for the later doses of RTS,S appears to be similar to what has been observed for other antigens.

Table 7. Reasons given for by PCGs for their children receiving only one or two doses.

Primary Issue	Variable Explanations Given
Access to care (n = 4)	Five mothers cited access reasons for not receiving subsequent doses of the vaccine. This included issues such as "*the nurses were not there*" (C12_006), "*there are times when I come here, I find vaccines are not available*" (C12_009_R), or "*when you go there […] they send us back and promise us that they will visit us*" (C19_004).
Personal situations, barriers (n = 3)	Several caregivers had personal or household challenges that prevented them from taking their child to the under-five clinics. For two of these mothers, this was personal sickness that prevented them from being able to make the journey to the clinic: "*I have been sick and at home and as such I never had a chance to bring him back for his vaccination visits*" (C18_006). For one mother she migrated out of the household for three months for work purposes, and this kept her away from the area where the under-five clinics were held.
Information gap (n = 2)	Two mothers said they had not been informed by the health worker of subsequent doses – or the timing for subsequent doses – and thus had failed to take the child back for the additional doses: *"They did not clarify to me that I need to take him back. I was only told about the one that he got that day before I took him."* (C16_006)
Perceived as received (n = 2)	Two mothers indicated their belief that their child has received all of the intended vaccines. One of these caregivers had an improperly documented vaccine card (no malaria vaccine stickers). This may be a case where the child was indeed taken for the subsequent doses, but this is not able to be verified through the child health card.
Complacency (n = 1)	One mother indicated that she had not yet taken the child for follow-up doses, because "*I can say I have just been lazy [chuckles]"* (C17_003). She did have other secondary possible threats (prior experiences of stock outs, having heard rumors), but this was the primary reason she cited for missing the later doses of the vaccine.
Anticipated at next appointment (n = 1)	One mother indicated that she anticipates her child receiving the vaccine at the next appointment, but the infant is not yet due for the third dose.

The majority of PCGs who were unable to present a vaccination card in R2 believed their children had received all recommended RTS,S doses to date. This perception may be a genuine reflection of children who have received all three doses but are missing a vaccine card to document receipt, or it may represent cases where the child has missed doses, but the PCG is not aware of it due to the lack of a child health card.

Table 8. Reasons given by PCGs missing vaccination cards for their children missing one or more RTS,S doses.

Primary Issue	Variable Explanations Given
Perceived as received (n = 5)	Many mothers without vaccine cards indicated their belief that their child has received all of the intended vaccines. This archetype may reflect mothers who genuinely have taken their child for the subsequent doses – but it is not able to be verified through the child health card – or mothers whose children have missed the latest doses but are not aware of it due to the lack of a child health card.
Access to care (n = 1)	One mother cited access reasons for not receiving subsequent doses of the vaccine. She specifically related this to the COVID-19 pandemic, saying that they *"we were pushed back… because of corona"* (C24_041).
Personal barriers (n = 1)	One caregiver had personal or household challenges that prevented them from taking their child to the under-five clinics, noting that "*I thought it wise to just be staying at home because I wasn't psychologically well*" (C27_063).
Unknown (n = 1)	One individual was missing a vaccine card in both Round 1 and Round 2. It is not clear why they did not receive the vaccine.

While we have grouped reasons non-adherence and partial adherence by main issue, it is important to emphasize that a confluence of factors is often at play and the tables above only document the most proximal factor. For example, one mother who said that she skipped the later RTS,S dose was because the facility is too far. But she also explains that her child had diarrhea since the last vaccine, which she perceived to be a side effect of RTS,S that seemed to confirm for her early negative rumors she heard about the vaccine. Thus, while the proximate barrier appears to be one of access, more distal barriers – exposure to rumors followed by perceived AEFI – may have influenced her decision to not seek the later doses. These varieties of factors – and the cumulative effect of several barriers or threats – may amplify caregiver vulnerability to under- or non-vaccination.

Factors promoting / threatening adherence to the RTS,S schedule through dose 3

To further understand issues affecting variable adherence to the RTS,S schedule through dose 3, we utilized our analytic framework applied to R1 data to identify factors that would likely promote or threaten RTS,S adherence. *Promotive* factors and *threats* shown in Table 9 represent a broad, deductive coding scheme used on R2 data, built from the existing R1 coding scheme. Additional themes were identified through inductive coding.

Table 9: Factors promoting (Promotive) or threatening (Threats) RTS,S uptake and adherence.

PROMOTIVE	THREATS

• Expressed confidence in:
  o vaccines/RTS,S safety and effectiveness
  o provider and health system competence
  o intentions of key actors (government, industry, research community)
• Historical reference to positive impact of vaccines on the population's health
• Positive experiences with child health/vaccination services
• Positive social support to receive vaccines/RTS,S (e.g. family member reminds PCG to take child for vaccination)
	• Exposure to rumors and misinformation about vaccines/RTS,S safety and effectiveness
	• Confusion and concerns about targeted (phased) RTS,S introduction
	• Fear of too many vaccines
	• Complacency or previous delays in vaccine uptake or refusal to receive vaccines/RTS,S
	• Negative clinical encounters and distrust in providers
	• Negative social support to receive vaccines/RTS,S (e.g., personal network member urges PCG to refuse vaccination)

PROMOTIVE	THREATS
	Added themes in R2: • Barriers to accessing services at the facility (e.g. stock outs, facility closures, or health worker strikes). • Personal or household challenges (e.g. ill family member or household responsibilities).

To visualize patterns of promotive and threat factors in the whole sample, coded text was subsequently reduced to binary present/absent variables and the results used to create spectrum displays shown in Figures 4 and 5. Each segment in the displays represents one individual. Bolded lines around blocks of individuals represents community sites. Position of individuals in the side-by-side promotive/threat displays are not necessarily the same.

We caution against over-interpretation of these initial data displays as systematic verification and internal validation of codes applied has yet to be done. Additionally, the absence of color, indicating no coded text, could be due to inconsistent probing or to participant reticence. With these precautions in mind, we find the patterns discovered "good to think with" and useful for directing future analytic focus.

Promotive Factors

Figure 4 (page 17) compares promotive factors found in data from R1 to R2. A majority of the PCGs in both rounds expressed one or more factors that were conducive to the acceptance of vaccines, however, the specific nature of promotive factors has evolved between the two rounds.

In R1, promotive factors were predominantly centered on trust in vaccines generally (indicated in dark green in the spectrum displays) and in the in the health system (indicated in light green in the spectrum displays). As a newly introduced vaccine, there was limited confidence in RTS,S, with participants instead citing their broad trust in the system and vaccines as a basis for having confidence in RTS,S:

> *If the government has approved something, I will go for it. I don't sit back and question it. The government has good reasons for launching any vaccine.* (C18_002, R1)

While similarly broad trust in the system and vaccines was evident in R2 replies, a strong majority of PCGs in R2 now also indicated specific confidence in RTS,S specifically (indicated in the spectrum displays in light purple), exemplified by the quote below:

> *Every year, a lot of children get malaria and some even die from it. Therefore, the vaccine was brought as a solution to this problem. So, it can also be beneficial to us, the parents. For me, I understand that this malaria vaccine is good.* (C5_007, R2)

Specific trust in RTS,S represents a shift in the overall pattern of promotive factors from R1 to R2. Most PCGs tied their confidence in RTS,S directly to firsthand observations or experience in their child: "[she's] not getting sick as often," "malaria does not attack him," and "now the malaria episodes have reduced." This observed change was directly attributed to the introduction of the RTS,S vaccine:

The fact is the child who has received the vaccine has been protected. A child may suffer from other diseases when we go to the hospital for a test they found out that it's not malaria. Also, when the child is sick the body temperature doesn't get so high, which means vaccine is really protecting. (C22_023)

Some PCGs directly compared the health of their vaccinated children their unvaccinated older children or others in the community as confirmation of the benefits of RTS,S:

Since I got my child vaccinated with the malaria vaccine I see that she is healthy. There's a mother in this household who doesn't vaccinate her child. I can see the difference between my child and hers. (C1_002)

Increasing trust in RTS,S was also associated with PCG observations that "nothing bad happened" after the vaccine was administered. Parents felt that AEFIs were generally not a problem and placed them in the category of "not severe," "normal," and thus manageable. The lack of scary side effects bolstered trust in RTS,S specifically.

Threats and Barriers

Figure 5 (page 18) compares threats to confidence in and uptake of RTS,S in R1 and R2. While similar threats are present in both rounds, R2 findings indicate a dramatic overall decline in threatening factors compared to R1. This is evidenced in Figure 5 by the increasing amounts of white space in the spectrum display. As with promotive factors, the nature of threats in R2 has shifted compared to R1.

Rumors (indicated in salmon red in the spectrum display) and negative clinical encounters (indicated in light pink in the spectrum display) persist as threats in R2. However, while several PCGs recounted having heard rumors about RTS,S or had seen someone refuse her child to receive the vaccine, most individuals now also display resilience to these rumors and doubts, saying they are "not true," "untrustworthy," "I found out they were lies". Lived experience and firsthand observation of RTS,S delivery in their communities – e.g., "personally, I've not seen that" – since launch of the vaccine contribute to observed declines in threats from R1 to R2, illustrated well by this PCG:

When I initially came for it, there was word going around that our children will be crippled, and many people avoided it. Since the implementation began, we have not heard any problem with it, not even a crippled child or even a bad swelling after an injection. The children are just okay. (C17_006)

Instead, the PCGs tend to recount their firsthand experiences of the health benefits of RTS,S, which outweighs the rumors:

At that time I heard that this vaccine is harming other kids as they are developing some itching things. But for me, when I accepted it because I saw that it was important and that my child won't be suffering from malaria. (C24_037)

In line with this decline in the potency of rumors, rumors and negative clinical encounters are no longer cited as key reasons for missing RTS,S doses.

R2 findings also show a decline in threats linked to the new vaccine introductions. In R1, many PCGs expressed concerns about the number of injections children are receiving (indicated in light blue in the R1 spectrum display). Confusion and specific fears about the phased introduction of RTS,S were also prevalent in R1 (indicated in navy blue in the R1 spectrum display). Both threats have almost disappeared from the dialogue in R2 data collection, so much so that they did not merit visualization in the spectrum displays in R2.

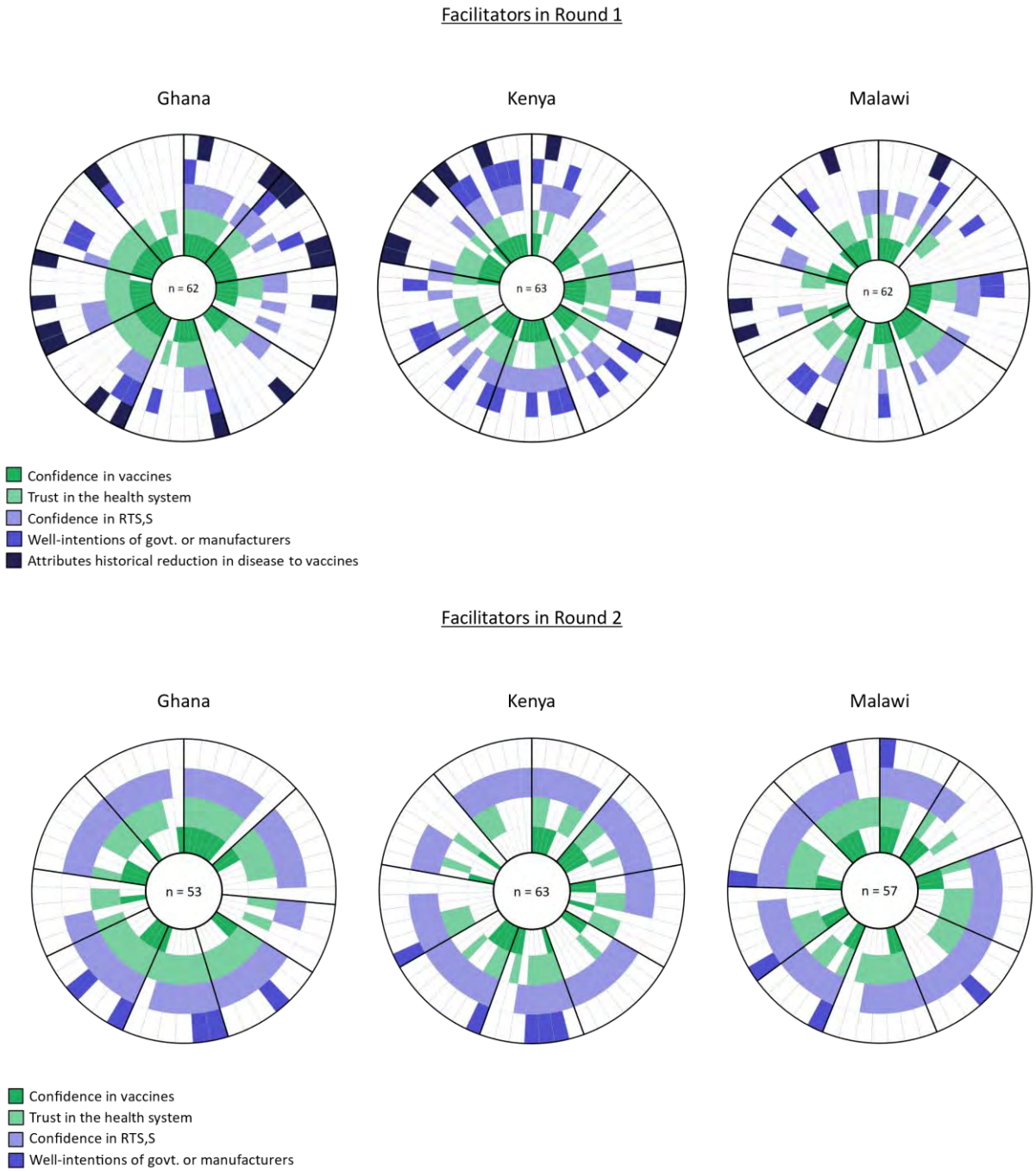
In the absence of these early threats around perception of the vaccine, access barriers have emerged as a slightly more predominant issue (indicated light blue in the R2 spectrum display). The threats that have emerged instead include health worker strikes (in Kenya), stock outs, or difficulty in accessing services (too far, too crowded, unable to access due to COVID-19 restrictions, or the health workers put preconditions to receive vaccination).

> *There are times when I come here to find vaccines aren't available. I go home and wait a while, then come back and to be told that the vaccines have still not been brought or the doctors are on strike then I would go back again.* (C12_009_R)

> *What I would like to let you know is that the way this RTS,S is timed, between six months, seven months, etc., when mothers go for it but are told that they are out of stock, it really discourages most of them. Let the ministry ensure that RTS,S is in all year round in the facilities.* (C14_001)

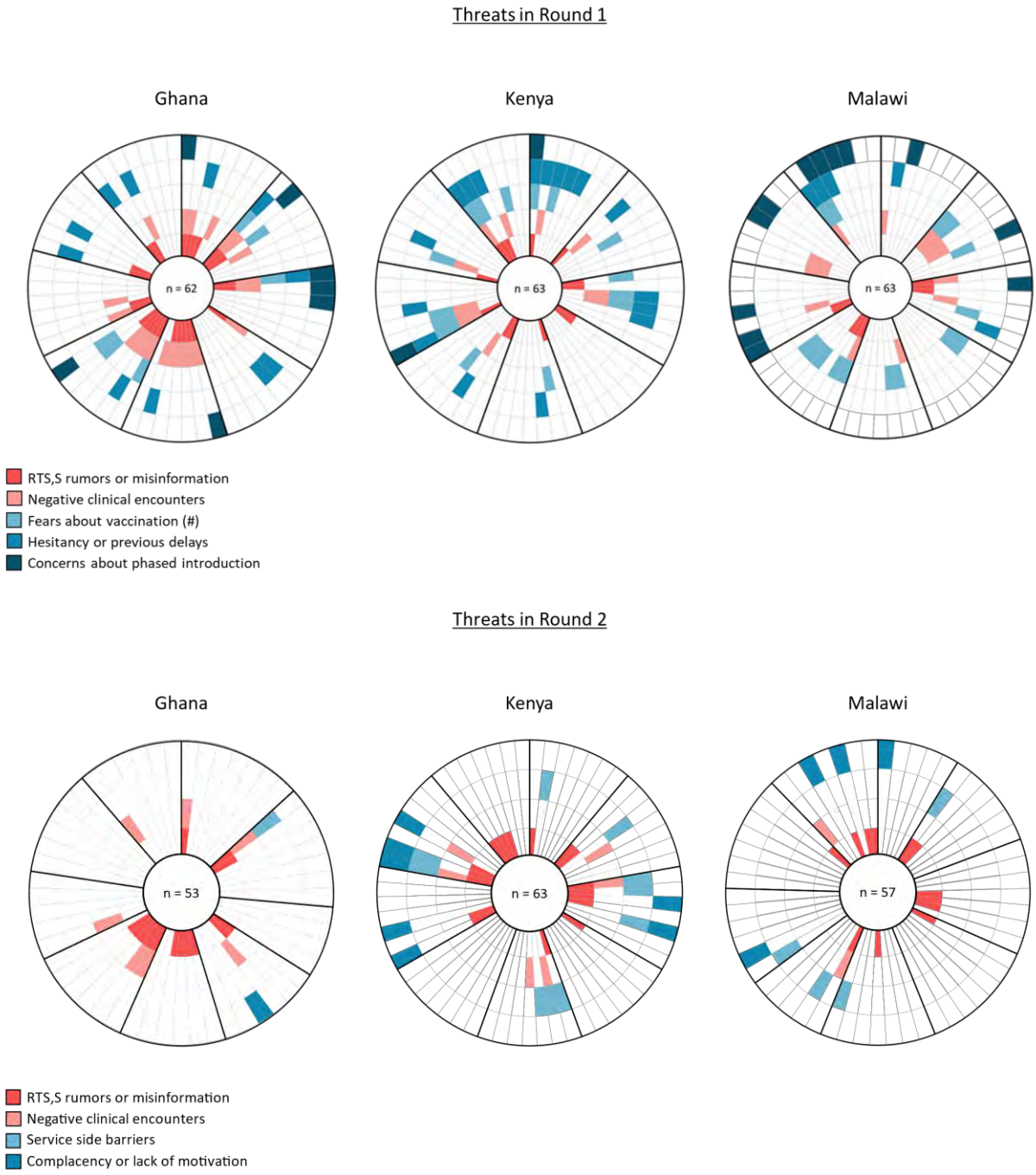
This pattern of access barriers becoming more important in R2 compared to R1 is consistent with the responses given by PCGs as to why their children have not received all recommended doses of RTS,S (see previous section).

Figure 4: Factors promoting RTS,S uptake and adherence reported in R1 compared to R2.



Note: Coded text was reduced to binary present/absent variables to visualize patterns of trust theme categories in the sample. Each color in the spectrum represents a trust category. Categories are not mutually exclusive, and individuals may have codes in zero, one, or multiple categories. Segments without any color indicate that the individual had zero trust themes coded to her. Segments with one of more colored ring(s) indicate that the individual had one or more trust themes coded to her. In short, more color indicates more trust. Different colors indicate different kinds of trust. Bolded lines are shown around blocks of individuals from the same community. Due to the very small numbers of reference to historical reduction in disease as a promotive factor for vaccines in R2, the category was omitted in the R2 spectrum. Individuals' side-by-side position in the promotive/threat displays are not necessarily the same.

Figure 5: Threats RTS,S uptake and adherence reported in R1 compared to R2.



Note: Coded text was reduced to binary present/absent variables to visualize patterns of threat categories in the sample. Each color in the spectrum represents a threat category. Categories are not mutually exclusive, and individuals may have codes in zero, one, or multiple categories. Segments without any color indicate that the individual had zero threat themes coded to her. Segments with one of more colored ring(s) indicate that the individual had one or more threat themes coded to her. In short, more color indicates more threats. Different colors indicate different kinds of threats. Bolded lines are shown around blocks of individuals from the same community. Due to the very small numbers of reference to fears about vaccines (injection and numbers) and to concerns about the phased introduction of RTS,S in R2, these categories were omitted in the R2 spectrum. Individuals' side-by-side position in the promotive/threat displays are not necessarily the same.

Malaria perceptions and behaviors in the context of RTS,S

In addition to lending further support for the key findings described above – that confusion and concerns about RTS,S are diminishing while enthusiasm is increasing – R2 data focused on malaria treatment and prevention behaviors add insight on other important questions for the MVIP evaluations, namely:

- How does the introduction of RTS,S affect other prevention behaviors? A related concern, is caregiver understanding and acceptance of partial protection of RTS,S?
- Similarly, how does the introduction of RTS,S affect treatment seeking behavior in the event of fever and other common malaria symptoms?
- More broadly, will child caregivers accept a partially protective malaria vaccine, and, if so, why, and if not, why not?

We review R2 findings focused on malaria treatment and prevention around these three questions below.

Impact of RTS,S uptake on other preventions

Of the 173 PCGs interviewed in R2, 145 (84%) reported that their RTS,S-eligible child slept under a bed net the previous night. Often accompanied by an explanation of partial protection from the malaria vaccine, most of the caregivers said that their prevention behaviors have not changed since their child started receiving RTS,S doses. Replies to the fixed-choice question, *How often does [RTS,S-eligible child] sleep under a bed net?*, are consistent with these qualitative findings (Table 10).

Table 10. How often does [RTS,S-eligible child] sleep under a bed net?

	Child Slept Under Bed Net Last Night		
	Yes	**No**	**Total**
Every time s/he is in bed	130	2	132
Most of the time s/he is in bed	3	4	7
Sometimes when s/he is in bed	12	5	17
Rarely	0	13	13
Total	**145**	**24**	**169**
Missing data	*1*	*3*	*4*

Equally small numbers of caregivers described either increasing or decreasing bed net use with the child since the introduction of RTS,S. Explanations for increasing bed net use tended to reflect more consistency in putting the net down every time the child was in bed, sometimes connected to messages emphasized by health workers. We found only eight cases where caregivers explicitly said that bed net use had declined since their child received RTS,S, two linking the decline to uptake of RTS,S.

Bed net use increased:

It has changed. At first, I could stay outside for long in the evening [but I did not] release the bed net unless I am also going to sleep. They [nurses] made me understand that I should put him in the net as soon as he is bed. (C5_001)

Bed net use decreased:

I wanted to see whether it [the vaccine] was good or not. That's why I stopped using it after 3 months. I used the coil too for sometimes and I also stopped it. After I stopped the coil and the bed net, till now, they have not had malaria. (C6_002)

Main Barriers to Bed Net Use

- Heat, suggesting net use may vary across the seasons
- Skin rashes, attributed to the insecticide and sometimes leading to washing the net prior to use
- Torn or damaged nets
- Not enough nets in the household

Findings from R2 suggest that uptake of RTS,S does not generally lead to reductions in bed net use. It is possible, in fact, that intensified messaging about malaria and malaria prevention with the introduction of RTS,S may help to maintain or increase bed net use. Data from R3 may shed more light on this possibility, but more definitive understanding of this dynamic will need to be confirmed in studies with representative samples.

Impact of RTS,S uptake on treatment seeking for malaria symptoms

Sixty-four of the PCGs reported that the RTS,S eligible child had one or more episodes of malaria since the R1 interview, Table 11).

Table 11. Bed net use and RTS,S uptake by recent malaria episode in the RTS,S-eligible child.

Reported Bed Net Use and Documented RTS,S Uptake		Malaria Episode Perceived in RTS,S-Eligible Child Since R1 Interview			
		≥1 reported (n = 64)		None (n = 108)	
Bed Net Use Last Night	Yes	52	81%	92	85%
	No	11	17%	16	15%
	Missing data	1	2%	0	0
RTS,S Doses Received	0 doses	8	13%	5	5%
	1-2 doses	10	16%	8	7%
	3 doses	45	70%	95	88%
	Missing data	1	2%	0	0

* 1 case missing data

Regardless of the number of RTS,S doses received, almost all of these 64 caregivers whose child experienced a malaria episode said they promptly sought help at a health facility or from a community health worker, 59 of whom said that malaria was diagnosed by finger prick or a lab. Over-the-counter fever medication was often also given to child initially and, less frequently, home remedies. But neither of these home-based treatment actions seemed to delay care seeking. Like R1 findings, the main triggering symptoms were fever, lethargy, child not eating, and other various symptoms.

Acceptance of partial protection in a malaria vaccine

A strong majority of caregivers expressed favorable impressions of how RTS,S is affecting child health in their own households and in the broader community. Among the 173 PCGs interviewed in R2, at least 130 perceived malaria in their household and in their community to occur less frequently (n≈117), to be less severe when it did occur (n≈26), and/or to be generally beneficial to child health (n≈13). These positive impressions were expressed with equal frequency by 45 caregivers whose children had recently experienced malaria despite having received three doses of RTS,S. All three quotes below, which exemplify caregivers' positive sentiments, are from this sub-set of 45 individuals:

Malaria is less frequent

I think the malaria vaccine has helped. I left the community and returned last Thursday but since I came, I have not seen anything like malaria. I can also say that it is good because, if it wasn't for her getting sick in XXX, she hasn't fallen sick the whole year. So, I will say that it is good for me. (C2_003)

Malaria is less severe

I would say that the attack was not severe [this time], but in the past when my twins got malaria, they would even have seizures. I have not seen this with this vaccine. Sometimes when you are at the market, you receive a call that the child is having seizures and when he is taken to the hospital, the report is that he had a high fever plus malaria. I have seen some beneficial changes with this vaccine. (C18_002)

The vaccine is beneficial to child health

It [the vaccine] is good and I can see it is helping her. This child had been sickly, but since she started receiving that vaccine, she does not have problems nowadays. Since she was vaccinated, she has only fallen sick once. (C11_007)

We coded eight instances where caregivers felt that the vaccine was not making any difference ("I don't think it's helping"; "even with the vaccine he still gets malaria") and one case where the caregiver perceived risk associated with the vaccine:

At first, I thought it [the vaccine] would protect her, but it has rather caused hardship on me. No one told me anything but if I look at the way she has been having diarrhea I thought maybe it could be from the vaccine. (C4_002; child had received fewer than 3 doses at time of interview)

Despite the prevailing perception among caregivers that RTS,S is having a positive impact on malaria in their communities and families, among the most frequently cited remaining questions about RTS,S had to do with the duration and level of protection the vaccine offers.

Experiences and information received at the last vaccination visit

Visit triggers, barriers, and overall satisfaction

> *When they told us when to take our kids for malaria vaccination, I kept the dates in my heart.* (C24_037)

A large majority of the caregivers described one or more ways they remembered vaccination visit dates. The most common way they remembered, cited by more than half of the participants, was to consult the child's health card. Whether the caregiver tried to "keep the date in my head" or to "write it down and put it in a special place," checking the child health book was an important reminder to not miss the vaccination visit date. Reminders from health staff, particularly on weighing day, but also community health worker announcements and outreach, were also important and frequently cited reminders: "*We are told by community health workers. On our own we can't remember*." (C26_056) Reminders from personal network members – husbands, neighbors, other

mothers – were another prominent trigger to take their child for vaccination, while radio or TV announcements, cell phone alerts, and prompts from and other health visits were other, but less frequently, cited reminders.

A wide variety of challenges to remember or make the vaccination visit were described by almost 50 caregivers. Various personal circumstances (e.g., cannot read, lack of time, extenuating circumstances, travel/migration, illness, etc.) were the most prominent reasons cited, followed by anticipated or known vaccine stockouts, health worker strikes, or off-putting health worker attitudes (n≈20), and various other issues (distance to facility, lack of documentation/lost card, information gap/confusion about dates, and conditions to receive care).

Interviewers did not consistently ask PCGs to describe their overall satisfaction with the last visit. Paralleling overall positive views about the health system, generally, when asked about the last vaccination visit, PCG responses were most often positive (e.g., “all that they do I like”, n=79) or neutral (e.g., “there were no problems”, n=33) in nature. Very few replies reflected a negative experience, and these tended to be based on specific complaints (painful for the child, stockout, not enough information was given, etc.)

Information received and perceived AEFIs

Close to two-thirds of caregivers recalled receiving one or more messages about RTS,S during their last vaccination visit, while the others replied that they “forgot what was said,” that they could not hear the health talk “because we were many,” “I got there late,” or that the providers “didn’t tell us anything.”

Among the caregivers who could recall hearing an RTS,S message at the last visit, reminders to bring the child for the fourth dose were cited most frequently (n=51). In giving fourth dose messages, providers often emphasized greater protection from receiving all four doses and/or reminded the caregivers to bring the child at 22 months or around two years of age:

> *The providers told me that even though she had received 3 doses, I should not stop there because for her to get full protection she must receive all the doses.* (C10_003)

Given that messaging from health talks was inconsistently heard or recalled, mothers at times recounted one-on-one encounters with the provider which, however brief, served as important vehicles for messaging:

> *I woke up very early that day and walked all the way to facility X. Many clients were already there, so we had to queue. The provider collected all our mother-child books and started calling our names in the order in which we had come in. She called the babies’ names one at a time, and as she gave the malaria vaccine, she urged us to complete all the four doses. She jabbed my son and told me that it was the third one and that he still had one more to go when he turns two.* (C14_002)

These encounters suggest that RTS,S messaging may be strengthened in the course of service provision through simple personalization or one-on-one exchanges with the provider. While the mother quoted above appears to be, on her own, motivated to accept the vaccine,

that the reminder was personalized to her child and delivered in a one-on-one exchange with the provider may have helped make the mother aware of key information about the timing of dose 4, instead of being potentially lost in a difficult-to-hear group education session.

Caregivers frequently recalled advice about managing mild adverse events following immunization (AEFIs) and information about when to seek professional help for an AEFI. Distinct from messages about AEFIs, eight caregivers alluded to providers emphasizing that the vaccine was safe:

> *Every day that we go for CWC, they tell us that we should not be afraid and that all those rumors that it will sterilize or paralyze the child are not true.* (C2_001)

Six of these eight individuals were from Ghana, likely reflecting the MOH's aggressive response to early rumors there about RTS,S.

The need to continue bed net use was infrequently recalled; messages about the need to seek care promptly in the event of fever was not cited by any of the participants. Combined with findings on persistent questions, the rare recall of malaria prevention and treatment messages from the last vaccination visit underscores the programmatic challenge to communicate effectively about partial protection.

Plans for receiving dose four

A strong majority of caregivers indicated that they intend on bringing their child to receive the fourth RTS,S dose. While some individuals replied simply that they will do as instructed and go when it is time, most of the caregivers expressed a rather strong commitment to ensuring their children received the last dose:

> *I have put it in mind that, when she turns two years, no matter what, she will receive the malaria vaccine. So, I'm planning toward it. No matter where am or what I'm doing, I will stop and take her to receive the vaccine when she's two.* (C1_001)

> *If I had second thoughts about it, I wouldn't have taken her to the clinic today.* (C16_009_R)

> *I am trying to keep track of the date to bring him back at twenty-four months. I won't get tired. It's just a regular clinic visit that you must keep bringing him to until the last clinic appointment. I'll make sure he gets all the vaccine doses.* (C17_001)

> *She already started receiving the vaccine, so I can't stop on the way. I need my child to complete it in December to make it better.* (C21_019)

Relatively few caregivers indicated that they had no clear plans to take their children for the last dose or were unaware of dose four details and timing.

Persistent questions and concerns

At three points in the R2 interview, participants were invited to share any questions, concerns, or thoughts they have about RTS,S. Specifically we asked:

- What questions did you have during the last vaccination visit?
- What concerns or worries to you have about the malaria vaccine?
- Do you have any final thoughts or questions about RTS,S or other topics we talked about today?

Additionally, PCGs sometimes volunteered their questions or concerns while responding to interviewer probes. This section summarizes findings on data from these open questions and probes. All told, we coded 122 questions/concerns cited by 98 caregivers. Questions/concerns were inductively coded and grouped into the following four broad categories: Protection, Eligibility/Schedule, AEFIs, and Other.

As described in Table 12, the most frequent questions/concerns related to the level, duration, and type of protection offered by RTS,S, often revealing persistent information needs about partial protection. Although understanding of these issues was much stronger in R2 compared to R1, many of the caregivers continued to have questions about the timing and number of doses their child should receive as well as about age-based eligibility. As relates to AEFI and safety concerns, far fewer caregivers expressed concerns about adverse events generally and injection-related AEFIs specifically. Most AEFI concerns focused on the seeing their child suffer from and managing "normal" AEFI, with only a few individuals having questions about the vaccine's safety.

Table 12. Persistent Questions and Concerns.

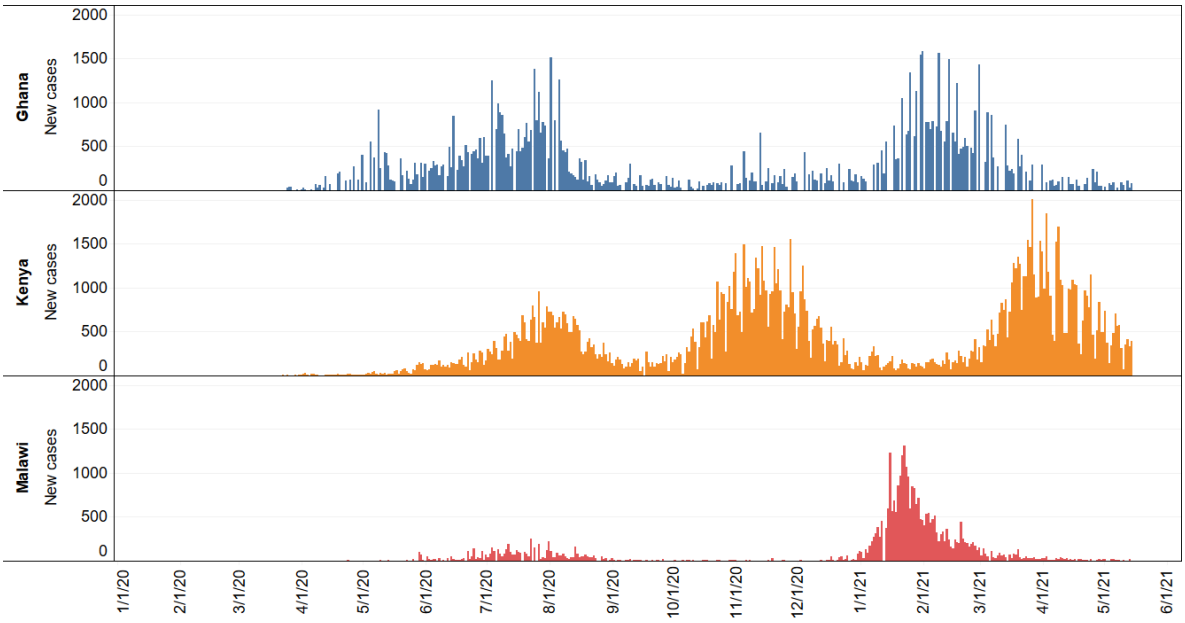
Category	Description and Examples
Protection (n = 54)	Questions about type, level, and duration of RTS,S protection, variably focused on: **Partial protection:** *I just wanted to know why the child gets sick despite being vaccinated.* (C19_006) **Duration of protection:** *I would only like to ask about how long this vaccine stays in the child's system because that is what I don't know.* (C11_005) **Protection after the 4th dose:** *I want to know if the baby will experience malaria after two years since the last dose would be taken at two years.* (C6_007) **Need for the 4th dose:** *But I wish to know… what would happen if the child does not receive the last dose?* (C9_007) **Severity of illness after receiving the vaccine:** *Should assume malaria when the child has a fever and . . . should take her to the hospital or just ignore.* (C16_002) **Protection against other diseases:** *I asked if it will protect my child from all sickness.* (C4_007) **General questions about reason RTS,S was introduced:** *Why did the government decide that children must get the malaria vaccine?* (C16_008_R)
Eligibility / Schedule (n = 33)	Issues focused on the timing and number of doses, as well as age of eligibility to receive RTS,S. Recurrent themes included: **Specific questions about the number of doses or the schedule:** *What I want to know is the number of times my child is supposed to take the vaccine*. (C3_007) *I asked her the reason for taking the third vaccine*. (C8_006) **What happens after dose 4:** *When she gets to 2 years, she wouldn't be injected again till she grows, or will she receive additional doses at a certain age?* (C1_007) **Eligibility age:**

Category	Description and Examples
	Why do you guys just dwell on the young children? Why can't those ones who are like five years or so be given a vaccine too? (C14_002) **Other issues:** *[If she misses a 6-month dose], can she take it maybe one month later?* (C1_001) *Why is the schedule so long, What happened to lengthen the months and days like that?* (C25_043)
AEFI and Safety (n = 19)	The majority of questions and concerns about adverse events related to mild or normal AEFIs and only a few reflecting greater concerns about safety and the rumors they had heard. Issues raised were included: **General questions about AEFIs:** *What I want to know is that, when my sister's child received the vaccine she had an adverse effect but when my child received hers nothing happened to her so I wanted to know.* (C8_002) *I would like to know why the baby develops fever after receiving this vaccine.* (C14_006) **Worries about managing normal AEFIs:** *What worries me is only fever whenever I take her, then I must deal with fever.* (C10_003). **Questions and lingering concerns stemming from rumors:** *What I want to ask is about those who are saying the malaria vaccine is not good. Is it true that that it is not good?* (C2_003) *Because of the rumors, sometimes I worry and ask myself, 'He is young and is taking this vaccine. Do I burden him if the rumors turn out to be true and as a result he ends up infertile?'. Then again, I tell myself that if the vaccine was not good, they wouldn't have injected him with it.* (C5_001)
Category	**Description and Examples**
Other issues (n = 15)	Various other issues include questions and concerns about: **Phased introduction and, closely related, how the vaccine came about:** *I would like to know where that vaccine came from and how it started because other children aren't getting it. Why can't these others [with same-age children] told that they were not eligible?* (C13_003) *I just ask myself that how did this vaccine came about?* (C27_063) *Who has brought it?* (C22_022) **Service access:** *Because most people are receiving it but, in this area, it is not yet there.* (C11_005) *I wanted to ask what happens when something [adverse event] happens at night and we come to knock the nurse's door, will they be willing to help us?* (C8_002)

COVID-19 Context

Ghana, Kenya, and Malawi had all recorded their first COVID-19 cases by early April 2020, with subsequent surges of new cases over the following year (see Figure 6). Governments in all three countries reacted swiftly with containment measures placing restrictions on public gatherings as cases emerged. Ghana and Kenya also introduced restrictions on public transit. Recommendations to stay at home were announced in all three countries several weeks after the first cases, though Kenya's were the most stringent of the three.[6]

Figure 6. Number of new COVID-19 cases, by date (month/day/year), in Ghana, Kenya, and Malawi[7].



Health facilities in all three countries were directed to remain open to continue providing essential health services, including immunization. Service delivery was adapted to mitigate spread of COVID-19. To understand the potential impact of COVID-19 on use of child health services, including adherence to RTS,S doses, in R2 interviews PCGs were asked about their experience of vaccination services during the COVID-19 pandemic, and whether they had noted any changes at their health facility.

While a few PCGs reported delays or interruptions to vaccination visits, by and large the caregivers reported that vaccination was ongoing and that they continued to access services as before. The main changes noted by the PCGs were:

a. Implementation of physical distancing and other risk reduction procedures, such as masks.
b. Attending the facility in smaller groups.
c. Increased wait times for services.
d. Increased concerns in the community about going to the facility due to fear of COVID-19.

[6] https://covidtracker.bsg.ox.ac.uk/

[7] Data from the COVID-19 Data Repository by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. Accessed May 15, 2021 from https://github.com/CSSEGISandData/COVID-19.

e. Suspension of health education talks or weighing (rarely).

Implementation of physical distancing and risk reduction procedures

The most frequently described effect of COVID-19 on vaccination services was the implementation of physical distancing and other risk reduction measures (hand washing, mask wearing, etc.) at the health facility. Some reported that if you did not come equipped with a mask, you would be turned away from the facility:

> *Anyone without a mask is not allowed to receive treatment. All of us women put them on when going there as we were given enough of them.* (C24_036)

Attending the facility in smaller groups

Several caregivers noted that facilities tried to limit crowding by having fewer clients attend child health clinics at the same time. Individuals described being able to attend clinic on a wider number of days, being given appointments for when to attend, or being broken up into smaller groups. Using these measures, facilities staggered the patient flow:

> *Before we used to sit and wait for others to join us before the welfare service starts and we were many. But now it is not like that. They provide services in batches. Even when you get there, there will be only two or three other mothers.* (C5_003)

Some PCGs noted that this has removed the collegial atmosphere where mothers were able to interact and socialize with one another at the clinic.

Increased concerns in the community about going to the facility due to fear of COVID-19

A small number of PCGs also noted that there was increased fear in the community about going to health facilities, particularly hospitals, due to the presence of COVID-19. Concerns ranged from exposing their child to sickness, being perceived as having COVID-19, or being caught up in containment policies (such as curfews). Caregivers who mentioned concerns about COVID-19 did not generally say that these fears had dissuaded them, instead expressing a preference for more localized care:

> *Yes, I was concerned about that. I knew that if I take her to the facility then there would be mingling with other people who may have already contracted the disease (COVID-19) which could make my baby sick too. I therefore preferred taking her to the CHV.* (C14_007)

Increased wait times for services

An equally small number of PCGs also noted that wait times at the clinic had increased, due to the adaptations in service delivery (such as physical distancing and staggering of clients). As a result, they described vaccination taking significantly more time than it had prior to COVID-19:

> *I remember it took me over 4 hours during my last visit. I was very annoyed and frustrated. I hadn't spent 1 hour and 30minutes at vaccination before [COVID], so it was very frustrating experiencing that.* (C1_006)

Suspension of services

Finally, a small number of mothers noted that clinics had initially reduced certain services due to the constraints of COVID-19. Some mothers reported hearing that they should not

attend the child health clinics or weighing sessions unless they were due for an injection (vaccination):

> *We're informed by the providers that if we have a scheduled vaccine, we can come, but other than that we should stay at home because there will be no weighing of the children.* (C6_007)

A small number of mothers also noted that health education sessions had also decreased at the outset:

> *When COVID started they stopped giving us health talks, like what they did every morning when we go for weighing. Now they have started giving health talk again.* (C4_002)

There were elements of community clustering observed in the responses around service suspension, suggesting that suspension of certain services or health education talks was discretionarily done only in certain facilities. Most participants also noted that services had since resumed as normal, suggesting that disruptions to services, if any, were temporary.

CONCLUDING REMARKS

As in R1, this report presents preliminary PCG findings, which have yet to be triangulated with other HUS, MVIP, or program data. Findings reported here are likely to change with deeper analysis and as new data from the final round are considered. Lastly, cross-country findings on PCG data require country-specific contextualization to better call out and understand consistencies and variations across the three countries, some of which is provided in country-specific reports as part of the packet of HUS R2 reports.

With these limitations in mind, there are a few emergent patterns worthy of highlighting. Despite some initial challenges in the introduction of RTS,S/AS01, it seems that many of the "growing pains" have been resolved. Most notably, acceptance of RTS,S is generally high while rumors and concerns about the vaccine have markedly declined. The PCGs in R2 display more positive sentiments about RTS,S, perceiving firsthand benefits of the vaccine for their children while also observing an absence of negative effects or unusual AEFIs. In this sense, uptake of RTS,S seems to be normalizing as PCGs become used to the vaccine being part of their children's vaccination schedule.

Additionally, in our qualitative sample RTS,S uptake did not interfere with malaria treatment seeking or prevention behaviors. Regardless of the number of RTS,S doses received, caregivers promptly sought professional help in instances of fever or suspected malaria in the child, several caregivers perceiving the episode to be less severe due to child's RTS,S vaccination status. Similarly, bed net use in our sample was neither negatively nor positively affected by RTS,S uptake. Although specific mention of bed net use messages received during the most recent vaccination visit was low, overall the caregivers understood and accepted the need for the child to continue sleeping under a net along with RTS,S vaccination. These findings suggest that malaria education was reinforced at additional vaccination visits, this has the potential to increase proper bed net use and prompt care-seeking. While our data do not shed light on the possible effect of RTS,S uptake on other vaccine uptake, they do indicate that child caregivers prioritize child health visits that include vaccination.

While RTS,S is now widely perceived as safe and beneficial to children, there are still barriers to access and unresolved questions for some individuals in our sample. Stockouts and health worker strikes hindered the ability of some participants to receive the vaccine, and many others still have questions about the duration and nature of protection offered by RTS,S. Data from the final round will allow us to investigate if and how these issues influence receipt of the fourth dose of RTS,S and what operational challenges still require resolution.

Notably, PCG findings through R2 shed light on unique programmatic challenges created by the sub-national ("phased") introduction of RTS,S, which to date has not been typical for new vaccines that target widespread diseases such as malaria. Although, from our purposive PCG sample, it is impossible to characterize the degree of impact on RTS,S uptake, our findings suggest that the sub-national introductions likely confounded initial acceptance of RTS,S and receipt of subsequent doses. An important early confounder in Ghana were

social media posts portraying RTS,S introduction as unethical research. In Malawi, a “silent introduction” of RTS,S was used to avoid creating demand that could not be met in non-MVIP areas. This silent introduction strategy led to substantial confusion among PCGs early on, with many conceptualizing RTS,S introduction as research to “know if the vaccine works,” possibly conflating the introduction with an ongoing RTS,S clinical trial in the country. While RTS,S introduction in Kenya was neither ‘silent’ nor affected by early rumors, several PCGs from Kenya expressed questions and concerns similar in nature. In all three countries, a small but important number of PCGs questioned why a malaria vaccine would be introduced sub-nationally when it could benefit all children.

The confusion and sometimes suspicion linked to the phased introduction of RTS,S may have resulted in lower uptake results than would otherwise be the case. While far less prevalent an issue in R2 data compared to R1, as the findings reviewed above show, it remains a source of confusion for a few PCGs and, in at least one case, may have contributed to dose 1 uptake delays resulting in the child becoming ineligible once the PCG was ready to adopt the vaccine. To ascertain if and the extent to which the sub-national introduction of RTS,S accounts for RTS,S refusals or delays, it may be useful to include in MVIP end-line surveys in representative samples, if feasible. The RTS,S phased introduction experience and findings from the PCG cohort also have relevance beyond MVIP. As WHO considers a recommendation on the broader use of RTS,S, including potentially sub-national introductions in some countries, insights from our PCG data may help vaccination programs to anticipate and preempt potential negative effects from questions and concerns people may have about why a vaccine is being provided in select communities or sub-populations.

In all three countries, the R2 findings from PCGs underscore substantial trust and confidence in child health programs generally and vaccines specifically. At the same time, the data reveal issues and events that may undermine this trust, namely: disinformation (e.g., early rumors in Ghana), inadequate information (e.g., the silent launch in Malawi), and service access barriers (e.g., health worker strikes and stockouts in Kenya). There is much to be learned from each of these situations and how they were identified, monitored, and dealt with by EPI programs.

The final round of data collection in PCGs will cover the main topics addressed in R1 and R2 but will focus on uptake of dose 4.

ANNEX 1: RTS,S SCHEDULES AND ELIGIBILITY GUIDANCE BY COUNTRY

GHANA

Dose schedule: 6 months, 7 months, 9 months, and 24 months

Health worker guidance:

- Give dose 1 to any child who is 6 months or older, the first dose can be given through 11 months of age.
- Give the first 3 doses of malaria vaccine with a minimum of 1 month between the doses.
- Give the 4th dose of malaria vaccine as close as possible to the child's 2nd birthday. The fourth dose can be given up to 3 years of age.

KENYA

Dose schedule: 6 months, 7 months, 9 months, and 24 months

Health worker guidance:

- Give Dose 1 as soon as possible after a child turns 6 months. All eligible children can receive the first dose from 6 months through 11 months of age and before they celebrate their first birthday.
- Although the 3rd dose can be given 4 weeks after the 2nd dose, the MoH recommends giving the third dose with the measles-rubella vaccine at 9 months of age to reduce the number of vaccination visits a child requires.
- Give the 4th dose at 24 months (2nd birthday). The 4th dose can be given up to 36 months of age (3rd birthday).
- if child is late, maintain 4 weeks between doses 2 and 3.

MALAWI

Dose schedule: 5 month, 6 months, 7 months, and 22 months

Health worker guidance:

- Children ages 5 months through 12 months are eligible for the first dose of the malaria vaccine.
- A minimum of 4 weeks should be maintained between the subsequent doses.
- Give the 4th dose of malaria vaccine from 22 months or soon after. The fourth dose can be given up to 3 years of age.

ANNEX 2: PCG RECRUITMENT SCRIPT, R1-R3 (EXAMPLE FROM GHANA)

Hello, my name is _____. I am from the University of Health and Allied Sciences.

We are doing research to learn about how people in your community view the new malaria vaccine, called [RTS,S].

You have been selected to participate in this study because you have a young child who can get vaccinations.

We would like you to take part in three interviews. The first interview will be today or another day that is convenient to you. A second interview will be after 6 months, and the third one, in about 18 months from today. Each interview will last for about one hour.

During the interview, we will ask you questions about malaria in your household and how you try to prevent it. We will also ask you about your experience taking your children for health care. We will ask you about your use of vaccination services and about what you think of the services. We will also ask you to tell us what you have learned about the RTS,S vaccine and if your child has received the vaccine.

No research activity will be conducted until you have had an opportunity to understand what the study is about, ask any questions you may have, and agree to the conditions of participating in the study.

Let me know if you would like me to tell you more about the study.

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

World Health Organization

RECOMMENDATIONS (FINAL)

Malaria Vaccine Implementation Programme (MVIP)
Data Safety Monitoring Board (DSMB)

27-28 July 2021, 13:00 – 17:15 CET

Background

In this meeting, the DSMB reviewed results from data collected through 24 months following the first vaccinations with the RTS,S/AS01 malaria vaccine. Meeting presentations included overall program progress for the Malaria Vaccine Pilot Evaluation (MVPE), results of midline household surveys in Malawi and Ghana, and quality assurance tracking and results for the primary safety and effectiveness endpoints for the MVPE. The DSMB also reviewed an *ad hoc* analysis by GSK of Phase 4 safety surveillance and reports from national pharmacovigilance surveillance in the MVIP countries.

During this meeting, the DSMB aimed to determine if safety concerns had been addressed according to the Framework for Recommendation on the RTS,S/AS01 vaccine endorsed by SAGE and MPAG in 2019. This framework stated that a WHO recommendation on the broader use of RTS,S/AS01 could be made if and when:

1. concerns regarding the safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria and sex-specific mortality) are satisfactorily resolved …
2. severe malaria data trends are assessed as consistent with a beneficial impact of the vaccine; or
3. mortality data trends are assessed as consistent with beneficial impact of the vaccine.

The 24-month analysis reviewed at this meeting was designed to be the primary analysis of the MVPE, with this DSMB report intended to inform the MVIP Programme Advisory Group, SAGE, MPAG and others who will be considering recommendations for use of RTS,S vaccine in the next few months. This DSMB report includes our assessment of the MVPE safety (meningitis, cerebral malaria, and sex-specific mortality) and effectiveness endpoints (severe malaria and mortality) for the primary analysis as well as other recommendations to consider as surveillance continues.

General statement from the DSMB

The DSMB congratulates the MVIP Team at WHO, implementing partners, and collaborators at GSK and PATH once again on the progress made on this ambitious program and for reaching this important 24-month primary analysis milestone.

Session 3: Malaria vaccine pilot evaluation (MVPE) 24-month primary analysis

DSMB Conclusions on the primary [MVPE] endpoints

1) The DSMB's interpretation of the MVPE 24-month results is that the safety signals seen among 10,306 infants and children who received RTS,S in the Phase 3 clinical trial of RTS,S (2009-2014)[1] 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 pilot evaluation sentinel hospitals (4,870 from implementation areas), during the period from start of vaccination in 2019 until 30 April 2021 . The DSMB concludes that the MVPE results indicate comparable burden for meningitis, cerebral malaria, and gender-specific mortality among age-eligible children living in implementation areas and those in the comparison areas. This conclusion is based on:

    a. The updated power calculations for the three safety endpoints indicating 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[2] on population-level effects.

    b. The MVPE results consistently show risk ratios near 1 (i.e., no association) for probable meningitis, cerebral malaria, and the vaccine-sex 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 that the vaccine was associated with increased risk levels for those specific three endpoints were rejected.

    c. The DSMB acknowledges that the pilot implementation of the vaccine and evaluations by in-country research partners are conducted in real-world settings and will generate an imperfect dataset—unlike a Phase 3 clinical trial. The MVIP team and partners seek to ensure as much complete and quality-assured data are available as possible for the analyses. The DSMB and PAG have sought to identify areas for improvement since the beginning of the programme, and the MVIP Team has largely acted upon these areas. Any deficiencies or missing data are expected to be equally distributed between the RTS,S/AS01 vaccine-implementing areas and non-implementing areas so as not to bias the analysis. The following limitations were noted, but these uncertainties do not alter DSMB conclusions regarding safety:

        i. Compared to the analyses of the other safety endpoints (deaths among girls and meningitis), the cerebral malaria analysis had an upper confidence limit (1.69) closer to the point estimate of the Phase 3 trial (1.8). The DSMB is less certain about the results on 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. This relative uncertainty should not stop a recommendation for broader use of RTS,S. We support plans to strengthen the safety assessment for cerebral malaria through further data collection in the MVPE that includes tracking of this endpoint.

[1] https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)60721-8/fulltext

[2] Contamination as defined in the context of the MVPE could occur due to various factors, including for example if children in comparator areas receive the malaria vaccine.

ii. The DSMB notes the challenges with meningitis surveillance, specifically the potential for many missed probable and confirmed cases because of variable performance of lumbar punctures among suspected cases. We have 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 we do not believe this under-detection biased the analysis.

d. The analysis of RTS,S coverage in the total intervention population compared to coverage among those with safety endpoints showed no differences for the three endpoints.

2) The DSMB also concludes that the MVPE findings demonstrate effectiveness of RTS,S vaccine against severe malaria but that, as expected, the results were not yet powered to detect an effect on mortality. These conclusions were based on:

a. 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.

b. The pooled analysis indicated that RTS,S vaccine significantly reduced the incidence of severe malaria in the implementation areas; a non-statistically significant reduction in all-cause mortality (excluding accidents/trauma) was also seen.

Other comments and recommendations

1. The DSMB does not have an opinion on preferred use of the broad versus more strict definitions for severe malaria. We found it helpful and reassuring that using either definition produced similar results.

2. For several malaria endpoints, the point estimates for Kenya continue to appear qualitatively different than those for Ghana and Malawi. We recommend that the MVIP team continue to explore why this might be the case.

Session 4: GSK *ad hoc* analysis

We agree with the sponsors' conclusion that the Phase 4 *ad hoc* analysis was not interpretable because of the differential missing or not yet entered data, which limited proper estimation of follow-up person-time, and inadequate numbers of completed visits for most participants. No safety signals were seen when reasonable assumptions were made about the missing data. We support GSK's plans to work with site investigators to strengthen data collection methods, improve completeness, and reduce risk of bias going forward. The *ad hoc* analysis should not be used to inform decisions.

Session 5: National pharmacovigilance surveillance

Collecting and investigating adverse events following vaccination remains a challenge for the three national pharmacovigilance programs, with most of the reports coming through the GSK EPI-MAL 003 study or through MVPE, and very few of the serious events or deaths investigated. We appreciate the difficulties of building such programs, with the COVID-19 pandemic adding significantly to the usual challenges. We encourage ongoing efforts to strengthen these important programs. Based on the data reviewed, the DSMB did not find evidence of new conditions that warrant closer safety tracking. Going forward, having clearer diagnoses for reported AESI and severe events would help, as would

investigation and synthesis of any commonalities for significant diagnoses occurring in multiple vaccinees (e.g. liver, renal conditions).

Appendix 1: **Meeting agenda and list of attendees**

AGENDA - Meeting chair: Cynthia Whitney

Day 1: Tuesday, 27 July 2021		
Time (CET)	**Session**	**Purpose & Lead**
13:00-13:15 (15’)	**Session 0: Welcome / introduction** • Introductory remarks • Brief introduction of participants • Review meeting objectives and agenda • Opening remarks • Declaration of interest	FOR INFORMATION DSMB Chair Kate O’Brien, WHO IVB Mary Hamel, WHO
13:15-13:35 (20’)	**Session 1: MVIP update** 15’ Presentation • General overview of COVID-19 situation in MVIP countries and impact on MVIP • Vaccination programmes & RTS,S/AS01 uptake • Malaria Vaccine Pilot Evaluations (MVPE) • Recap pathway for full RTS,S evidence review in 2021 and implications 5’ *Discussion*	FOR INFORMATION Mary Hamel, Malaria Vaccine Team Lead
13:35-14:05 (30’)	**Session 2: Household survey summary** 15’ Midline household survey results: Ghana & Malawi 15’ *Discussion*	FOR REVIEW Patricia Njuguna, WHO/GMP
14:05-15:05 (60’)	**Session 3a: MVPE Quality assurance (up to Apr 2021)** 40’ presentation • QA data from sentinel hospital surveillance • QA data from mortality surveillance • Inclusions and exclusions • Number of events and power 20’ *Discussion*	FOR REVIEW Kerryn Moore, LSHTM Paul Milligan, LSHTM
15:05-15:20	**Break**	
15:20-16:50 (90’)	**Session 3b: MVPE safety and impact outcomes** 30’ presentation • Rate ratios • Limitations 60’ *Discussion*	FOR REVIEW Kerryn Moore, LSHTM Paul Milligan, LSHTM *Report & reference files shared in advance*
16:50-17:10 (20’)	**Closed session – Day 1** **Draft initial recommendations**	DSMB members only

Day 2: Wednesday, 28 July 2021		
Time (CET)	**Session**	**Purpose & Lead**
13:00-13:20 (20')	**Session 0: Welcome / introduction** • Brief introduction of participants • Review meeting objectives and agenda • Recap of Day 1 / any updates • Opening remarks	FOR INFORMATION DSMB Chair, Cynthia Whitney Kate O'Brien, WHO Immunization, Vaccines & Biologicals
13:20-14:50 (90')	**Session 4: GSK Phase 4 safety data review and *ad hoc* analysis** • Presentation of result tables from *ad hoc* analysis (to 5th March 2021 – rates)	FOR REVIEW Miloje Savic, GSK Ana López Bautista, GSK Lode Schuerman, GSK
14:50-15:00	**Break**	
15:00-16:00 (60')	**Session 5 : AEFI data from MVIP country regulators** 30' presentation (TBC if pooled data) • Ghana FDA • Kenya PPB • Malawi PMPB 30' *Discussion*	FOR DISCUSSION Eun Mi Kim, WHO Adela Gwira, FDA Lydia Tutai, PPB Anderson Ndalama, PMPB
16:00- 16:40 (40')	**DSMB closed session – Day 2** **Draft final recommendations**	DSMB members only
16:40-17:00 (20')	**Final outcomes and way forward:** • Receive overall DSMB feedback • Agree on way forward for sharing DSMB review with MVIP Programme Advisory Group (either 5 August and/or 24 August)	DSMB Chair, Cynthia Whitney

List of attendees

DSMB members

Jane Achan, Malaria Consortium, United Kingdom
Charles Newton, KEMRI-Wellcome Trust Research Programme, Kenya
Larry Moulton, The Johns Hopkins University, USA
Esperança Sevene, Eduardo Mondlane University, Mozambique
Cynthia Whitney, Emory University, USA

MVIP national regulatory authorities

Adela Gwira, Ghana Food and Drugs Authority (FDA)
Anderson Ndalama, Malawi Pharmacy, Medicines, and Poisons Board (PMPB)
Lydia Tutai, Kenya Pharmacy and Poisons Board (PPB)
Martha Mandale, Kenya PPB

WHO Headquarters

John Francis, Vaccine Product & Delivery Research
Eliane Furrer, Vaccine Product & Delivery Research
Mary Hamel, Vaccine Product & Delivery Research
Mayuko Takamiya, Vaccine Product & Delivery Research
Patricia Njuguna, Global Malaria Programme
Kate O'Brien, Immunization, Vaccines & Biologicals
Madhav Balakrishnan, Pharmacovigilance

WHO AFRO

Benido Impouma, AFRO Communicable and Non-Communicable Diseases
Sujeet Jain, AFRO Intercountry Support Team
Eun Mi Kim, AFRO Vaccine Preventable Diseases
Mgaywa Magafu, AFRO Vaccine Preventable Diseases
Jackson Sillah, AFRO Tropical and Vector Borne Diseases
Khoti Wanangwa Gausi, AFRO Tropical and Vector Borne Diseases

WHO consultant

Paul Snell, Data management
Kerryn Moore, Statistical analysis
Paul Milligan, Statistical analysis
Nelli Westercamp – Pilot evaluations
Cynthia Bergstrom – MVIP Team

PATH

Ashley Birkett, Center for Vaccine Innovation and Access – Malaria
Scott Gordon, Center for Vaccine Innovation and Access – MVIP

GlaxoSmithKline Vaccines

Hiwot Amare Hailemariam, Safety
Ana Lopez Bautista, Safety
Cristina Cravcenco, Safety
Yolanda Guerra-Mendoza; Safety
Francois Roman, Clinical Development
Lode Schuerman, Global Medical Affairs

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)

Content:

Annex 7a: African Advisory Committee on Vaccine Safety (AACVS). Report of the extraordinary meeting. 9 August 2021

Annex 7b: Global Advisory Committee on Vaccine Safety (GACVS). Report of the special virtual meeting to examine safety data of the RTS,S/AS01 malaria vaccine. 10 August 2021

World Health Organization
REGIONAL OFFICE FOR Africa

MEETING REPORT

EXTRAORDINARY MEETING OF THE AFRICAN ADVISORY COMMITTEE ON VACCINE SAFETY (AACVS)

Virtual Meeting

9 August, 2021, 13:00 – 17:00 CET

Background

The African Advisory Committee on Vaccine Safety (AACVS) was established by the WHO Regional Director for Africa to provide independent advice and make recommendations on how to strengthen vaccine safety and surveillance in the countries of the WHO African Region. Recognizing the generally low reporting of adverse events following immunization (AEFI); the variability in vaccine pharmacovigilance, safety monitoring and management in Member States; and the introduction of new vaccines, some limited to only the African Region, it was necessary to identify a group with the expertise required to advise the WHO African Region and help in defining the priorities, monitoring implementation of key activities, and advising on how WHO and partners can better support Member States.

The AACVS provides independent expert advice on technical issues related to the safety, effectiveness and use of approved and new vaccines by reviewing the safety information of newly introduced vaccines. The 3rd Extraordinary AACVS meeting was organized to provide updates on the vaccine safety surveillance and readiness of safety monitoring of COVID-19 vaccines and the RTS,S/AS01 malaria vaccine in the African Region, and to solicit recommendations for Member States in the region.

In March 2021, the first COVID-19 vaccine doses were administered in Africa through the COVAX Facility. Up to now, six new COVID-19 vaccines have been introduced in Africa through the COVAX Facility – including Oxford/AstraZeneca, Johnson & Johnson, Moderna, Pfizer/BioNTech, Sinopharm, and Sinovac – all of which have been authorized for emergency use (EUL) by WHO. Additional new COVID-19 vaccines were also administered, either via bilateral arrangements or donations. In order to monitor safety issues of the above-mentioned vaccines, WHO has been closely working with Member States to collect and analyze the safety data at regional and global levels. During the second AACVS meeting in April 2021, the need to establish a sub-working group under the AACVS was recognized and agreed. Therefore, the extraordinary meeting was planned to further discuss the roles and operation of the sub-working group on COVID-19 vaccines. AACVS members were invited to review the safety data and trends of reported safety cases in the region to provide recommendations for better

monitoring of safety profiles of newly introduced COVID-19 vaccines and for prompt actions upon any safety issues.

The RTS,S/AS01 malaria vaccine is the world's first malaria vaccine which has been approved with indication of protecting young children from malaria. Since April 2019, the vaccine is being implemented through national immunization programmes in selected areas of three sub-Saharan African countries (Ghana, Kenya and Malawi) as part of a pilot programme. RTS,S/AS01 received a positive scientific opinion from the European Medicines Agency (EMA) in 2015 and was recommended by WHO for a pilot implementation programme to assess the feasibility of administering the four doses of the vaccine in children, the vaccine's role in reducing deaths and severe malaria, and to review its safety in the context of routine use (with particular focus on safety signals observed in the Phase 3 trial for which causality has not been established: meningitis, cerebral malaria, and female mortality). As interim evaluation results of the safety data from the Malaria Vaccine Implementation Programme (MVIP) were expected to become available at the end of July 2021, the AACVS members were

Meeting Objectives and Expected Outcomes

Objectives of the AAVCS Meeting

- To discuss the roles and responsibilities of AACVS in reviewing the safety data of newly introduced vaccines
- To update the members on 1) regional status of COVID-19 vaccines rollout and 2) safety monitoring activities of COVID-19 vaccines
- To discuss the roles and operation of the sub-working group on COVID-19 vaccines
    a. Sub-working group on COVID-19 vaccines is expected to focus on the following activities:
        i. To review regional safety data (AEFI, AESI, etc.)
        ii. To discuss challenges and strategies in causality assessment of serious AEFI cases following COVID-19 vaccination
        iii. To recommend strategies and provide advice to Member States for improving vaccine safety and vigilance systems, including AEFI reporting, investigation for causality assessments of COVID-19 vaccines
        iv. Provide advice on communication of risks and benefits of COVID-19 vaccines
- To brief the members on 24-month safety evaluation results of RTS,S/AS01 Malaria Vaccine Implementation Programme (MVIP)
- To recommend strategies and provide advice to Member States on safety issues to prepare for the expansion of the use of RTS,S/AS01 malaria vaccine in African Region

Expected Outcomes of the AAVCS Meeting

- To update the members on regional status of COVID-19 vaccines rollout and safety monitoring of newly introduced COVID-19 vaccines
- To establish the sub-working group on COVID-19 vaccines and agree on the roles and operation of the group
- To agree on the roles and responsibilities of AACVS in reviewing the safety data of newly introduced vaccines
- To provide recommendations on safety monitoring of the RTS,S/AS01 malaria vaccine post-introduction should it be recommended for broader use in the African Region

AACVS Pre-Meeting (Closed session)

Session Objectives

- To adopt the agenda of the meeting
- To discuss the roles and responsibilities of AACVS in reviewing the safety data of newly introduced vaccines

Summary of the Pre-Meeting

Dr. Dicky Akanmori (Regional Advisor for Vaccine Regulation, Communicable and Non-Communicable Diseases (UCN) Cluster, Vaccine Preventable Diseases (VPD) Programme, WHO Regional Office for Africa, and secretariat for AACVS) welcomed the members of AACVS to the extraordinary meeting of AACVS on the safety review of RTS,S/AS01 malaria vaccine. Members of AACVS were briefed by the secretariat on the finalized agenda and adopted it for the meeting. The meeting objectives were also presented by the secretariat and endorsed by the AACVS members. The secretariat also briefed on the expected outcomes of the meeting and members of AACVS agreed on their roles in reviewing newly introduced vaccines in the region.

Session 1: Safety Review of RTS,S Malaria Vaccine

Session Overview

- Presentations: *Moderated by Prof. Beckie Tagbo (Member of the AACVS)*
- Brief introduction of the Malaria Vaccine Implementation Programme (MVIP); its background, objectives, progress to date, and key findings of the pilot evaluation: *by Dr. Mary Hamel (WHO HQ)*
- Progress update on RTS,S/AS01 malaria vaccine implementation in Ghana, Kenya and Malawi: *by Dr. Mgaywa Magafu (WHO AFRO)*
- Overview of sources of safety data and evaluation design to assess safety questions of RTS,S/AS01 in the MVIP: *by Dr. Patricia Njuguna (WHO HQ)*
- Observations from routine pharmacovigilance by National Regulatory Authorities: *by EunMi Kim (WHO AFRO) and the NRA focal points in the MVIP countries*
- Assessment and recommendations by the MVIP Data Safety and Monitoring Board (DSMB): *by Dr. Cyndy Whitney (Chair of MVIP DSMB)*
- Discussions/Q&A: *Moderated by Prof. Beckie Tagbo (Member of the AACVS)*
- (Closed session) Discussion to form recommendations
- Expected Outcomes: List of recommendations

Summary of Session 1

The meeting was opened by Dr. Dicky Akanmori on behalf of Dr. Richard Mihigo, Programme Area Coordinator for the Vaccines Preventable Diseases Programme of the WHO Regional Office for Africa. Dr. Pedro Alonso, Director, WHO Global Malaria Programme (WHO GMP), delivered opening remarks by emphasizing the importance of the introduction of the first ever malaria vaccine to save the lives of millions of children.

Dr. Shanthi Pal, Team Lead, Pharmacovigilance, Regulation and Safety, WHO, also added her voice on the importance of ensuring the safety of the RTS,S malaria vaccine in preparation for wider use of the vaccine in the African Region, where safety surveillance systems still need to be strengthened. She also expressed her warm welcome for AACVS members who are expected to play an important role for Global Advisory Committee on Vaccine Safety (GACVS) through regional recommendations on post-authorization safety monitoring.

Dr. Mary Hamel (WHO HQ) presented a brief introduction of the MVIP, including its background, objectives, progress to date, and key findings of the pilot evaluation. She explained that the MVIP supports routine introduction of RTS,S/AS01 by the ministries of health in selected areas of Ghana, Kenya and Malawi, as well as evaluation of the programmatic feasibility of administering the recommended four doses, the vaccine's impact on mortality, and its safety in the context of routine use. She then explained that over 2.1 million doses were administered and over 740,000 children reached with at least one dose in participating countries. Safety data from pilot evaluations have been regularly reviewed by the MVIP Data Safety and Monitoring Board and also the data regularly been submitted by GSK to the European Medicines Agency (EMA), who have maintained a positive scientific opinion under article 58. She explained that a full evidence review of RTS,S/AS01 – including data from the pilot evaluation – will be conducted by SAGE and the Malaria Policy Advisory Group (MPAG) on 6 October 2021 to inform a potential WHO recommendation for broader use of the vaccine in sub-Saharan Africa.

Dr. Mgaywa Magafu (WHO AFRO) presented the progress update on the RTS,S/AS01 malaria vaccine implementation in Ghana, Kenya and Malawi. He presented the vaccine uptake in each country and explained the successful vaccination compared to other vaccines despite the challenges such as the COVID-19 pandemic and a healthcare workers' strike.

Dr. Patricia Njuguna (WHO HQ) presented the overview of sources of safety data and evaluation design to assess safety questions of RTS,S/AS01 in the MVIP. She explained the design of the evaluation programme by emphasizing that the routine pharmacovigilance in the pilot countries may be insufficient to reliably classify meningitis and cerebral malaria (which often are diagnoses made clinically) without laboratory confirmation. Sentinel hospital surveillance with clinical and laboratory support was established in the MVIP countries. Similarly, to measure impact and gender-specific mortality, community-based mortality systems were established throughout the pilot areas. GSK is conducting a Phase 4 study, which follows approximately 45,000 children prospectively, and includes active follow-up after vaccination as part of the Risk Management Plan (RMP) with the EMA. She explained that an interim and final analysis of these data will be available in 2023 and 2025 respectively, after the completion of the pilots and a potential recommendation for use.

Prof. Paul Milligan then presented the results of analysis of data obtained through MVIP evaluation.

He explained that the evaluation was well powered to detect effects of RTS,S/AS01 introduction on the incidence of hospital admission with meningitis and with cerebral malaria in pooled analysis of the data from the three MVIP countries. High coverage of RTS,S-1 was achieved and sufficient events observed to allow effects of the magnitude observed in the Phase 3 trial to be detected with 90% power. There was no evidence that RTS,S/AS01 introduction increased incidence of hospital admission with meningitis. The incidence rate ratio (RTS,S:comparator) was 1.0 (95%CI 0.50, 1.97). There was no evidence that RTS,S/AS01 introduction was less effective against hospital admission with cerebral malaria than other forms of severe malaria. The incidence rate ratio for admission with cerebral malaria was 0.75 (95%CI 0.37, 1.53), and 1.11 (95%CI 0.73, 1.69) when a broader definition was used.

He also explained that the evaluation was not powered at this time point to assess impact of vaccine introduction on mortality, but the evaluation was well powered to detect gender imbalance in all-cause mortality, in children up to ~2 years of age. 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.

RTS,S/AS01 introduction was associated with a reduction in incidence of hospital admission with severe malaria. The reduction of 25% was consistent with the reduction that would be expected on the basis of the efficacy observed in the Phase 3 trial, given the level of coverage of three doses of RTS,S/AS01 achieved in the evaluation areas.

EunMi Kim (WHO AFRO) and the national regulatory authority (NRA) focal points in the MVIP countries presented the observations from routine pharmacovigilance by the NRAs: Adela Gwira, Ghana Food and Drugs Authority (FDA); Anderson Ndalama, Malawi Pharmacy, Medicines, and Regulatory Authority (PMRA); and Lydia Tutai, Kenya Pharmacy and Poisons Board (PPB).

EunMi Kim presented the summary of adverse events following immunization (AEFI) and adverse event of special interest (AESI) reported in three MVIP implementing countries and the sources of safety data. NRA focal points from Ghana FDA, Kenya PPB and Malawi PMRA presented country AEFI data, including the results of causality assessments of severe cases and fatal outcomes. They concluded their presentations with their findings which did not show any safety signals related to the RTS,S vaccine detected through routine surveillance systems. EunMi Kim also explained that the routine pharmacovigilance systems have been strengthened through training for healthcare workers and investigation teams as well as a causality assessment committee.

Dr. Cyndy Whitney, Chair of MVIP Data Safety and Monitoring Board (DSMB), presented the assessment and recommendations by the MVIP DSMB, well as the summary of DSMB activities and their findings. She presented that DSMB recommended continuation of MVIP and congratulated on the progress made by this ambitious programme and for reaching this important 24-month primary analysis. She explained that there was adequate power (number of events) accrued to exclude associations of a similar magnitude to those observed in the Phase 3 trial, after accounting for observed levels of coverage and contamination on population-level effects.

She explained that safety signals seen in Phase 3 clinical trial (2009-2014) – after 10,306 infants and children received RTS,S – were not seen in the pilot implementation after 652,673 children received their first dose (and 494,745 children received their third dose) or among the 10,032 RTS,S vaccine-eligible children admitted to pilot evaluation sentinel hospitals (4,870 from implementation areas) during the period from start of vaccination in 2019 to April 2021.

DSMB concluded that pilot evaluation results indicate comparable burden for meningitis, cerebral malaria, and gender-specific mortality among eligible children living in implementation and comparison areas. Pooled point estimates for safety endpoint risk ratios were consistently near 1 (no association); inconsistent with corresponding risk ratios observed in the Phase 3 trial (i.e., hypotheses that the vaccine was associated with increased risk levels were rejected). DSMB noted limitations in diagnosing cerebral malaria and challenges with meningitis surveillance, but that any uncertainty does not alter DSMB's conclusions regarding safety concerns.

She concluded that DSMB did not find evidence of new conditions that warrant closer safety tracking based on data reviewed from the national pharmacovigilance programmes. However, she mentioned that collecting and investigating AEFI remains a challenge for national pharmacovigilance programmes as most of the reports came from Phase 4 or the Malaria Vaccine Programme Evaluation (MVPE); very few serious events or deaths were investigated by national expert/AEFI committees. She further concluded that DSMB encourages ongoing efforts to strengthen these important programmes.

Professor Beckie Tagbo (Member of the AACVS) was pre-selected at the pre-meeting as the moderator for the discussion at the end of the first session. Prof. Tagbo started the discussion to provide opportunities for members and participants to ask questions on presentations. AACVS members raised serious questions regarding the country capacity in capturing safety signals through routine surveillance and raised


MALARIA VACCINE (RTS,S also known as MOSQUIRIX)
squirix

concerns regarding the readiness for introduction of the new vaccine. Dr. Beatriz Thome mentioned that it would be important to put in place active pharmacovigilance studies as part of the safeguards for wider rollout and asked whether there is an active component to the design of the GSK Phase 4 study. Dr. Hamel confirmed that the GSK Phase 4 study was designed to actively collect AESI cases to address safety questions raised.

Dr. Afework Assefa Mitiku raised a clarifying question regarding the lineation looking for cerebral malaria as the observed ratio for cerebral malaria is 1.11, and 0.75 for other types of severe malaria, but the conclusion was no difference between the ratios.

Dr. D.S. Akram asked a question regarding any qualitative difference in data coming from different countries.

Dr. Dorothy Omono Esangbedo raised a concern that most data came from GSK. She also questioned if causality assessments were done properly for meningitis, as the diagnoses could have been due to procedure or vaccine. She also mentioned that the onset time interval of some cases is very long and asked if standard case validation tools were used for classification of AEFI cases.

Dr. Aggrey Omu Anzala also raised concerns regarding the timeliness of causality assessments. He also asked a question to confirm if baseline data on malaria cases were considered for analysis.

Dr. Winfred Oppong-Amoako raised a question regarding the difference in the number of administered doses across countries and asked if there was any specific reason for the gap.

Dr. Kwadwo Odei Antwi-Agyei commented on the need for support to conduct timely investigations of serious AEFI for causality assessment. He advised the use of WHO standard indicators to help understand the reporting rate of AEFI per country instead of just classifying them as low.

Professor Beckie Tagbo provided further background information on the MVIP to ensure correct understanding of the programme, which was not a clinical trial although DSMB was set up to review safety data. Prof. Tagbo then asked questions to clarify: 1) if identical hospitals were used for GSK Phase 4 study and sentinel hospitals, 2) reasons for no meningitis reported as valid diagnosis of serious cases for causality assessment in Ghana, 3) issues of low reporting of AESI cases, as all AESI cases were from the GSK site in Kenya, 4) proportion of fatal outcomes causally related to the RTS,S vaccine, and 5) reasons for no causality assessment done in Malawi.

Presenters answered questions and addressed concerns raised by the AACVS members starting with Dr. Mary Hamel. Dr. Hamel explained the reasons for setting up the Malaria Vaccine Programme Evaluation (MVPE) to answer safety questions (i.e., cerebral malaria, meningitis and female mortality imbalance) with the recognition that current routine surveillance systems may not be sufficient due to the expected low reporting rate of AEFI and AESI cases. The sentinel hospitals were specifically set up to evaluate the linkage between the higher incident rate of cerebral malaria and meningitis. A household survey was also designed to answer the question related to female mortality imbalance. She explained the hospitals set up by GSK for Phase 4 are differently located compared to the sentinel hospitals used for the MVPE. She also addressed the question raised by Dr. Afework by explaining that the impact of the vaccine in reducing the cerebral malaria was not different from the impact of vaccine in reducing severe malaria.

Anderson Ndalama from the Malawi NRA explained the challenges in conducting causality assessments although the expert committee exists.

Dr. Mgaywa Magafu explained the difference of vaccination coverage/uptake among countries, especially with Kenya being 10% lower than the other countries. He explained that there are always differences in vaccine coverage among countries.

Dr. Peter Smith made comments on the challenges of routine surveillance. The long-term interval of onset time of events after vaccination indicates low temporal causal relationships of cerebral malaria and severe malaria. He emphasized that it will be difficult to pick up the cerebral malaria cases through routine surveillance systems due to the long-term interval. Regarding the impact of the vaccine in the real world, the 25% reduction of severe malaria was comparable to the results from the Phase 3 study. He explained that the members of Programme Advisory Group (PAG) were reassured that there is no safety concern with respect to the vaccine and the impact of the vaccine is similar to what was observed during the Phase 3 trial.

Prof. Beckie Tagbo requested to prepare a slide which shows if safety concerns were answered through the different sources of safety data. The slide was presented accordingly and is included in the findings of this meeting report (see below).

Dr. Cyndy Whitney explained that there were no special safety signals detected which can raise red flags. Although the routine surveillance systems did not pick up many adverse events, including meningitis, the GSK Phase 4 study was able to capture good data and it seems probable that meningitis cases were not picked up through routine surveillance due to the low number of cases and interval for onset time.

Lydia Tutai from the Kenya NRA explained that there were issues in conducting timely investigations and causality assessments in Kenya. However, Kenya is in the process of improving the reporting of AEFI through a newly introduced reporting portal. She explained that the occurrence of reported meningitis in Kenya were not the cases associated with the RTS,S vaccine and may consider the comparison later on. Dr. Christable Khaemba from Kenya NRA further explained their efforts to improve AEFI reporting.

During the closed session, Prof. Tagbo led the discussion to solicit recommendations for wider use. Members of AACVS agreed that there is strong need to improve routine pharmacovigilance systems and worried if the capacity is available to detect important safety signals. Dr. Dorothy emphasized the need to utilize harmonized and standard definitions for classification of AEFI cases across countries for implementation of the vaccine. Dr. Afework emphasized the need for long-term sustainability, especially funding for timely and effective investigation of serious cases and causality assessments. Prof. Tagbo emphasized the use of existing sentinel hospitals for active surveillance to complement weak routine surveillance systems.

The members of AACVS found that no red flags were raised with regards to the RTS,S vaccine as the results of the MVIP so far did not show any causal relations to increased incidents of cerebral malaria and severe malaria which were observed in the Phase 3 study. The members of AACVS found that the safety evaluation data presented by the MVIP seems robust, as the duration of evaluation seems reasonable, and the sources of data seem appropriate and diverse to answer safety questions raised by the SAGE.

Dr. Afework also commented that the methods used for safety data collection and design for data evaluation were found to be robust under the limited capacity of routine surveillance systems. Other members also agreed on the robustness and adopted the statement as a finding. Members also found that no red flags were raised on the safety signals, trends or clusters regarding the RTS,S vaccine as presented by the MVIP as well as NRAs in MVIP countries; however, members raised concerns about the limited capacity of routine surveillance in countries.

Session 2 (Closed session): Sub-working Group for COVID-19 Vaccines

Session Overview

- Expected Outcomes: To establish the sub-working group on COVID-19 vaccines and agree on the roles and operation of the group
- Brief updates on regional safety monitoring status of COVID-19 vaccines: *by Dr. Dicky Akanmori, Dr. Sujeet Jain, Amabi Edinam*
- Discussions/Q&A and Summary of Recommendations: *Moderated by Dr. Afework Assefa Mitiku (Member of the AACVS)*

Summary of Session 2

Dr. Dicky Akanmori presented the key points regarding the operation of the sub-working group for COVID-19 vaccines. Dr. Afework Assefa Mitiku, member of the AACVS, who was pre-selected as a moderator at the pre-meeting, led the discussion to agree on the operation principles and expected roles and outcomes of the sub-working group for COVID-19 vaccines. Dr. Afework suggested to expand the membership of the sub-working group by including wider expertise in the group. AACVS members and the secretariat agreed to look for experts in vaccinology, immunology, pathology and other relevant areas.

AACVS members suggested and agreed to review the draft Terms of Reference, which will be shared by the secretariat for finalization. AACVS members agreed to meet biweekly to make the sub-working group operational in the beginning, and to readjust the intervals of meetings based on the needs and urgency of any emerging safety issues in the future.

Findings from the Extraordinary AACVS Meeting

Table 1. Sources of safety-related data as part of the MVIP and their ability to address different objectives

Responsible	WHO contracted evaluation partners (Malaria Vaccine Pilot Evaluation)	Ministry of Health		GSK contracted investigators
Source of data → Safety objective / endpoint ↓	Sentinel hospital surveillance	Community based mortality surveillance	Routine vaccine pharmaco-vigilance	Active surveillance as part of GSK-led Phase IV study
Rare, temporally related events	No new signals detected		No new signals detected	Nothing of concern reported to date
To assess the potential association between vaccination and lab confirmed meningitis, cerebral malaria (of magnitude suggested in the signals from the Phase 3 trial)	Not seen, with adequate sample size reached			Ongoing No signal on meningitis (MaxSPRT); CM not above baseline rates
Mortality Gender imbalance (of magnitude suggested in the signals from the Phase 3 trial)		Not seen, with adequate sample size reached		Ongoing

1. Safety evaluation data presented by the MVIP seems robust, as the duration of evaluation seems reasonable, and the sources of data seem appropriate and diverse to answer safety questions raised by the SAGE. Methods used for safety data collection and design for data evaluation were found to be robust under the limited capacity of routine surveillance systems.
2. No red flags were raised on the safety signals, trends or clusters regarding the RTS,S vaccine as presented by the MVIP as well as NRAs in MVIP countries.
3. No evidence of causal relations of the RTS,S vaccine to increase the chance of cerebral malaria, meningitis or the gender imbalance in mortality was found, according to the safety evaluation presented by MVIP.

Recommendations from the Extraordinary AACVS Meeting

1. In general, there is a need to further improve the pharmacovigilance system for wider use in African Region.

- Definitions and classifications used to collect data such as AEFI need to be harmonized across countries.
- Funding for routine surveillance is needed and long-term sustainability needs to be considered with country ownership.
- Strengthening pharmacovigilance surveillance needs to be done for continuous safety monitoring.
- Routine surveillance needs to be strengthened in all African countries in adverse event reporting, data collection, and causality assessment.
- Community based actors, community health workers and outreach teams must be utilized to increase the timeliness of information collection and communication of surveillance data for decision-making.

2. Recommend continuing support of the existing networks of sentinel hospital sites and laboratories currently in use across Africa to collect AEFI for all vaccines if funding allows, to continue sentinel hospital surveillance for AEFI and AESI.

Annex 1: AACVS Meeting Agenda

9 August 2021	
13:00 - 13:30	**African Advisory Committee on Vaccine Safety (AACVS) Pre-meeting** Session Objectives: 1) To adopt the agenda of the meeting 2) To discuss the roles and responsibilities of AACVS in reviewing the safety data of newly introduced vaccines
13:30 - 16:30	**SESSION I: Safety review of RTS,S Malaria Vaccine**
13:30 - 13:45	**Opening remarks** by *Dr. Richard Mihigo, Coordinator VPD Programme, WHO/AFRO* *Dr. Shanthi Pal, Team Lead, Pharmacovigilance, Regulation and Safety (HQ PV)* *Dr. Pedro Alonso, Director, Global Malaria Programme (HQ GMP)* **Expected Outcomes:** To brief the members on 24-month safety evaluation results of RTS,S/AS01 Malaria Vaccine implementation Programme (MVIP) and to provide recommendations for the safety monitoring of the vaccine post-introduction should it be recommended for broader use in the African Region **Presentations:** *Moderated by Prof. Beckie Tagbo, member of the AACVS*
13:45 - 14:15	**Brief introduction of Malaria Vaccine Implementation Programme (MVIP); its background, objectives, progress to date, and key findings of the pilot evaluation (30 mins):** by Dr. Mary Hamel (WHO HQ)
14:15 - 14:25	**Progress update on RTS,S/AS01 malaria vaccine implementation in Ghana, Kenya and Malawi (10 mins):** by Dr. Mgaywa Magafu (WHO AFRO)
14:25 - 14:40	**Overview of sources of safety data and evaluation design to assess safety questions of RTS,S/AS01 in the MVIP (15 mins)**: by Dr. Patricia Njuguna (WHO HQ)
14:40 - 15:00	**Observations from routine pharmacovigilance by National Regulatory Authorities (20 mins):** by EunMi Kim (WHO AFRO) and the NRA focal points in the MVIP countries
15:00 - 15:10	**Assessment and recommendations by the MVIP Data Safety and Monitoring Board (10 mins):** by Dr. Cyndy Whitney, Chair of MVIP DSMB
15:10 - 15:40	**Discussions/Q&A (30 mins)**: *Moderated by Moderated by Prof. Beckie Tagbo, member of the AACVS*
15:40 - 16:30	**(Closed session) Discussion to form recommendations (50 mins)** **Expected Outcomes:** List of recommendations
16:30 –17:00	**SESSION 2 (Closed session): Sub-working group for COVID-19 vaccines** **Expected Outcomes:** To establish the sub-working group on COVID-19 vaccines and agree on the roles and operation of the group **Brief updates on regional safety monitoring status of COVID-19 vaccines (10 mins):** by Dr. Dicky Akanmori, Dr. Sujeet Jain, Amabi Edinam **Discussions/Q&A Summary of Recommendations (20 mins)**: *Moderated by Dr. Afework Assefa Mitiku, member of the AACVS*

Annex 2: List of Attendees

AACVS Members

Dr. Afework Assefa Mitiku

Dr. Aggrey Omu Anzala

Dr. Beatriz da Costa Thomé

Dr. Beckie Tagbo

Dr. Charles Shey Umaru Wiysonge

Dr. Dorothy Omono Esangbedo

Dr. Jane Florence Gidudu

Dr. Kwadwo Odei Antwi-Agyei

Dr. Mouhoudine Yerima

Dr. Nicola Christofides

Dr. Winfred Oppong-Amoako

WHO AFRO

Dr. Dicky Akanmori, Vaccine Preventable Diseases

Amabi Edinam, Intercountry Support Team

Dr. Diadie Maiga, Vaccine Preventable Diseases

EunMi Kim, Vaccine Preventable Diseases

Dr. Mgaywa Magafu, Vaccine Preventable Diseases

Dr. Randy George Mungwira, Malawi MVIP focal point

Dr. Rafiq Nii Attoh Okine, Ghana MVIP focal point

WHO Headquarters

Dr. Shanthi Pal, Team Lead, Pharmacovigilance, Regulation and Safety (HQ PV)

Madhav Balakrishnan, Pharmacovigilance, Regulation and Safety (HQ PV)

Dr. Pedro Alonso, Director, Global Malaria Programme (HQ GMP)

John Francis, Vaccine Product & Delivery Research

Eliane Furrer, Vaccine Product & Delivery Research

Mary Hamel, Vaccine Product & Delivery Research

Mayuko Takamiya, Vaccine Product & Delivery Research

Patricia Njuguna, Global Malaria Programme

Kate O'Brien, Immunization, Vaccines & Biologicals

MVIP national regulatory authorities (NRA) focal points

Adela Gwira, Ghana Food and Drugs Authority (FDA)

Anderson Ndalama, Malawi Pharmacy and Medicines Regulatory Authority (PMRA)

Lydia Tutai, Kenya Pharmacy and Poisons Board (PPB)

Dr. Christabel Khaemba, Kenya Pharmacy and Poisons Board (PPB)

WHO consultant

Paul Snell, Data management

Paul Milligan, Statistical analysis

GlaxoSmithKline Vaccines

Ana Lopez Bautista, Safety

Lode Schuerman, Global Medical Affairs

Programme Advisory Group

Ifedayo Adetifa, London School of Hygiene and Tropical Medicine and Kenya Medical Research Institute

Eusebio Macete, Manhiça Health Research Centre (CISM), Mozambique (co-chair)

Peter Smith, London School of Hygiene and Tropical Medicine (chair)

World Health Organization
REGIONAL OFFICE FOR Africa

GACVS meeting report, Version 13 September 2021

Annex 7b: Global Advisory Committee on Vaccine Safety: Report of the special virtual meeting to examine safety data of the RTS,S/AS01 malaria vaccine - 10 August 2021

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999 to provide independent, authoritative, scientific advice to WHO on vaccine safety issues of global or regional concern.[1] GACVS held a special virtual meeting, on 10 August 2021 to examine safety data on the RTS,S/AS01 malaria vaccine, collected through the Malaria Vaccine Pilot Evaluation, which is the evaluation component of the Malaria Vaccine Implementation Programme (MVIP).[2]

Malaria Vaccine Implementation Programme

Following a positive scientific opinion of the RTS,S/AS01 malaria vaccine by the European Medicines Agency[3], and the 2016 WHO recommendation for pilot implementation[4], the Malaria Vaccine Implementation Programme (MVIP) was set up to support routine introduction of the RTS,S/AS01 vaccine by the ministries of health and to evaluate the feasibility, safety and impact of the vaccine when deployed through routine immunization programmes in selected areas of three pilot countries (Ghana, Kenya and Malawi). At the recommendation of the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Group (MPAG), the safety evaluation is focused on potential safety signals identified in the large multisite RTS,S/AS01 Phase III trial, i.e., an excess of meningitis cases and cerebral malaria cases, and a post-hoc finding of an imbalance in deaths among girls who received the RTS,S/AS01 vaccine compared with those who did not.

In each country areas of moderate-to high-transmission settings were selected by the respective MoHs in 2019 for RTS,S/AS01 pilot introduction. Within the pilot region in each country, districts or similar areas were randomly assigned to introduce the vaccine in 2019 (vaccinating areas), or to delay introduction until a decision is reached about safety and effectiveness in routine use (comparison areas). A total of 158 areas were randomized, i.e., 66 districts in Ghana, 46 sub-counties in western Kenya, and 46 groups of immunization clinics and their associated catchment areas, in Malawi. Each area has a total population of about 100,000 and an expected birth cohort of about 4,000 per year.

Household surveys were conducted in the vaccinating and comparison areas before vaccine introduction in each country. The primary objective of the midline household survey was to estimate the percentage of age-eligible children who had received three doses of RTS,S/AS01 by 12 months of age. The secondary objectives were to evaluate the impact of RTS,S/AS01 introduction on:

- the uptake of the other EPI vaccines
- other malaria preventive interventions (insecticide treated bed net use)

[1] Vaccine safety Vaccine Safety Advisory Committee. WER 1999;74(41):337–338.
[2] The malaria vaccine implementation programme (MVIP)
[3] European Medicines Agency assessment: Mosquirix: Opinion on medicine for use outside EU. Available from: https://www.ema.europa.eu/en/mosquirix-h-w-2300, accessed 10 August 2021.
[4] World Health Organization. Malaria vaccine: WHO position paper – January 2016. WER 2016;91(4):33–52.

- health-seeking behaviour for febrile children

The endline household surveys to estimate the percentage of age-eligible children who had received four doses by 27 months of age, and similar secondary objectives, will be carried out in 2022.

The MVIP has four approaches for the evaluation of the safety of RTS,S/AS01 in routine, (real-world) use. These are (i) routine pharmacovigilance by the ministries of health for spontaneous adverse event following immunization (AEFI) reporting of rare, unexpected AEFIs; (ii) WHO-commissioned community mortality surveillance to measure the impact of vaccination and also sex-specific mortality rates; (iii) WHO-commissioned hospital surveillance of meningitis and cerebral malaria at sentinel hospitals; and (iv) a GSK phase-IV cohort study with scheduled visits for AEFIs, sex-specific mortality and in-patient surveillance for meningitis, cerebral malaria, AEFIs and adverse events of special interest (AESIs). A 2-step approach for analysis has been planned with the aim of ensuring that a recommendation can be made as soon as the benefit-risk ratio of the vaccine is established so that the vaccine will not be unnecessarily withheld from countries in need. The first planned analysis in 2021, after 2 years aimed to confirm if the safety signals had been satisfactorily resolved for meningitis and cerebral malaria and sex related mortality, and if the data available for effectiveness for the reduction of severe malaria and mortality were consistent with a beneficial impact of the vaccine. On the basis of these data, and other new evidence on the vaccine since the recommendation for pilots in 2015, a decision will be made by WHO to recommend a broader use of RTS,S/AS01. The second analysis is planned in 2023 to assess the value of the 4th dose and the vaccine's effectiveness to reduce mortality. On the basis of these final results, WHO may adjust its recommendation.

The malaria vaccine is given as a 3-dose initial series with a minimum 4-week interval between doses, followed by a 4th dose 15 to 18 months after the 3rd dose delivered by the national immunization programme in each country. Since the pilot programme started, over 2.1 million doses of RTS,S/AS01 have been administered and more than 740,000 children have received at least one dose. The vaccination coverage for one dose was 88%, 71% and 69% in Malawi, Ghana and Kenya, respectively, in 2020 and 92%, 76% and 81%, respectively, for April to June 2021. Vaccination coverage for three doses was 80%, 74% and 72%, respectively, for April to June 2021.

Safety data obtained in these evaluations is reviewed by a data safety monitoring board (DSMB) meets quarterly to review data quality; outcomes of interest, including meningitis, cerebral malaria and deaths by sex; pharmacovigilance reports presented by the regulatory authorities; and GSK safety surveillance data from the phase-IV studies. Based on their evaluation the DSMB recommends if the MVIP should continue or not. The programme is overseen by a programme coordination group, a programme advisory group, GACVS and SAGE and MPAG.

An extraordinary meeting of the GACVS was held on 10 August 2021 to review the conclusions and recommendations about the primary safety analysis at 2 years (data cut off April 2021) made by the DSMB and the African Advisory Committee on Vaccine Safety (AACVS). GACVS provided recommendations on what post authorization safety monitoring system should be in

place should the vaccine be recommended for broader use in sub-Saharan Africa by SAGE and MPAG in October 2021.

Household surveys: results from midline survey

The primary objective of the midline survey was to estimate the percentage of children aged 5 to 48 months old who had received three doses of RTS,S/AS01 by 12 months of age, assessed using their vaccine card or by recall. The secondary objectives were to assess the impact of RTS,S/AS01 introduction under real-world conditions on the coverage with other EPI vaccines, the use of other insecticide-treated bed nets and the health-seeking behaviour for children with febrile episodes, in comparison with the baseline results. Data were available from Ghana (collected November 2020) and Malawi (collected March to April 2021).

The results showed that the malaria vaccine coverage was comparable with the coverage reported from routine administrative data, although the point estimates were lower in Malawi and higher in Ghana. There was no negative impact on the uptake of routine vaccines, use of bed nets or health-seeking behaviour, following the introduction of the malaria vaccine. Vaccine uptake was equitable, with similar uptake across wealth rankings, based on household assets, and by gender, and was similar among children in relation to use of ITNs.

Malaria Vaccine Pilot Evaluation: results of safety data analysis 24 months after RTS,S/AS01 introduction

The objectives of the 24-month primary analysis was to evaluate if there was an association between RTS,S/AS01 introduction and the incidence of hospital admission with meningitis, or severe malaria, including cerebral malaria and incidence of gender-specific mortality (all cause, except injuries) in the vaccinating areas. Using the combined data from the three countries, sufficient events had accrued by April 2021 to address safety signals and to assess effectiveness against hospital admission with severe malaria with sufficient (90%) power.

Overall 13/28 (46.4%) of age-eligible children hospitalized with meningitis had received at least one dose of RTS,S/AS01 compared with 2506/4684 (53.5%) of those who were hospitalized for other reasons (odds ratio 0.92 (95% CI: 0.43, 1.97)). In the three countries, there were 28 and 23 cases of hospitalized meningitis among the age-eligible and non-eligible children in the vaccinating areas, compared with 23 and 36, respectively, in the non-vaccinating areas. The rate ratio was 1.0 (95%CI: 0.50, 1.97), excluding the association of RTS,S/AS01 introduction with the increased incidence of meningitis reported in the phase III trial.

Of the patients with cerebral malaria in vaccine-eligible age groups from implementation areas, 44% (23/52) had received RTS,S/AS01 vaccine, compared to 54% (2496/4662) of all other admissions in this age group from implementation areas (odds ratio 0.81 (95% CI: 0.46, 1.42)). In the three countries, there were 52 and 227 cases of cerebral malaria among the age-eligible and non-eligible children in the vaccinating areas, compared with 54 and 227 respectively, in the non-vaccinating areas. The rate ratio was 1.1 (95%CI: 0.73, 1.69), excluding the association of RTS,S/AS01 introduction with the increased incidence of cerebral malaria reported in the phase III trial.

Using the data collected up to 31 March 2021 by the network of village-based reporters who collected data from verbal autopsies that classed the death as due to injury or other causes, and from hospital records for hospital deaths in Malawi, cause of death was established for 4280/4729 (90.5%) deaths in vaccine eligible age groups. In Malawi, using data from the 2018 census to estimate the denominator, the mortality rate was 4.38/1000 person-years, similar to that reported in the census, i.e., 5.08/1000 person years. In the three countries, there were 1421 and 4218 deaths among the age-eligible and non-eligible children, respectively in the vaccinating areas, compared with 1443 and 3874, respectively, in the non-vaccinating areas. The rate ratio was 0.93 (95%CI: 0.84, 1.03) which, while the upper 95% CI limit is >1, is compatible with the reduction expected from the reduction reported in clinical trials. The rate ratio for female to male mortality was 1.08 (95%CI: 0.93, 1.25), p=0.321, and this was similar by age group. Among the deaths in the vaccinating area, there were 495/841 (58.9%) and 502/881 (57%) age-eligible children who had received at least one dose of RTS,S/AS01.

Successes and challenges in safety monitoring and country experiences in countries that implemented the RTS,S/AS01 vaccines

One element of the success of the MVIP is the good quality of the household survey data that have been collected, despite the very challenging setting of the COVID-19 pandemic.

Overall reporting from routine surveillance systems

The focal points of national regulatory agencies share their country safety information for pooled analysis and reported the summary at the quarterly DSMB meetings. They meet with WHO regional focal points to review safety data and discuss the recommendations made by DSMB, following the DSMB meetings, which they attend.

Following RTS,S/AS01 vaccination, 2496 AEFIs and AESIs, were reported in all three countries of which 603 were serious and 93 were fatal. Almost 90% were reporting through the phase 4 study with others through routine surveillance systems and MVPE sentinel hospitals. Among the 7318 AEFIs reported to the routine surveillance systems, 150 (2.05%) were following RTS,S/AS01 vaccination. Among the 334 serious AEFIs, 9 were following RTS,S/AS01 vaccination. So far, no safety signals for previously-unknown rare events have been reported.

The limitations of these passive surveillance include the low reporting rate and the limited resources for monitoring, data analysis and follow-up for the serious AEFIs. The current COVID-19 pandemic contributes to the limited resources available for causality assessments.

Country-specific AEFI reporting

Ghana and Malawi provided data for 26 months, from May 2019 to June 2021 and Kenya for 21 months, from October 2019 to June 2021. In Ghana 299/2058 (14.5%) AEFIs following RTS,S/AS01 were serious, compared with 98/201 (48.8%) and 206/237 (86.9%) in Malawi and Kenya, respectively. The majority of the events were reported via the phase IV study. In Ghana causality assessment has been done for all 33 serious AEFIs reported via routine passive surveillance and MVPE sentinel hospitals, but no information is available for the 266 events in the phase IV trial. In Malawi causality assessment for the four serious AEFIs reported via routine passive surveillance has not been done, but it has been done by GSK for the 94 events reported in

the phase IV study. In Kenya causality assessment has not been done for the 83 serious AEFIs reported via routine passive surveillance but 135 and 44 of the serious AEFIs reported in the phase IV study have undergone causality assessment by GSK and the national expert committee, respectively. In Ghana, 11/22 fatal AEFIs occurred 11 to 30 days after vaccination, in Malawi, 16/36 fatal AEFIs occurred 151 to 480 days after vaccination, and in Kenya 14/33 fatal AEFIs occurred 151 to 360 days after vaccination.

The conclusions from all three countries are that there are no safety concerns or unknown rare events have been identified since the initiation of RTS,S/AS01 vaccination. Reporting via the routine passive surveillance system is low and the future challenge will be to improve reporting rates and also to have sufficient resources to perform investigations and causality assessments in a timely manner.

MVIP DSMB recommendations

DSMB recommended continuation of MVIP and congratulated the MVIP on their progress made on this ambitious program and for reaching this important 24-month primary analysis. They said that the number of events accrued was adequate to provide sufficient statistical power to exclude associations between RTS,S/AS01 and meningitis, cerebral malaria, and higher mortality in females 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 DSMB noted limitations in diagnosing cerebral malaria and challenges with meningitis surveillance but any uncertainty does not alter their conclusions regarding safety concerns. They concluded that the pilot evaluation results pooled from all three countries demonstrate effectiveness of RTS,S/AS01 against severe malaria, with both broad or strict definitions of severe malaria. As expected, there is not sufficient power yet to detect any impact on mortality.

The DSMB agreed with the sponsors' conclusion that the phase 4 ad hoc analysis was not interpretable due to incomplete or missing data. However, no safety signals were seen when reasonable assumptions were made about missing data. The DSMB noted that the planned interim analysis is expected in late 2023. Based on data reviewed from the national routine passive surveillance systems, the DSMB did not find evidence of new conditions that warrant closer safety tracking. They noted that collecting and investigating AEFIs remains a challenge for the national systems and that most of the reports were via the phase 4 or the MVPE sentinel hospitals and that very few serious events or deaths have been investigated. The DSMB encourages ongoing efforts to strengthen these important systems.

AACVS recommendations on the safety of the RTS,S/AS01 vaccine

The AACVS agreed that the safety evaluation data presented by MVIP programme seemed to be robust and the sources of data seemed appropriate and sufficiently diverse to answer safety questions about the RTS,S/AS01 vaccine raised by the SAGE and MPAG. No safety signals, trends or clusters of AEFIs associated with the RTS,S/AS01 vaccine were reported by the MVIP evaluation or the national routine passive surveillance systems. They concluded that there was no evidence of causal associations between the RTS,S/AS01 vaccine and meningitis, cerebral malaria or gender mortality imbalance based on the safety evaluation presented by MVIP.

The AACVS recommended that the pharmacovigilance systems in the African region need to continue to improve and be strengthened for continuous adverse event reporting, data collection, causality assessment. The definitions and classification used to collect data for AEFIs should be harmonized between countries. Funding for routine surveillance is needed and long-term sustainability needs to be considered with country ownership.

They also recommend that support for the existing networks of sentinel hospital sites (which are currently used for other vaccines) as well as the laboratories should be continued, if funding allows, to enable the sentinel hospital surveillance for AEFIs and AESIs to be continue.

Recommendations from GACVS

GACVS agreed with the conclusions of the MVIP DSMB and the AACVS based on the initial data analysis from the extensive pilot programme, i.e., that the data for the three safety signals (meningitis, cerebral meningitis and imbalance of mortality in females) is reassuring, with no evidence of any safety signal. They noted the good RTS,S/AS01vaccination uptake and the absence of any negative impact on the EPI coverage or other malaria preventive measures.

GACVS applauded the hard work and efforts that have enabled the robust assessment of the safety of the RTS,S/AS01 vaccine in the three countries participating in the MVIP pilot evaluations. GACVS understands that the MVIP pilot evaluations will continue for another two years, as planned and the final results will be considered.

GACVS acknowledged that GSK's post-marketing evaluation is ongoing and will continue, with a planned interim analysis due in 2023 and the final analysis in 2025.

GACVS noted the current limitations of the routine passive surveillance systems in countries where the RTS,S/AS01 vaccine was introduced, as well as in countries where it may be introduced more widely, if recommended by WHO. They strongly recommended that efforts to strengthen these surveillance systems should be continued.

GACVS reiterated more generally that sentinel surveillance systems should be considered for all new vaccine introduction, including for the RTS,S/AS01 vaccine, when possible, and at least, an enhanced passive surveillance with active follow up and causality assessment of AEFIs of potential interest.

GACVS stated that these recommendations for strengthening surveillance systems are not intended to be a pre-requisite or barrier for expanding use of the RTS,S/AS01 vaccine.

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

Annex 8a: An update to transmission modelling predictions of the RTS,S/AS01 malaria vaccine's public health impact and cost-effectiveness to include preliminary evidence on the cost of delivery from the Malaria Vaccine Implementation Programme 1

Annex 7

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Annex 8a: An update to transmission modelling predictions of the RTS,S/AS01 malaria vaccine's public health impact and cost-effectiveness to include preliminary evidence on the cost of delivery from the Malaria Vaccine Implementation Programme

Authors: Swiss TPH, Melissa A Penny, Sherrie L Kelly, Andrew J Shattock, Amanda Ross, Josephine Malinga, **Imperial College,** Peter Winskill, Alexandra Hogan, Pancho Mulongeni, Hayley Thompson, Bob Verity, Azra Ghani, **PATH,** Farzana Muhib, Ranju Baral, and Saira Nawaz

Objective(s)

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

Background

From 2015 onwards, modelled predictions of RTS,S malaria vaccine public health impact and cost-effectiveness were produced to compliment empirical observations from trial data and, more recently, the MVIP. Modelled predictions were produced by multiple groups using harmonized inputs that draw on data from the RTS,S 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 vaccine across the wide range of settings modelled. At $5 per dose and a *Pf*$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 (1). All currency is in US dollars.

Methods

Two previously harmonized and validated models produced by Imperial College and Swiss TPH were used to predict the public health impact and cost-effectiveness of the RTS,S malaria vaccine. Model

descriptions are reproduced below from Penny *et al* 2015. Models used harmonized inputs and baseline scenarios to assess vaccine impact and cost-effectiveness.

Imperial College. The model is a stochastic, individual-based simulation of a single population of humans linked to a stochastic compartmental model for mosquitoes. The model captures the combined effect of multiple interventions, including first-line treatment, LLINs and the RTS,S vaccine. The human infection process tracks individuals through stages of infection, with pre-erythrocytic and blood-stage immunity incorporated to capture the changing patterns of severe disease, clinical diseases and asymptomatic infection with age and exposure. The vector model includes larval stages as well as adult female mosquitoes to capture the feedback of vector control that kills adults on the population dynamics. Human infectiousness is related to asexual parasite dynamics and lagged to allow for development of gametocytes. Multiple vector species and heterogeneity in exposure is included. The model has been extensively fitted to data on the relationship between the entomological inoculation rate (EIR) and parasite prevalence, clinical disease, severe disease and deaths using Bayesian methods.

Swiss TPH – OpenMalaria. The model is a stochastic, individual-based, simulation model of malaria in humans linked to a deterministic model of malaria in mosquitoes. The simulation model includes sub-models of infection of humans, blood-stage parasite densities, infectiousness to mosquitoes as a lagged function of asexual parasite density, and incidence of morbidity, hospitalisation, and mortality. Pre-erythrocytic and blood-stage immunity comprise separate sub-models, with blood-stage immunity predominating as infection-blocking immunity occurs only in those with very high cumulative exposure. The model considers heterogeneity in transmission for within-host variability, with transmission modelled through periodically varying vectorial capacity. The model is capable of capturing the synergistic effects of a range of user-defined preventative and therapeutic interventions, including vaccines. A range of model parameters are fitted to clinical data based on key relationships between the entomological inoculation rate (EIR), parasite prevalence, morbidity, and mortality. The methodology used to generate these estimates has been previously described (2).

Model inputs and data sources

Model inputs and assumptions are summarized in Table 1. For both the OpenMalaria and Imperial College models, the underlying model structure and vaccine parameterization has remained stable since the previous round of modelling. Although data availability and timing precluded the evaluation and validation of the model estimates against the sub-national estimates of impact from the MVIP, model predictions are expected to fall within the estimated confidence levels from the national MVIP data. This preliminary suggests that the model estimates, including the current parameters, are broadly consistent with the current pooled estimates of impact from the MVIP. Key differences in model inputs include more comprehensive coverage and cost of delivery data that have been informed by MVIP. Where applicable, ranges shown in parentheses in Table 1 (vaccine coverage, cost of delivery) are explored in a sensitivity analysis.

Table 1: 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 (1)	No

Transmission intensity	Parasite prevalence among 2–10-year-olds between 3% and 65%, representing current transmission levels in Africa.	MAP	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 (1)	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 (1)	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 (1)	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] (6–9 months old with fourth dose). The first two doses of the primary series are assumed to have 0% efficacy.	Penny et al (1)	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 (1)	No
Vaccine price	$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 (see Annex table 1).	Penny et al (1)	No
Cost of delivery estimate	We assumed an (economic, recurring) cost of delivery per dose of $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 $1.07 to $2.27 per uncomplicated case, and from $21.78 to $55.58 per severe case.	Penny et al (1)	No

Cost of Delivery. In previous analyses, RTS,S 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 in pilot countries means that

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

[3] Results of the seasonal use case for RTS,S are included different part of the PAG report.

introduction costs were spread across a smaller number of doses delivered during the MVIP, particularly when compared to a full national roll out.

The cost per dose delivered was calculated from the provider perspective and consisted of the cost of vaccines (at an assumed cost per dose), injection and reconstitution syringes, safety boxes, freight, insurance and wastage as per Penny et al 2015, plus delivery cost (Table 2).

Table 2: Cost of delivery from the MVIP analysis included in Swiss TPH and Imperial college models All data presented US$.

Cost per vaccine dose	Cost per vaccination including vaccine cost	Cost of delivery per dose (economic, recurring)			Total cost per dose delivered		
		Mean	Min	Max	Mean	Min	Max
2	2.69	*1.62*	*0.96*	*2.67*	4.31	3.65	5.36
5	6.52	*1.62*	*0.96*	*2.67*	8.14	7.48	9.19
10	12.91	*1.62*	*0.96*	*2.67*	14.53	13.87	15.58

Vaccine Coverage. In addition to using updated cost of delivery estimates, revised assumptions for vaccine coverage were used to produce updated modelled predictions. Previously in 2015, vaccine coverage for the first 3 doses was assumed to be 90%, and the fourth dose had a drop of 20% from the third, resulting in 72% coverage of the fourth dose. After a review of the MVIP and based on feedback from the 2015 model, we assumed vaccine coverage of 80% for the first three doses and a 20% drop off from the third dose, resulting in 64% coverage for the fourth dose for the purpose of this analysis and noting that the MVIP is currently not powered to analyze the fourth dose of RTS,S. To remain consistent with the original vaccine schedule of 3 doses, for all scenarios we define fully vaccinated children as those who have received the first 3 doses of the schedule.

Findings

We present vaccine impact and cost-effectiveness predictions summarized across a range of parasite prevalence levels among 2–10-year-olds of 10%–50%, to reflect 2020 prevalence levels in perennial settings (Table 2, Figure 1). A separate analysis has been conducted to look at the public health impact and cost-effectiveness of RTS,S in seasonal settings. Predictions of the potential public health impact of the RTS,S vaccine remain largely unchanged as both modelling groups have 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 3, Figure 1: D, E and F) have 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 RTS,S is still predicted to be cost-effective compared with standard norms and thresholds. The relative impact of the added cost of delivery predictions is larger at the lower ($2) assumed cost per dose level.

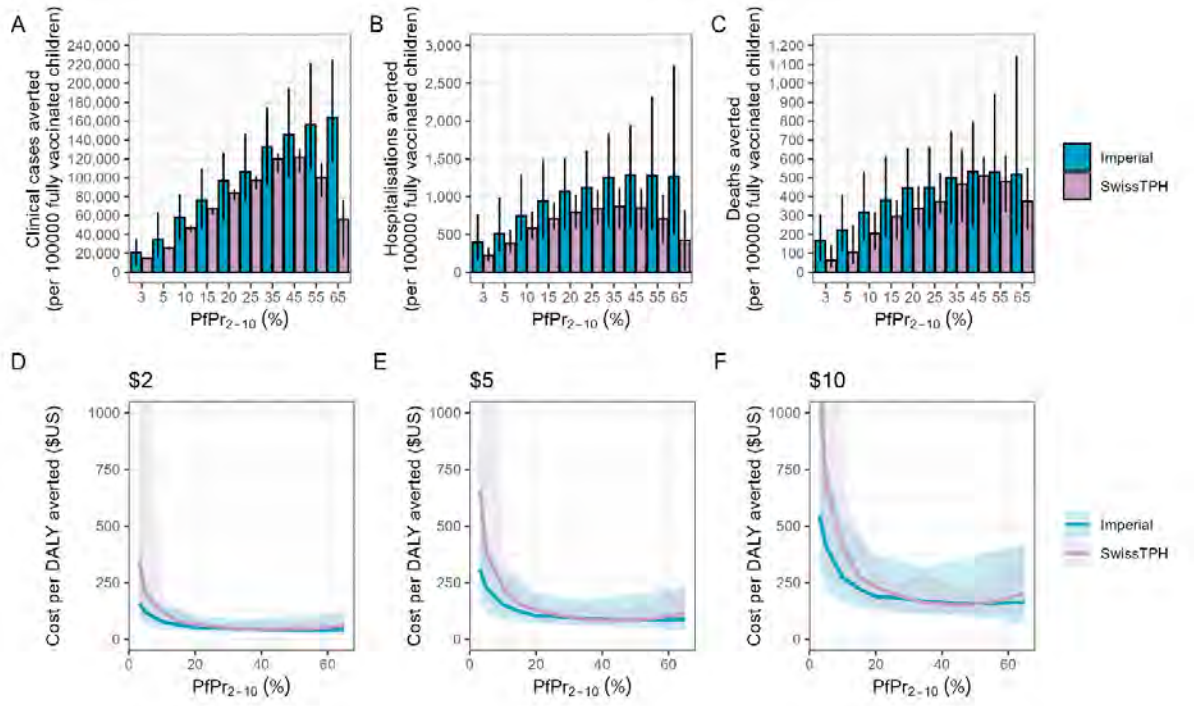
Table 3: Public health impact and incremental cost-effectiveness ratios (ICER) for 4-dose schedule at 15 years of follow-up in regions with a parasite prevalence among 2–10-year-olds of 10–50%.

	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) [4]	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 ($) 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)	$187 (157 to 274)
ICER ($) 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)

Estimates show the median and range of model predictions across transmission settings. Please note that summary statistics are not directly comparable between the current analysis and Penny *et al* (2015), due to the way the estimates are presented. Updated predictions show the median and range of model predictions (at 80% coverage), whilst predictions from Penny *et al* (2015) (1) show the median (range) across four models' medians (at 90% coverage). Additionally, the estimates in the table above show the summary statistics over a *Pf*Pr range of 10-50% (current prevalence in 2021), whilst predictions from Penny et al show summary statistics across a *Pf*Pr range of 10-65%.

Figure 1. Summary of impact and cost-effectiveness predictions for RTS,S across transmission settings of 3-65%.

[4] 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.



Figures above reflect 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) $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.

Annex

***Comparison of predictions to Penny et al 2015 for Pf*Pr of 10-65%**

Outputs from individual models, when summarized for regions with a *Pf*Pr among 2–10 year olds of 10%–65%, as in Penny *et al* 2015, were consistent with the range presented for the four models included in in Penny *et al* 2015 (Table 4).

Table 4: Comparison of current and Penny et al 2015 predictions of the public health impact and cost-effectiveness predictions for 4-dose schedule at 15 years of follow-up in regions with a *Pf*Pr among 2–10 year olds of 10%–65%.

	Median estimate (range)		Median estimate (range) across four models' medians
	Swiss TPH model	**Imperial College Model**	**Penny *et al* 2015**
Percentage of malaria deaths averted in children younger than 5 years	8.95% (5.3 to 10.1)	17.5% (3.9 to 20.8)	18.0% (6.0 to 29.1)
Percentage of clinical cases averted in children younger than 5 years	12.2% (7 to 14.6)	20.3% (18.1 to 23.6)	21.1% (7.9 to 30.6)
Malaria deaths averted per 100,000 fully vaccinated children	396.5 (205 to 540)	474 (315 to 534)	484 (189 to 859)
Malaria clinical cases averted per 100,000 fully vaccinated children	82336.5 (46978 to 121182)	119198 (57839 to 163206)	116480 (31450 to 160410)
ICER per DALY averted			
$2 per dose	$55.5 (42 to 120)	$49 (43 to 78)	$38 (18 to 97)
$5 per dose	$105.5 (81 to 230)	$97 (86 to 151)	$87 (48 to 244)
$10 per dose	$189.5 (146 to 412)	$177 (157 to 274)	$154 (99 to 487)
ICER per clinical case averted			
$2 per dose	$38.5 (25 to 183)	$12 (9 to 26)	$10 (6 to 93)
$5 per dose	$74 (48 to 345)	$24 (17 to 50)	$25 (16 to 222)
$10 per dose	$132.5 (87 to 616)	$44 (32 to 91)	$51 (28 to 437)

Table 4 shows the updated predictions show the median and range of model predictions (at 80% coverage) whilst predictions from Penny *et al* (2015) show the median (range) across four models' medians (at 90% coverage) using the same PfPr as the Penny et al analysis. Although we cannot make a direct comparison of the estimates, we note that the Swiss TPH model predicted lower proportion of events averted in higher versus low transmission settings is partly explained by age-shifting of disease in higher transmission areas.

Sensitivity of cost-effectiveness predictions to cost of delivery and vaccine coverage

We conducted a sensitivity analysis with the updated cost of delivery estimates and vaccine coverage. Overall, estimates varied when using minimum and maximum cost of delivery estimates (Tables 5-6, Figures 2-3) and remain fairly constant across range of coverages (Tables 7-8, Figures 4-5).

Cost of Delivery

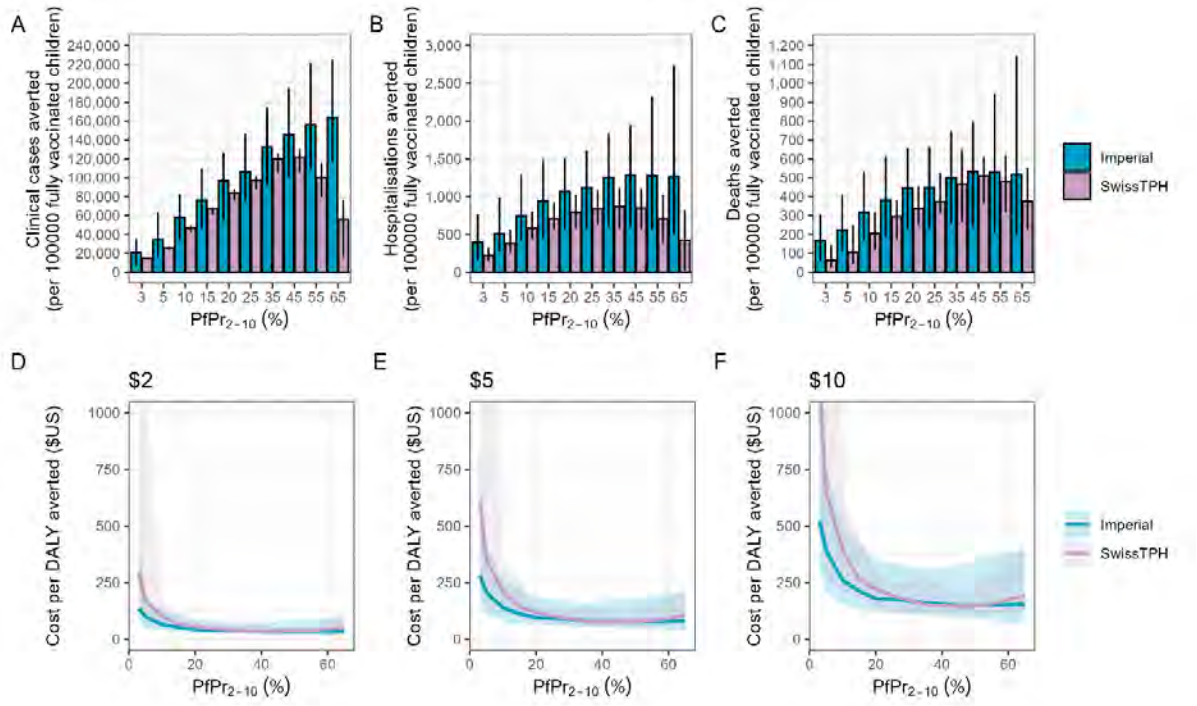
Tables and figures below include sensitivity analysis for minimum ($0.96) and maximum ($2.67) cost of delivery estimates. The predicted public health impact of the RTS,S vaccine is not affected by

variations in the estimated cost of delivery. Variations in the cost of delivery do have an impact on the total cost of the vaccination programme and therefore the estimate of the cost per DALY averted and cost per clinical case averted. At the minimum estimate for cost of delivery ($0.96), this additional cost contributes a relatively smaller proportion of the total costs that at the maximum estimate for cost of delivery ($2.67). The impact of changes to cost of delivery also interact with the assumed cost per dose. As the assumed cost per dose falls, the relative contribution of cost of delivery to the total costs becomes larger and therefore sensitivity in changes to the cost of delivery increase. For example, when varying the cost of delivery between the minimum and maximum, the cost per DALY averted at $2 per dose increases by approximately 50%, at $5 a dose by approximately 24%, whilst at $10 per dose the increase falls to approximately 12% (Table 5-6).

Table 5: Public health impact and cost-effectiveness predictions (medians and range) for 4-dose schedule at 15 years of follow-up in regions with a parasite prevalence among 2–10 year olds of 10%–50% for minimum ($0.96) cost of delivery estimate.

	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)	11.5% (8.3 to 13.5)
Percentage of clinical cases averted in children younger than 5 years	13.2% (11.2 to 14.6)	13.3% (12.6 to 15.1)
Malaria deaths averted per 100,000 fully vaccinated children	417 (205 to 540)	449 (313 to 536)
Malaria clinical cases averted per 100,000 fully vaccinated children	108824 (46978 to 121182)	98174 (57938 to 145881)
ICER per DALY averted		
$2 per dose	$42 (36 to 101)	$44 (36 to 67)
$5 per dose	$89 (74 to 211)	$94 (79 to 140)
$10 per dose	$167 (139 to 393)	$179 (150 to 263)
ICER per clinical case averted		
$2 per dose	$26 (21 to 39)	$12 (8 to 22)
$5 per dose	$54 (44 to 82)	$27 (18 to 46)
$10 per dose	$100 (83 to 152)	$51 (34 to 86)

Figure 2. Summary of impact and cost-effectiveness predictions for RTS,S across transmission settings for minimum ($0.96) cost of delivery estimate.

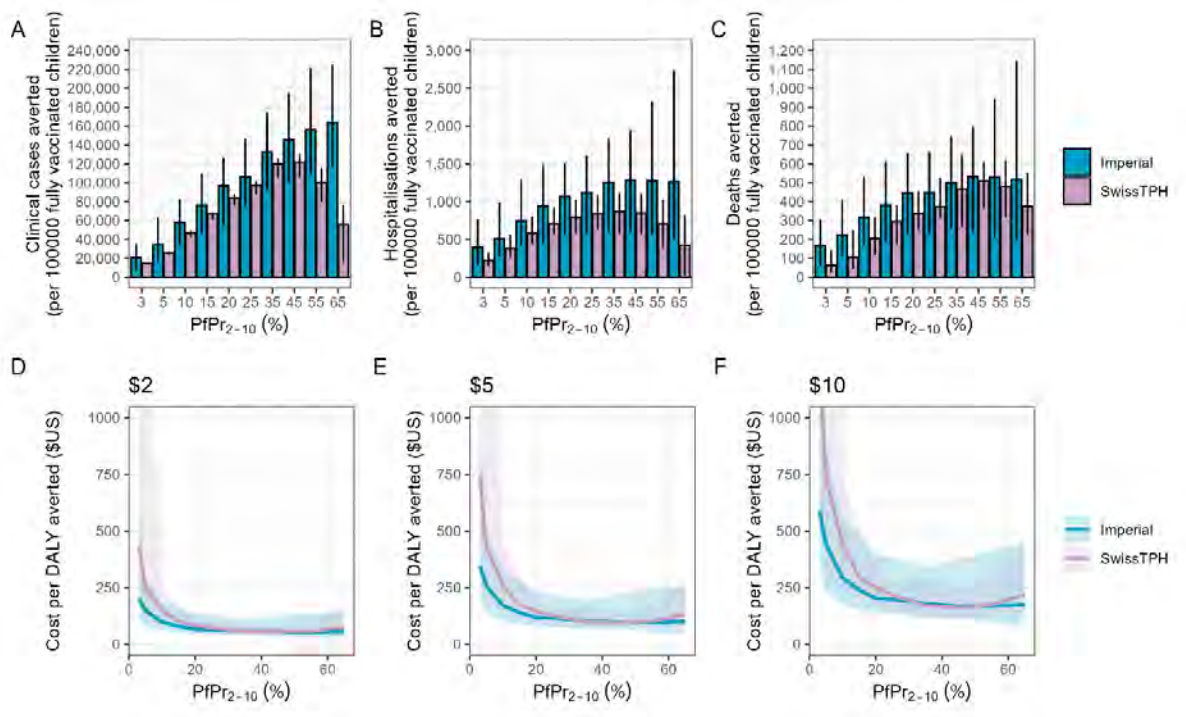


Panels in the top row show predictions of impact of A) clinical cases, B) hospitalizations and C) malaria deaths avert per 100,000 fully vaccinated children as a function of baseline parasite prevalence among 2–10 year olds (*Pf*Pr_{2-10}) from Imperial (blue bars) and SwissTPH (mauve bars) models. Bars represent the median estimate and error bars 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) $2, E) $5 and F) $10 for Imperial (blue lines) and SwissTPH (mauve lines) models. Lines represent the median estimate and shaded areas the 95% credible intervals.

Table 6: Public health impact and cost-effectiveness predictions (medians and range) for 4-dose schedule at 15 years of follow-up in regions with a parasite prevalence among 2–10 year olds of 10%–50% for maximum ($2.67) cost of delivery estimate.

	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)	11.5% (8.3 to 13.5)
Percentage of clinical cases averted in children younger than 5 years	13.2% (11.2 to 14.6)	13.3% (12.6 to 15.1)
Malaria deaths averted per 100,000 fully vaccinated children	417 (205 to 540)	449 (313 to 536)
Malaria clinical cases averted per 100,000 fully vaccinated children	108824 (46978 to 121182)	98174 (57938 to 145881)
ICER per DALY averted		
$2 per dose	$63 (53 to 150)	$66 (55 to 99)
$5 per dose	$110 (92 to 260)	$117 (98 to 173)
$10 per dose	$188 (156 to 442)	$201 (169 to 296)
ICER per clinical case averted		
$2 per dose	$38 (32 to 58)	$19 (12 to 32)
$5 per dose	$66 (55 to 101)	$33 (22 to 57)
$10 per dose	$113 (94 to 171)	$57 (38 to 97)

Figure 3. Summary of impact and cost-effectiveness predictions for RTS,S across transmission settings for maximum ($2.67) cost of delivery estimate.

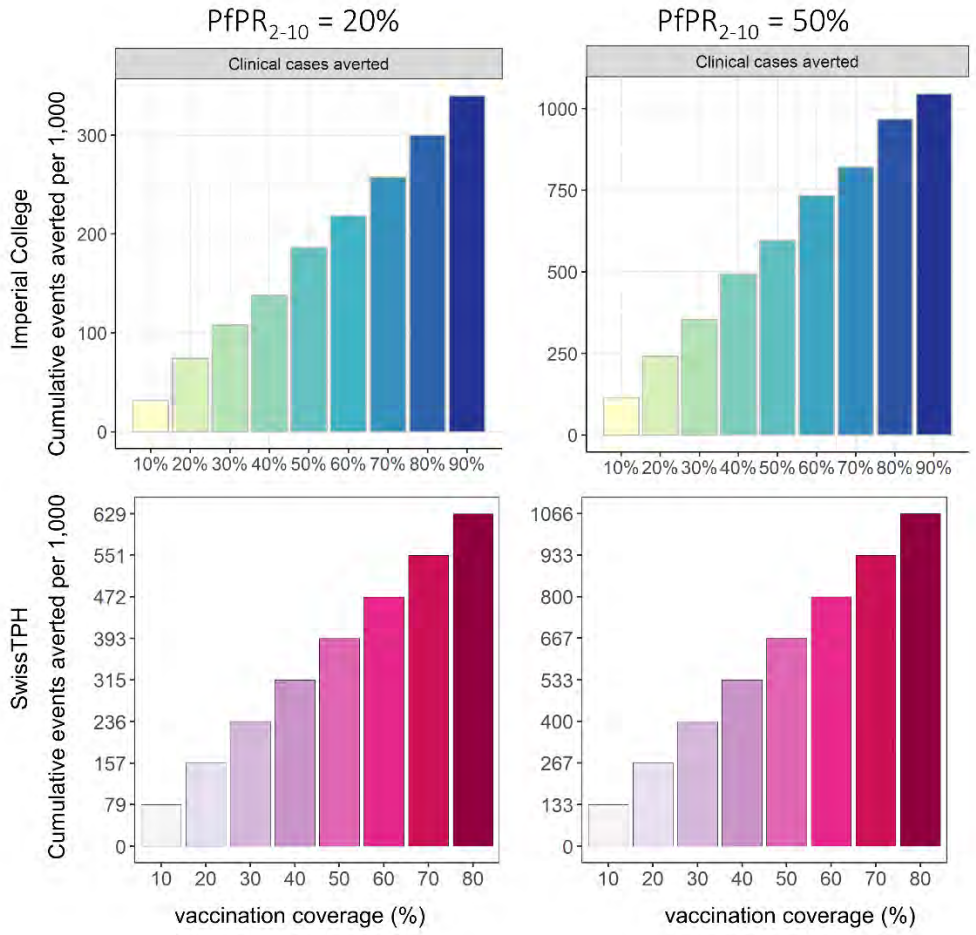


Panels in the top row show predictions of impact of A) clinical cases, B) hospitalizations and C) malaria deaths avert per 100,000 fully vaccinated children as a function of baseline parasite prevalence among 2–10 year olds (*Pf*$Pr_{2\text{-}10}$) from Imperial (blue bars) and SwissTPH (mauve bars)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

Vaccine Coverage

Predicted vaccine impact has been previously shown to scale linearly with vaccine coverage (Figure 4). As a result, outputs per 100,000 fully vaccinated children and ICER predictions remain fairly constant across the range of coverages (50%–90%).

Figure 4: Illustration of linear scaling of modelled vaccine impact with respect to vaccine coverage for two representative transmission levels (*PfPr:* 20% and 50%).



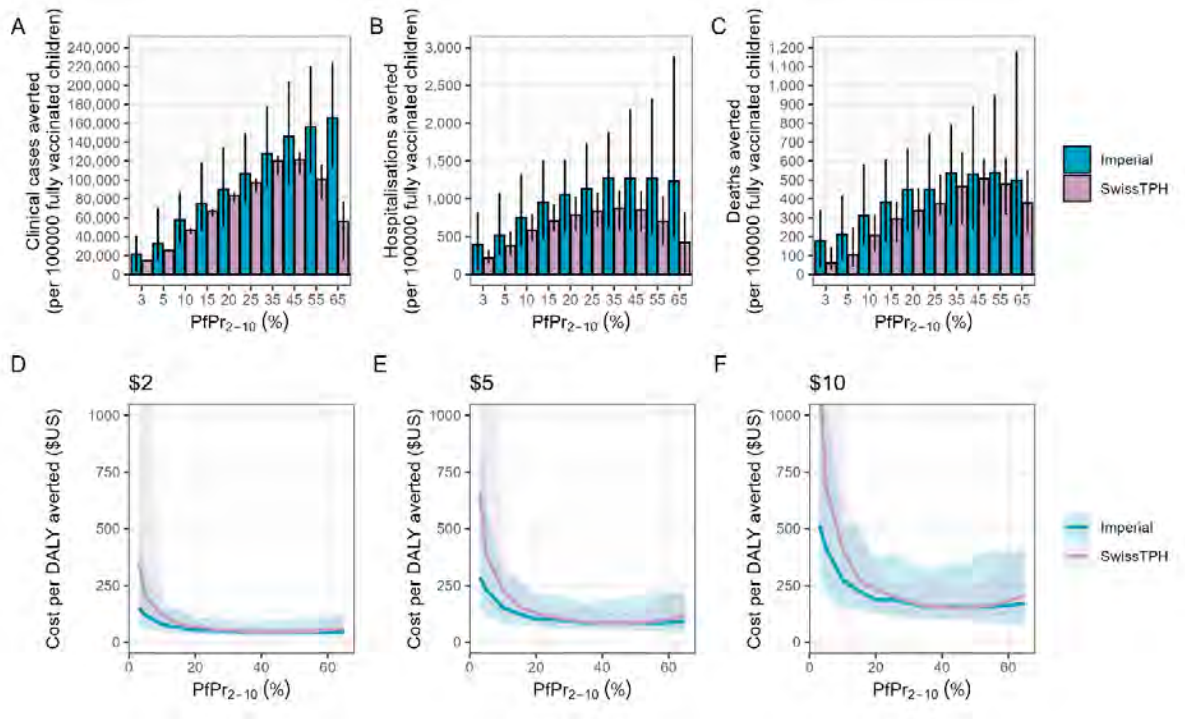
Each bar shows cumulative number of clinical events averted over 5 years per 1000 children under 5 for a given coverage. Similar trends are seen for deaths averted. This figure reproduced from previous MVIP modelling.

The tables and figures below include a sensitivity analysis at lower (50%) and higher (90%) vaccination coverage. Whilst the absolute predictions of public health impact vary with coverage, estimates per 100,000 fully vaccinated children and ICER estimates are insensitive to changes in coverage. When varying coverage both the impact and costs also vary linearly, leading to similar proportional changes in the numerators and denominators of these estimates (Table 7-8). Small differences in the Imperial college model predictions are a result of stochastic variation between simulation runs.

Table 7: Public health impact and cost-effectiveness predictions (medians and range) for 4-dose schedule at 15 years of follow-up in regions with a parasite prevalence among 2–10 year olds of 10–50% for lower (50%) vaccine coverage.

	Median estimate (range)	
	Swiss TPH model	**Imperial College Model**
Percentage of malaria deaths averted in children younger than 5 years	5.7% (5.4 to 6.3)	11.5% (8.3 to 13.5)
Percentage of clinical cases averted in children younger than 5 years	8.3% (7 to 9.1)	13.3% (12.6 to 15.1)
Malaria deaths averted per 100,000 fully vaccinated children	417 (205 to 540)	449 (313 to 536)
Malaria clinical cases averted per 100,000 fully vaccinated children	108824 (46978 to 121182)	98174 (57938 to 145881)
ICER per DALY averted		
$2 per dose	$50 (42 to 120)	$52 (43 to 79)
$5 per dose	$97 (81 to 230)	$103 (86 to 153)
$10 per dose	$175 (146 to 412)	$187 (157 to 276)
ICER per clinical case averted		
$2 per dose	$31 (25 to 46)	$15 (10 to 26)
$5 per dose	$59 (48 to 89)	$29 (19 to 50)
$10 per dose	$105 (87 to 160)	$54 (35 to 91)

Figure 5. Summary of impact and cost-effectiveness predictions for RTS,S across transmission settings for lower (50%) vaccine coverage for PfPr 3-65%.

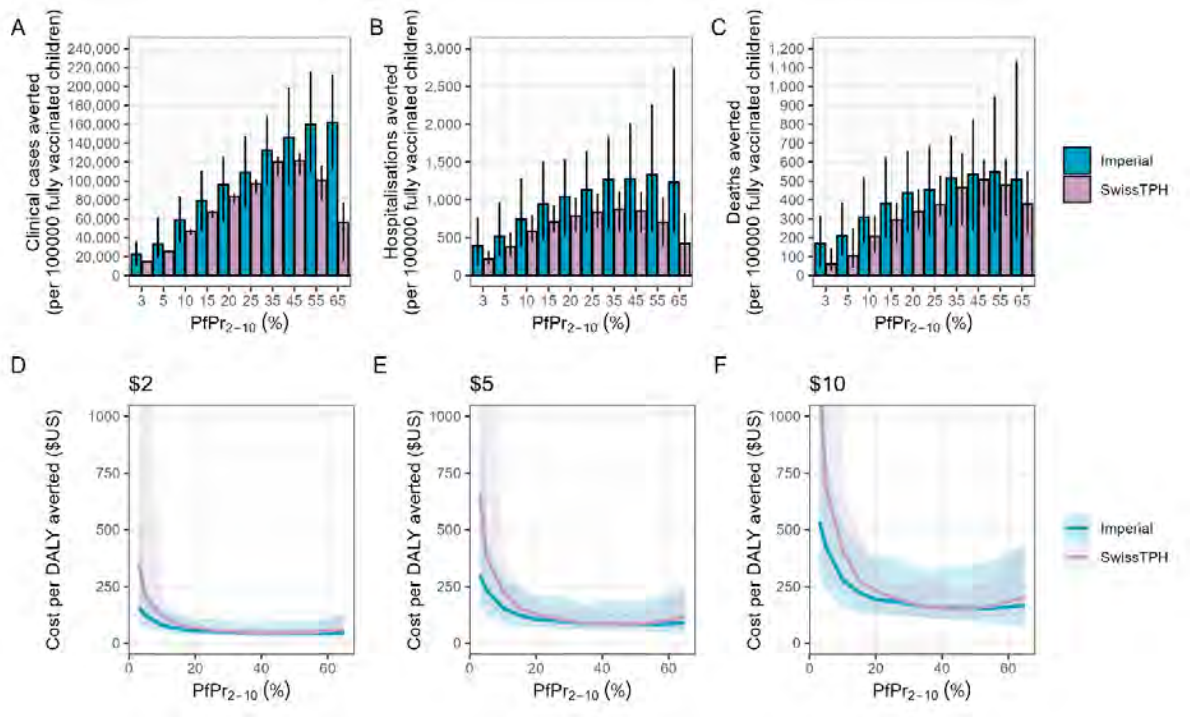


Panels in the top row show predictions of impact of A) clinical cases, B) hospitalizations and C) malaria deaths avert per 100,000 fully vaccinated children as a function of baseline parasite prevalence among 2–10 year olds (*Pf*Pr_{2-10}) from Imperial (blue bars) and SwissTPH (mauve bars) models. Bars represent the median estimate and error bars 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) $2, E) $5 and F) $10 for Imperial (blue lines) and SwissTPH (mauve lines) models. Lines represent the median estimate and shaded areas the 95% credible intervals.

Table 8: Public health impact and cost-effectiveness predictions (medians and range) for 4-dose schedule at 15 years of follow-up in regions with a parasite prevalence among 2–10 year olds of 10%–50% for higher (90%) vaccine coverage.

	Median estimate (range)	
	Swiss TPH model	**Imperial College Model**
Percentage of malaria deaths averted in children younger than 5 years	10.3% (9.7 to 11.4)	21% (15 to 23)
Percentage of clinical cases averted in children younger than 5 years	14.9% (12.6 to 16.4)	23.2% (22.5 to 26.1)
Malaria deaths averted per 100,000 fully vaccinated children	417 (205 to 540)	446 (308 to 535)
Malaria clinical cases averted per 100,000 fully vaccinated children	108824 (46978 to 121182)	102537 (58622 to 145484)
ICER per DALY averted		
$2 per dose	$50 (42 to 120)	$53 (42 to 80)
$5 per dose	$97 (81 to 230)	$104 (85 to 155)
$10 per dose	$175 (146 to 412)	$188 (156 to 279)
ICER per clinical case averted		
$2 per dose	$31 (25 to 46)	$14 (10 to 26)
$5 per dose	$59 (48 to 89)	$28 (20 to 50)
$10 per dose	$105 (87 to 160)	$51 (36 to 90)

Figure 5: Summary of impact and cost-effectiveness predictions for RTS,S across transmission settings for higher (90%) vaccine coverage.

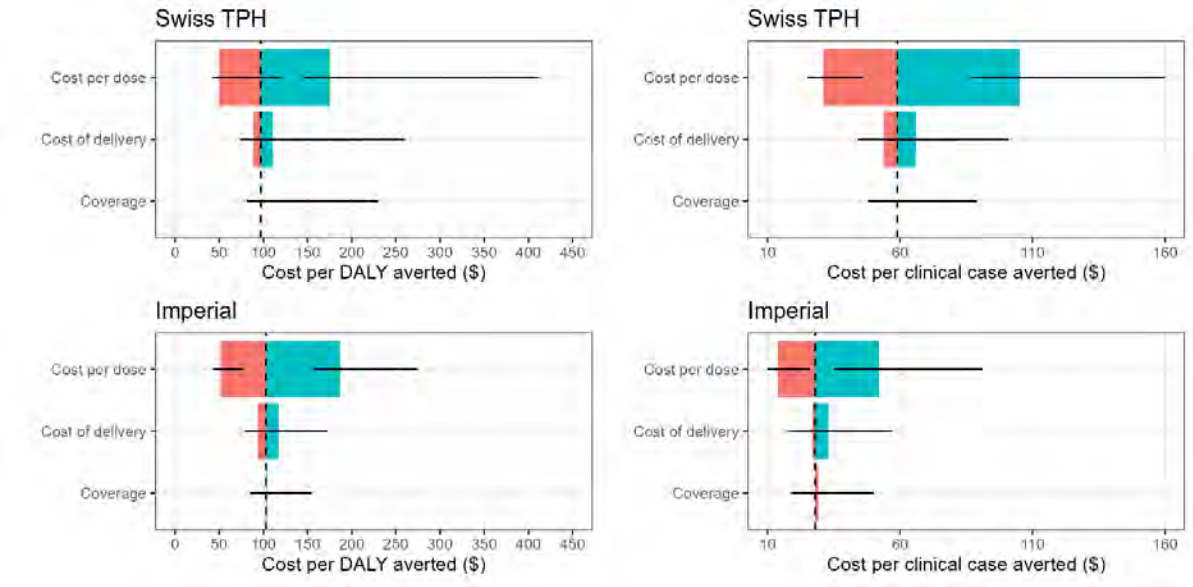


Panels in the top row show predictions of impact of A) clinical cases, B) hospitalizations and C) malaria deaths avert per 100,000 fully vaccinated children as a function of baseline parasite prevalence among 2–10 year olds (*Pf*Pr_{2-10}) from Imperial (blue bars) and SwissTPH (mauve bars) models. Bars represent the median estimate and error bars 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) $2, E) $5 and F) $10 for Imperial (blue lines) and SwissTPH (mauve lines) models. Lines represent the median estimate and shaded areas the 95% credible intervals.

Incremental Cost-Effectiveness Ratio

Figure 1. One-way sensitivity of ICER predictions to cost per dose, cost of delivery and coverage estimates.



Colored bars indicate the minimum (coral) and maximum (teal) cost per event averted when varying the cost per dose, cost of delivery or coverage between their minimum and maximum value. Solid black lines show model uncertainty for the minimum and maximum estimate. All values are summarized over settings with parasite prevalence among 2–10 year olds of 10%–50% and presented in comparison with a baseline scenario of $5 per dose, mean cost of delivery estimate and 80% coverage (vertical black dashed line). It shows that the ICER estimates are most sensitive to dose cost, somewhat sensitive to delivery cost and not sensitive to coverage estimates.

Conclusion

Both the Swiss TPH and Imperial College models predict a positive public health impact of the introduction of RTS,S in settings with *Pf*Pr_{2-10} between 10% and 50% over a 15-year time horizon, as well as in the 50-65% range which is consistent with previously published estimates. Although the cost per averted cases and cost per DALY have slightly increased respectively, due to the inclusion of more comprehensive cost of delivery, RTS,S is still considered cost-effective by general thresholds and standards. The predicted cost per DALY averted for RTS,S is higher than estimates for some other malaria interventions such as LLINs and IRS (2) but care should be taken when making direct comparisons as measures are sensitive to methodology and context. Furthermore, RTS,S has the potential to reach/protect those that are not reached by other malaria interventions. It is also important to note that RTS,S continues to be evaluated in the context of the consistent use of other malaria interventions.

References

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2. Conteh L, Shuford K, Agboraw E, Kont M, Kolaczinski J, Patouillard E. Costs and cost-effectiveness of malaria control interventions: A systematic literature review. Value in Helath. 2021:24(8):1213-1222.

Annex 8b: Mathematical modelling to inform policy decisions about a seasonal use-case for the RTS,S/AS01 malaria vaccine

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Summary

- Population-level modelling indicates that in settings with seasonal malaria transmission seasonally targeted RTS,S vaccination (SV) results in greater absolute reductions in malaria cases and deaths over 15 years compared to RTS,S delivery though an age-based Expanded Programme on Immunization (EPI) schedule.
- While SV may avert more cases than EPI, further exploration of SV clinical trial data and model results highlights that SV will result in delayed age at first vaccination depending on birth month, with the potential for this to leave some 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 SV + SMC predicted to result in the largest burden reductions when compared with either intervention implemented independently.
- In seasonal settings with medium to high transmission intensity and the absence of SMC, cost-effectiveness analysis, while illustrative, suggests that RTS,S vaccination is cost-effective at a cost per dose of $5. In the same seasonal transmission settings when SMC is already in use, RTS,S is not as cost-effective because benefits and costs are incremental to SMC. When RTS,S is used as a complement to SMC, ICERs are higher but of a similar magnitude as those reported elsewhere for EPI RTS,S delivery in perennial settings.
- When considering RTS,S vaccination in seasonal settings the potential achievable coverage will likely determine the most beneficial delivery approach locally. In addition, a Hybrid vaccination strategy (EPI priming with seasonal fourth and fifth doses) could potentially combine the advantages of EPI (maintaining young age at first vaccination) and SV (fourth and fifth dose efficacy maximised to peak risk) along with distributional benefits. However further modelling is needed to understand the implications of such a schedule.

Background

The RTS,S/AS01 vaccine for *P. falciparum* malaria is being considered for future introduction into the EPI childhood vaccination schedule in malaria-endemic regions with perennial transmission. In addition, there is potential for this vaccine to be used, either in combination with or separately to Seasonal Malaria Chemoprevention (SMC), in regions where malaria transmission fluctuates seasonally. The seasonal malaria vaccination Phase 3b clinical trial assessed the relative impact of these interventions in two locations in Mali and Burkina Faso. In this report, we use data from the trial and an individual-based transmission model of *P. falciparum* malaria transmission, to estimate the impact of a seasonal use-case of the RTS,S vaccine. We consider the population level reductions in clinical malaria cases and deaths over 15 years and the cost-effectiveness of several RTS,S strategies in the absence of SMC and incremental to SMC.

Methods

Model estimates of seasonal intervention impact were validated against the results of the seasonal malaria vaccination Phase 3b clinical trial by capturing the site-specific epidemiology at the

administrative-1 level, and implementing the intervention delivery schedules, coverage, and age cohorts as reported in the trial. With several biologically-motivated assumptions about the levels and decay of RTS,S and SMC efficacy over time, model outputs aligned closely with trial results (Annex 1.1). Without the present capacity for re-fitting, multiple intervention models are presented here to represent our uncertainty in intervention effects (Annex 1).

The transmission model was parameterised as set out in Annex 2. Model comparisons were made across two seasonality archetypes, characteristic of the seasonality patterns across the Sahel (highly seasonal) and Sub-Sahel (seasonal) regions (Figure A5) with a baseline $PfPR_{2\text{-}10}$ between 3-65%. Vector control interventions are assumed to remain static over follow up and are therefore reflected in the baseline $PfPR_{2\text{-}10}$. Moderate levels of access to care were assumed (Effective coverage (i.e., treatment with parasitological cure) for clinical malaria of 45%).Three potential vaccination strategies were considered: EPI (age-based primary series and age-based fourth dose), SV (seasonally targeted primary series and seasonal fourth and fifth doses), and a Hybrid strategy (age-based primary series and seasonal fourth and fifth doses) (Table A2). The model structure cannot currently capture Hybrid vaccination strategies, therefore a simplified model of these schedules is presented in Annex 2.1, with the main results showing only EPI and SV deployment. Further population-level modelling of a Hybrid strategy is underway. Note that EPI is used as a shorthand descriptor of an age-based strategy (i.e. delivery of the first three doses between 5 and 9 months of age) and is not meant to imply a different role for immunization programs in delivering RTS,S vaccine seasonally.

RTS,S impact – SV compared to EPI

The model simulations showed that SV resulted in greater reductions in cases and deaths than EPI vaccination across all endemicity settings in both seasonal and highly seasonal settings over 15 years. An additional fifth dose and/or higher fourth and fifth dose efficacy against infection increased this impact (Figure 1).

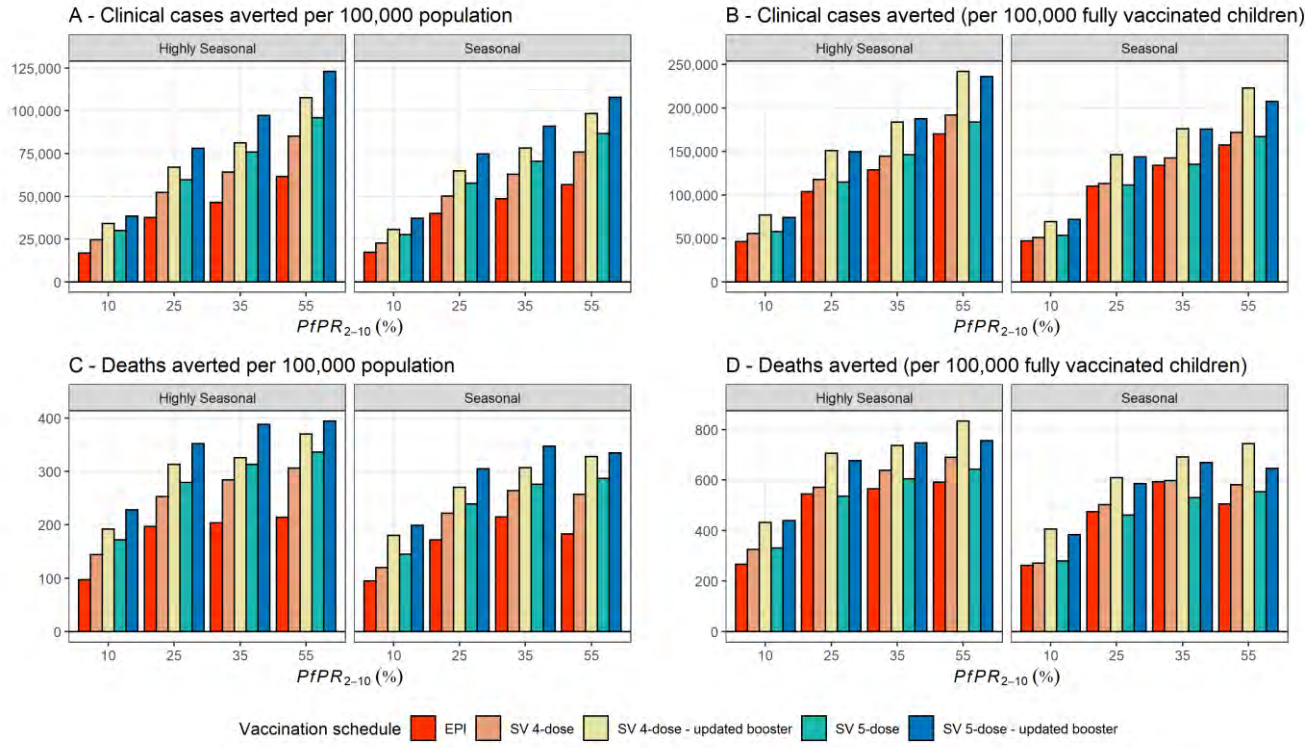

Figure 1 Cumulative clinical cases averted over 15 years as a function of baseline *PfPR*$_{2\text{-}10}$ (four settings representative of medium to high transmission intensity are shown) and seasonality **A&C**) per population and **B&D**) per 100,000 fully vaccinated children. Coverage is fixed at 80% for the first three doses with a 20% drop off (from the 3rd dose) for the fourth and fifth doses (coverage is the same for the 4th and 5th dose). Fully vaccinated children are defined as those receiving the primary series (first three doses). EPI- is the four-dose age-based strategy, SV 4&5-dose is the seasonal strategy assuming the original vaccine efficacy profile from the Phase 3 RTS,S trials, SV 4&5-dose – updated booster is the seasonal strategy assuming the updated higher efficacy against infection for the 4th and 5th dose based on our validation to the seasonal malaria vaccination Phase 3b clinical trial (Annex 1).

Considering the effect of seasonality in the absence of SMC, the incremental benefit of SV over EPI (defined as the proportion of additional events averted with an SV 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). 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 SV schedule (Figure 1B, 1D).

Despite SV resulting in the largest reductions in malaria cases and deaths over the 15-year period, modelling results showed EPI be more beneficial than SV 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 2.1). A Hybrid strategy that uses EPI delivery for the primary series could potentially be more impactful than SV by preserving a young age at first vaccination and retaining the

population level benefits of seasonally targeted fourth and fifth doses that result in greater aggregate reductions in morbidity and mortality at older ages (Annex 2.1).

RTS,S impact with SMC delivery

The model simulations indicated the combination of RTS,S and SMC to be substantially more impactful than either intervention alone in seasonal settings. The combination of SV + SMC resulted in a greater number of cases and deaths averted compared to EPI + SMC (Figure 2). The inclusion of SMC alongside a vaccination schedule also reduces the effect of disparity in age at first vaccination between SV and EPI (Figure A11).

On average across both seasonality profiles and endemicity levels, SV + SMC averted an additional 61% more cases than SMC alone, with EPI + SMC averting an additional 31% more cases than SMC alone. When interventions were combined, the additional impact of vaccination over SMC was higher in seasonal settings , where the burden is spread over more of the year, than in highly seasonal settings. This may reflect the greater importance of protection from 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.

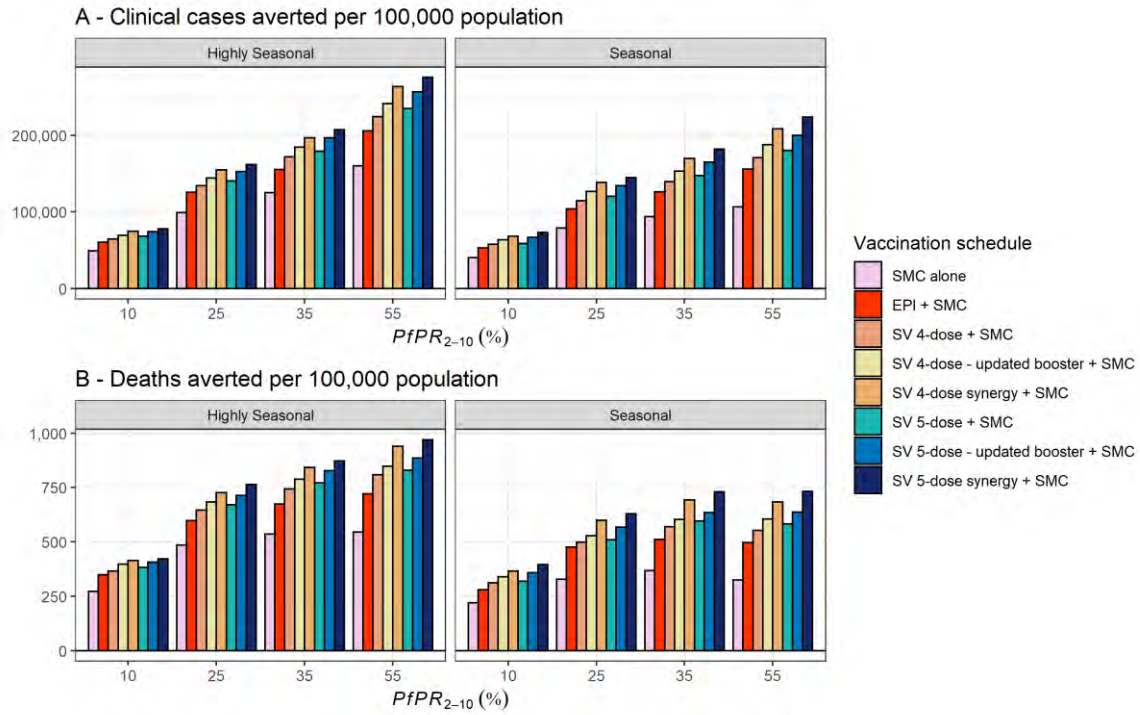

Figure 2 Cumulative clinical cases and deaths averted over 15 years per population as a function of baseline *PfPR*$_{2\text{-}10}$ (four representative of medium to high transmission intensity are shown) and seasonality. Coverage is fixed at 80% for the first three doses with a 20% drop off for the fourth and fifth doses. SMC coverage at 75%. EPI- is the four-dose age-based strategy, SV 4&5-dose is the seasonal strategy assuming the original vaccine efficacy profile for the Phase 3 RTS,S trials. SV 4&5-dose – updated booster is the seasonal strategy assuming the updated higher efficacy against infection for the 4th and 5th dose and synergy the increase in the modelled total RTS,S and SMC efficacy against infection above that of each intervention when they are considered alone based on the seasonal malaria vaccination Phase 3b clinical trial.

Cost-effectiveness

As no seasonal delivery cost data or introduction data is yet available for RTS,S, costs were assumed to be equivalent to EPI vaccination costs informed by MVIP data (Annex 3).

When compared with no-vaccination, no SMC and standard levels of access to treatment and existing vector control at an assumed cost per dose of $5, ICERs for RTS,S vaccination alone in seasonal settings

were generally around $100 per DALY averted and less than $35 per case averted for a *PfPR*$_{2\text{-}10}$ between 10%-50% for all vaccination schedules (Table 1, Figure A14). Incremental cost-per-case and cost-per-DALY averted for each vaccination schedule were lowest at intermediate to high levels of baseline *PfPR*$_{2\text{-}10}$. Overall, the model estimated that ICERs were marginally lower for all SV schedules (i.e. more cost-effective) than for EPI schedules, despite SV's higher number of overall doses delivered (Table 1, Table A5).

We also consider whether the addition of RTS,S to SMC is cost-effective relative to 4 monthly cycles of SMC alone. The cost-per-additional-case and -DALY averted were lowest at intermediate to high levels of baseline PfPR$_{2\text{-}10}$. For an assumed cost per dose of $5, ICERs were generally lower than $160 per DALY averted and less than $50 per case averted for a *PfPR*$_{2\text{-}10}$ between 10%-50% (Table 1, Figure A15). Again, ICERs were lower for all SV schedules relative to EPI when combined with SMC (Table 1, Table A6). ICERs for SV and EPI schedules are higher but of a similar magnitude to those reported elsewhere for EPI RTS,S delivery in perennial settings

Table 1. Comparison of cost-effectiveness estimates after 15 years of intervention delivery in regions with a *PfPR*$_{2\text{-}10}$ between 10-50%. Results are averaged across both seasonality profiles. Results presented for a mean vaccine delivery cost of $1.62 per dose and unit cost of SMC of $1.07 per monthly cycle.

	Interventions			
	EPI[1]	SV[1,3]	EPI + SMC[2]	SV + SMC[2,3]
ICER per DALY averted				
$2 per dose	$58.04	$47.63	$81.58	$60.09
$5 per dose	$112.84	$93.25	$157.63	$117.39
$10 per dose	$204.28	$169.36	$284.59	$212.98
ICER per clinical case averted				
$2 per dose	$17.66	$14.04	$26.30	$18.18
$5 per dose	$34.29	$27.44	$50.80	$35.31
$10 per dose	$62.03	$49.80	$91.67	$64.01

[1]Incremental to no SMC and standard levels of access to treatment and existing vector control

[2]Incremental to SMC delivery at 75% coverage and standard levels of access to treatment and existing vector control

[3]Averaged across all SV intervention efficacy and dose models

Annex 1 – Model validation results

Annex 1.1 Seasonal intervention model changes

The seasonal malaria vaccination Phase 3b clinical trial occurred in two locations in southern Burkina Faso and Mali over the years 2017–2020. There were three trial arms: SV alone; SMC alone; and SV and SMC combined. We used the Imperial College London malaria transmission model to simulate the trial, by capturing the site-specific epidemiology at the administrative-1 level, and implementing the intervention delivery schedules, coverage, and age cohorts as reported in the trial.

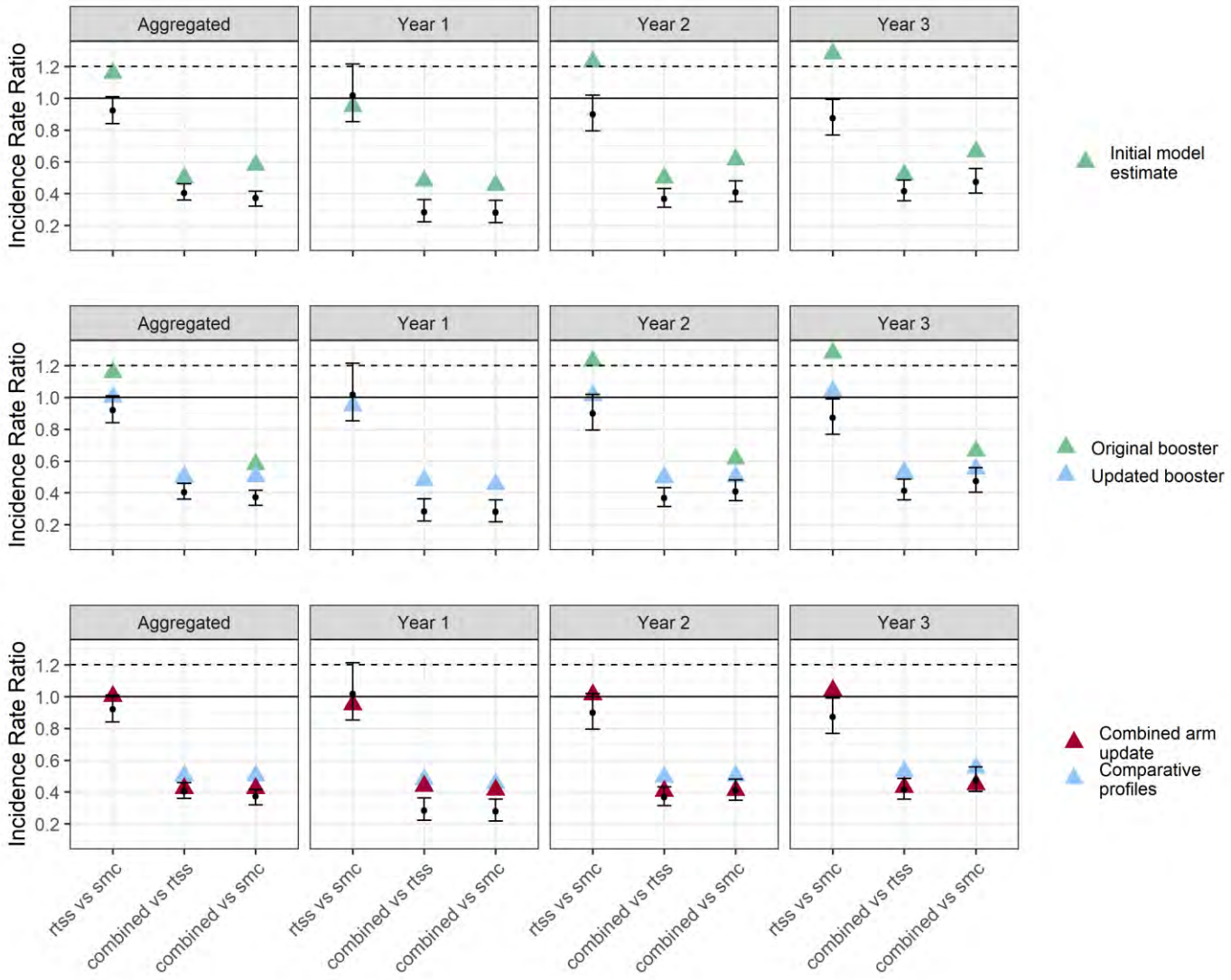

Figure A1 Model validation results. The datapoints in black are the trial reported pairwise Hazard Ratios for the intervention comparisons (Intention-to-treat) listed on the x-axis and the coloured triangles the model predictions. Dashed horizontal line represents the trial specified non-inferiority margin at 1.2 for RTS,S compared to SMC alone and the solid line the equivalence limit at IRR = 1. Colours represent the validation steps and the intervention efficacy model changes implemented in Annex results and Figure A2. Initial model estimate refers to the baseline intervention efficacy models of RTS,S and SMC from previous fittings. Original booster represents the RTS,S fourth dose efficacy profile fitted from the Phase III trial data. Updated booster represents increasing the efficacy of the fourth and fifth dose to the same level as after the primary series. Combined arm update represents an increase in the modelled RTS,S and SMC efficacy above that of each intervention when they are considered alone.

Preliminary model validation revealed several inconsistencies between the trial and model results. Figure A1 row 1 compares model estimated Incidence Rate Ratios (IRRs) aggregated over both countries at four different time points to those reported in the trial. While the model estimated IRR between SV and SMC fell within the 95% Confidence Interval of the trial results for Year 1, the model underestimated the remaining IRRs across all comparison arms and time points. We explored several variations to model parameterisation to investigate these differences.

Firstly, the RTS,S efficacy profile implemented in these simulations assumes that efficacy following the fourth dose does not reach the same levels as after the primary series [1] (Figure A2). However yearly trial results suggest that efficacy of additional doses is comparable with that of the primary series (Figure A1). This increased efficacy could potentially result from the reduction in time between doses from 18 to 12 months having an impact on immune responses or reduced parasite exposure between doses over the dry season. Therefore, a modified fourth and fifth dose efficacy model was considered in which fourth and fifth dose efficacy reaches the same level as after the primary series (Figure A2). The results from this updated efficacy profile fell within or on the edge of the 95% CI of the IRR between SV and SMC across all time points (Figure A1 row 2).

However, the model still underestimated the impact of the combined intervention arms when compared to each single intervention alone (Figure A1 row 2). This could be a result of synergies that occur when interventions are combined that are not currently captured in the model. For example, such synergies could potentially result from the vaccine induced reduction in the liver-to-blood inoculum of parasites resulting in more efficient clearance of parasites by SP+AQ. To test this, a third comparison was conducted where we employ the efficacy models shown in red in Figure A2 for the combined arm only. With these changes the model results for the combined arm comparisons were more closely aligned to the trial results falling within the 95% CI for the majority of time-points (Figure A1 row 3).

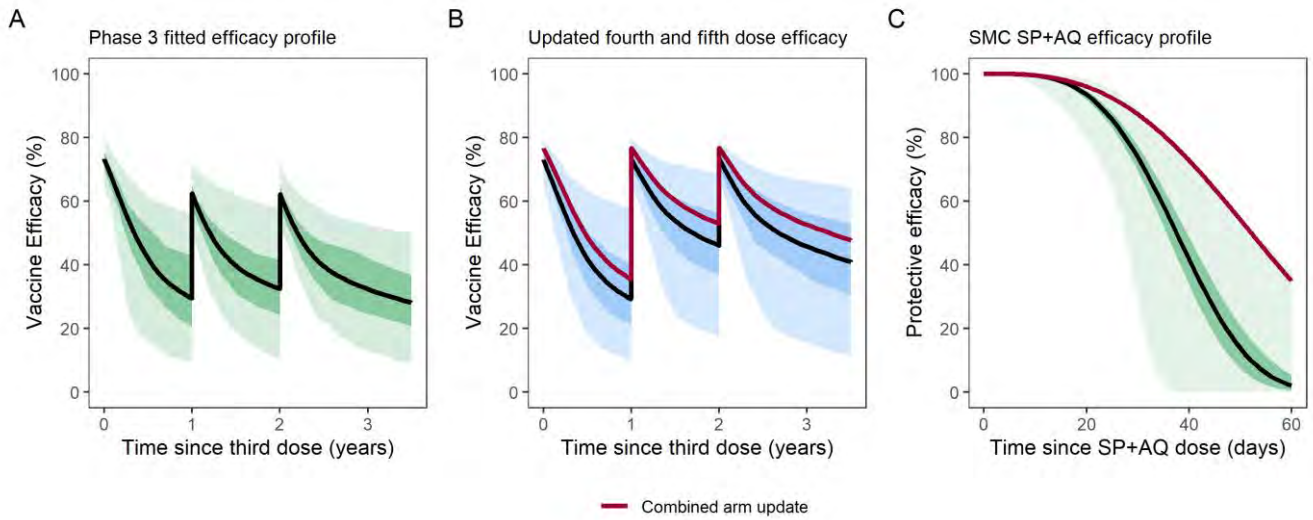

Figure A2 Intervention efficacy models. A) Efficacy profile for the seasonal vaccination schedule based on the parameters from fitting to Phase III trial data. **B)** Updated Efficacy profile for the seasonal vaccination schedule whereby the efficacy following the fourth and fifth doses returns to the same level as following the primary series but wanes at the rate described by the Phase III fitted model of the fourth dose. **C)** SP+AQ efficacy profile. The red line corresponds to the efficacy profiles selected for the combined arm synergy updates. Models were selected through sampling over the parameters draws that describe the uncertainty in our efficacy profile and selecting the parameters that brought validation results closest to those reported in the trial. Black lines in all three plots correspond to the median parameters that describe efficacy with the shaded areas the 50% and 90% Credible Intervals.

The trial finding of SV non-inferiority to SMC depends not only on the performance of the vaccine under seasonal conditions but also the performance of SMC. SMC programmes with four monthly cycles have been shown to be too short for the seasonality patterns in trial locations and five-monthly cycles are now the standard of care in Hounde, Burkina Faso. If five cycles of SMC had been delivered the modelling suggests that the results comparing RTS,S alone to SMC alone would have been less favourable for RTS,S, and more favourable for SMC (Figure A3).

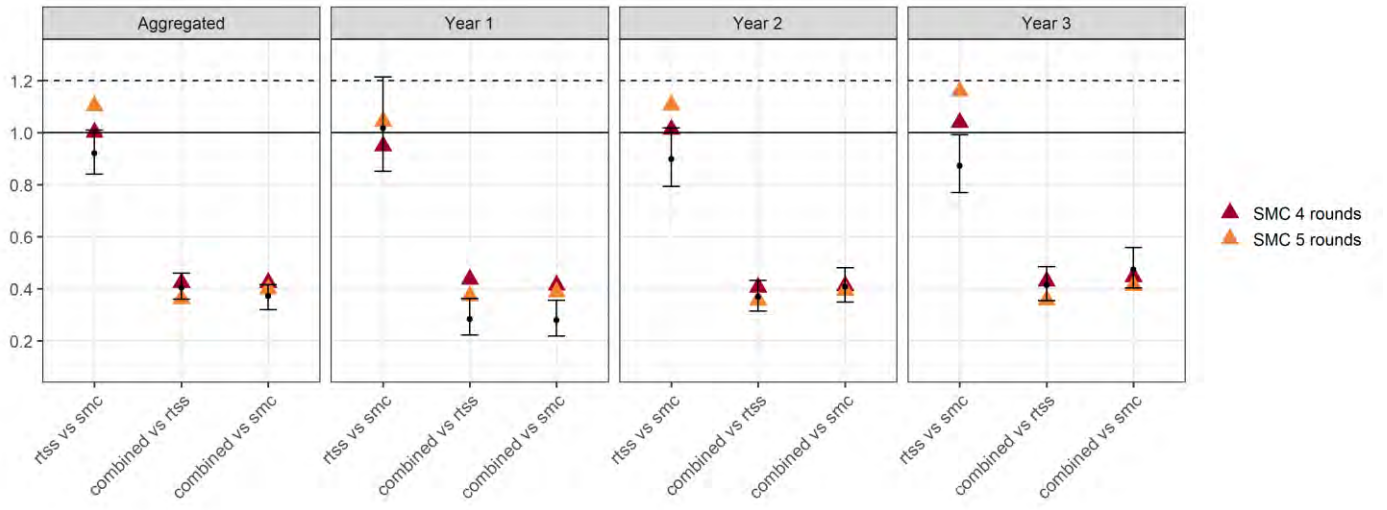

Figure A3 Sensitivity analysis of trial comparisons when a fifth round of SMC is included. The datapoints in black are the trial reported pairwise Hazard ratios for the intervention comparisons (Intention-to-treat) listed on the x-axis and the coloured triangles the model predictions. The dashed horizontal line represents the trial specified non-inferiority margin at 1.2 for RTS,S compared to SMC alone and the solid line the equivalence limit at IRR = 1.

1.2 Caveats for interpretation of the trial results, and extension of SV-SMC trial results to programme settings

A potential difference between SMC and seasonal vaccination in a programmatic context, but which is not captured by the seasonal malaria vaccination Phase 3b clinical trial, is the incidence prior to the first vaccination contact as a result of the age of eligibility for RTS,S vaccination. Children aged ≥5 and <17 months at enrolment in April 2017 were <5 months of age in April 2016, and thus would not have been eligible for vaccination prior to the 2016 rainy season. However, children in the SMC groups would have been eligible for SMC once at least 3 months of age (Figure A4).

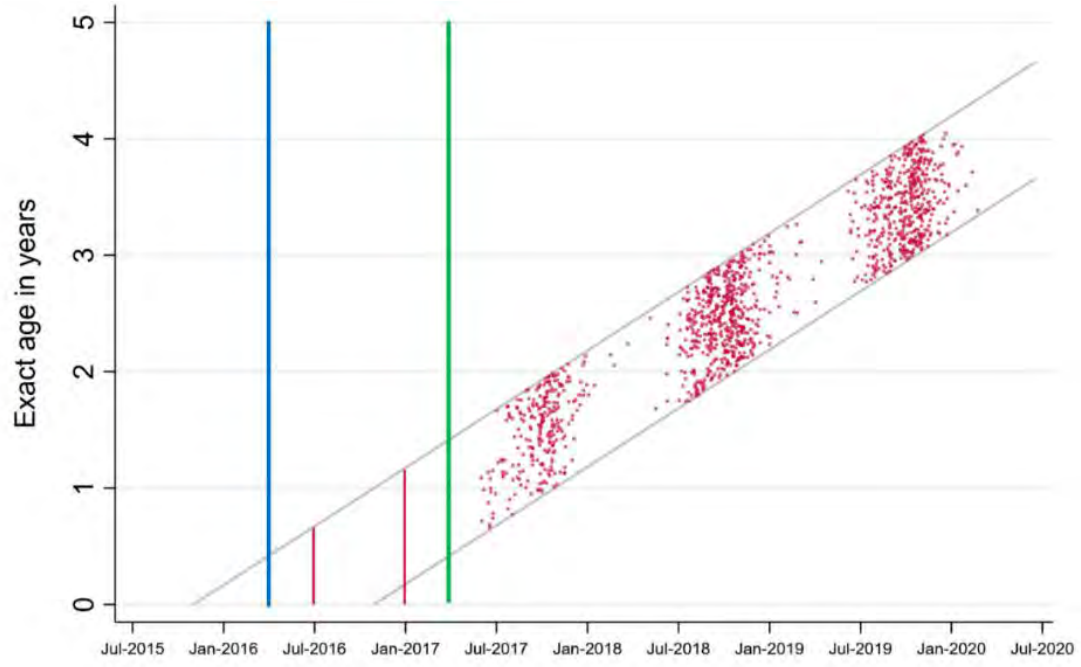

Figure A4 Timing of episodes of clinical malaria in the RTS,S alone group from the seasonal malaria vaccination Phase 3b clinical trial. Clinical malaria defined temperature ≥ 37.5°C, or a history of fever within the past 48 hours, and P. falciparum parasitemia ≥ 5,000/mm3. The green line shows the start date of vaccination for children aged between 5-17 months (April 2017). Grey lines the maximum and minimum ages of these children over time. The blue line indicates April 2016 the year before vaccination commenced. Red vertical lines show the approximate timing of the 2016 transmission season. Given the high incidence among vaccinated children in 2017, 2018 and 2019, there would likely have been a high incidence of malaria in 2016 among unvaccinated children, particularly during the peak transmission period which was not captured in this trial.

Annex 2 – Impact estimates

The model parameterisation and description is consistent with that in the accompanying perennial report: "An update to transmission modelling predictions of the RTS,S/AS01 malaria vaccine's public health impact and cost-effectiveness to include preliminary evidence on the cost of delivery from the Malaria Vaccine Implementation Programme".

Table A1 Parameterisation and set-up of the malaria transmission model.

Transmission intensity	Baseline $PfPR_{2\text{-}10}$ 3%, 5%, 10%, 15%, 20%, 25%, 35%, 45%, 55%, 65%
Seasonality	"Highly Seasonal" archetype based on seasonality patterns in Fatik, Senegal and "Seasonal" archetype based on seasonality patterns in Upper East, Ghana.
Demographics	Constant population size and demography based on the life table for Butajira, Ethiopia, with an average life expectancy at birth of 46.6 years.
Case management	Effective coverage for clinical malaria 45%.
Vaccine scenarios	2 main vaccination scenarios are considered, routine age-based immunisation with RTS,S through the EPI, with primary doses given at 6, 7.5 and 9 months of age with a fourth dose at 27 months of age. Seasonal RTS,S vaccination (SV) primary doses are delivered to all children aged between 5-17 months old in the three months preceding the transmission season with a fourth dose delivered 12 months after the third dose and a fifth dose 24 months after the third dose. A 4-dose SV and 5-dose SV are considered.
Vaccine efficacy and waning	Model estimates of RTS,S efficacy are based on fitting to Phase III trial data [1]. All vaccination scenarios are run assuming this fitted profile. In addition, given the results of the model validation several additional changes to the RTS,S efficacy profile are considered for seasonal vaccination to represent uncertainty in the potential vaccine efficacy under this schedule: 1. Improved fourth and fifth dose efficacy to replicate the trial results 2. Improved fourth and fifth dose efficacy and improved efficacy of RTS,S when combined with SMC to replicated potential synergies in the trial results.
Vaccine coverage	80% coverage of the first three doses is assumed with a 20% drop off in coverage of the fourth and fifth doses. Total vaccine coverage of 64% presented in the main results. Sensitivity analysis in the range 40–72%.
Other interventions	Predictions assume that ITN, IRS and access to treatment remain at static levels following vaccine introduction in all scenarios. Seasonal Malaria Chemoprevention with SP+AQ is explicitly modelled when assessing the impact of vaccination and SMC combined. This was modelled as 4 monthly cycles of SMC delivered to children aged 3months-5years old during the peak in transmission season. With a coverage of 75% [2]. For vaccination comparisons alone we assume no SMC delivery in these settings.
Time horizon	15 years

Outcomes and outcome measures

The outputs considered in this analysis were clinical malaria cases and deaths from malaria. Events or events averted are presented per 100,000 population or per 100,000 fully vaccinated children. Fully vaccinated children are defined as those receiving the initial primary series. Events averted are presented as the cumulative number of events averted over a 15-year period following the

introduction of vaccine dose 3. Unless otherwise stated events averted are calculated relative to a baseline no-vaccination scenario. We report health outcomes for the entire population and disaggregated by 1-year age groupings. Outcome measures are presented as the median values of the model outputs.

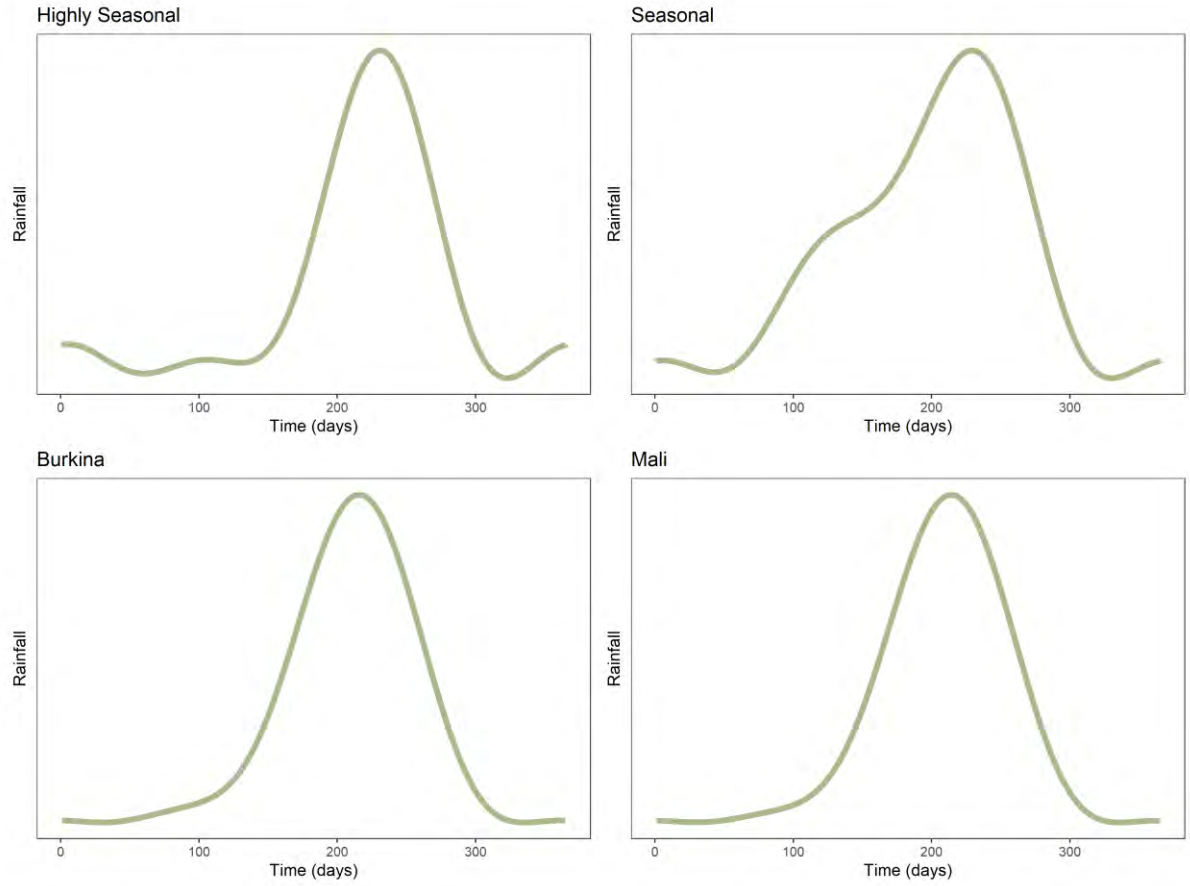

Figure A5 Rainfall seasonality profiles considered in this modelling analysis. The top panel depicts the annual average rainfall of the generalised seasonality archetypes chosen for the analysis in Part 2. The Highly seasonal profile is based on rainfall patterns across Fatick, Senegal and the Seasonal profile across Upper East, Ghana. The bottom panel compares these archetypes to the rainfall time-series used for the two trial locations considered for the analysis in Part 1 Haut-Bassins, Burkina Faso and Sikasso, Mali.

2.1 Simplified modelling of potential vaccination strategies in seasonal settings

The primary modelling analysis looked at two potential vaccination strategies: EPI (age-based primary series and age-based fourth dose) and SV (seasonally targeted primary series and seasonal fourth and fifth doses). However, a hybrid vaccination strategy (age-based primary series and seasonal fourth and fifth doses)may have the advantage over seasonal vaccination of i) preserving a young age at first vaccination, and thus ii) avoiding the situation where children have substantial exposure to malaria before their first dose of vaccine. A hybrid strategy may also have the advantages over EPI of i) maximising the efficacy of the fourth and fifth doses (by timing them according to the time of peak risk) and ii) providing scope to give additional doses (which may be easier to do through annual mass campaigns than through the EPI). The safety and efficacy of up to seven RTS,S doses (3-dose primary series, plus four additional annual doses) will be available from the Seasonal malaria vaccination Phase 3b clinical trial in mid-2022.

Table A2 Key features of EPI, Seasonal and Hybrid vaccination strategies

Vaccine Strategy	Potential Advantage(s)	Potential Disadvantage(s)
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.	• Calendar time of first vaccination varies. In seasonal settings, vaccination may occur several months before period of peak risk, vaccine efficacy may wane in the meantime. • In some areas, EPI coverage is very low. • No obvious EPI contact for doses beyond dose 4.
Seasonal vaccination: 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.	• Age at first vaccination varies from 5-17 months. • Some children will be exposed to the peak malaria transmission season prior to their first vaccination. • Effectiveness / cost-effectiveness of additional doses needs further evaluation.
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.	• Calendar time of first vaccination varies, so vaccine efficacy may wane before exposure. • In some areas, EPI coverage is very low. • Effectiveness / cost-effectiveness of additional doses needs further evaluation • A decision will be needed about the minimum spacing between 3rd and 4th dose.

To investigate the importance of the potential differences between these approaches, a simple model of the effectiveness of different vaccine schedules over the first five years of life was set up. The intention of these models was not to make quantitative predictions of impact, but rather to understand the advantages and disadvantages of the three different potential vaccination approaches in a simple framework.

Figure A6 below shows a schematic representation of vaccination schedules for children born since the initiation of different vaccine programmes. Small black squares show the months at risk for a birth cohort of children born between months 1 and 12, over calendar time, as children age. Yellow, orange and red shading of these boxes indicates the timing of the first, second and third priming dose of RTS,S, respectively. Blue shading indicates the timing of the fourth dose. The months of peak malaria risk (which would dictate the scheduling of seasonal vaccination, and SMC) are shown with dashed red lines.

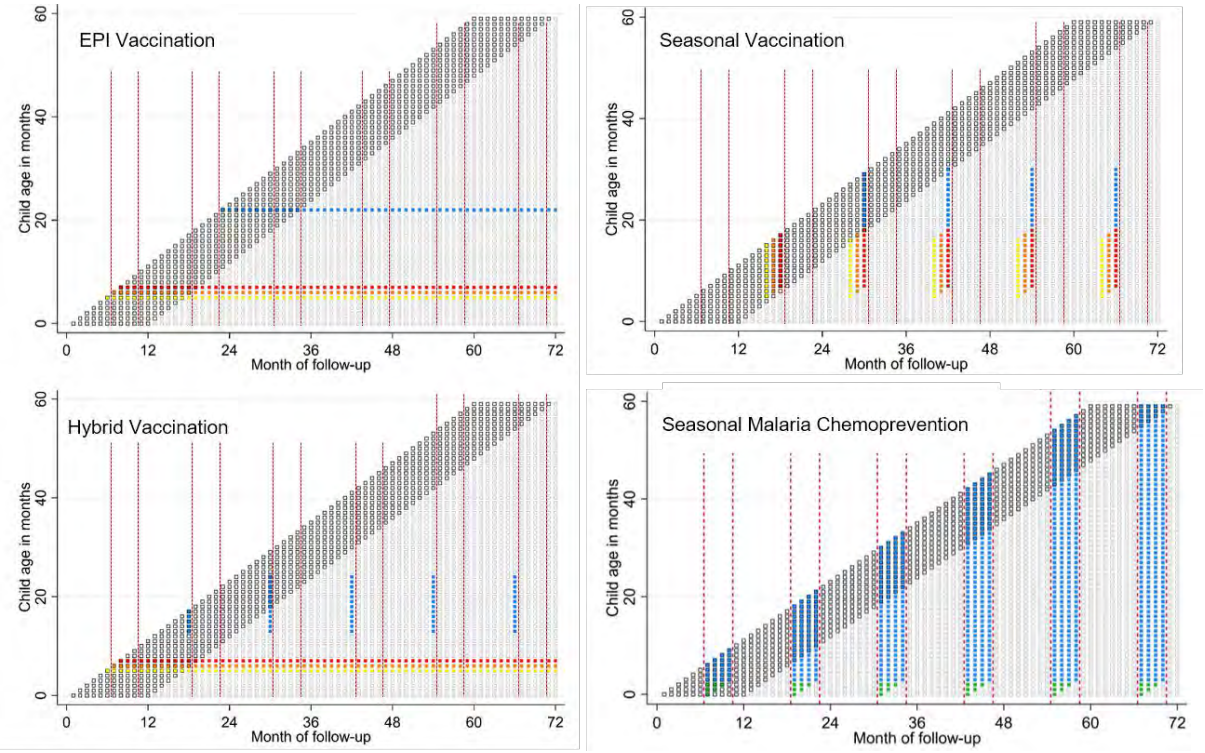

Figure A6 Schematic showing timing of vaccine doses and SMC by calendar time, and child age, under different strategies. The cohort of children born in the first year after implementation of the different strategies is shown in bold. Yellow, orange and red shading of these boxes indicates the timing of the first, second and third priming dose of RTS,S, respectively. Blue shading indicates the timing of the fourth dose or SMC delivery. Green cells indicate children who would be aged <3 months at the beginning of the transmission season, but who would become old enough to receive SMC later in the SMC period. The months of peak malaria risk (which would dictate the scheduling of seasonal vaccination, and SMC) are shown with dashed red lines.

Vaccination schedules shown are:

- EPI, with age-based timing as in Malawi, with the primary series given at 5, 6 and 7 months of age, and fourth dose at 22 months.
- Seasonal vaccination, with the first dose of the 3-dose primary series given to children at least 5 months of age, 3 months prior to the transmission peak, with the fourth dose given 1 month before the transmission peak, in the subsequent year.
- Hybrid vaccination, with the primary series given at 5, 6 and 7 months of age, and seasonal doses given 1 month before the transmission peak. For illustration here, it is assumed that the minimum time between dose 3 and dose 4 would be at least 6 months, but this condition could be varied and will need further research to determine optimal timing.

An example SMC schedule, targeting the peak 4 months is also shown. Blue cells indicate the months in which SMC would be administered.

Incidence was estimated for each month of age from 0-59 months, for children in the birth cohort born between January and December of the first year of implementation. The incidence can be varied by calendar month, to capture the impact of different seasonality patterns on the performance of the different intervention schedules. The efficacy of RTS,S was assumed to decay as a simple step function, as reported in the WHO position paper based on the Phase III data [3]. The efficacy of SMC was assumed to be 80% in the month of administration, and 0 otherwise.

Figure A7 shows the range of seasonality patterns included in the schedule models, based on routine HMIS data from different sub-prefectures of Guinea in 2018. Data on confirmed cases of malaria in individuals above the age of five years were used, to avoid any influence of SMC (which is deployed in some sub-prefectures of Guinea) on the seasonality patterns.

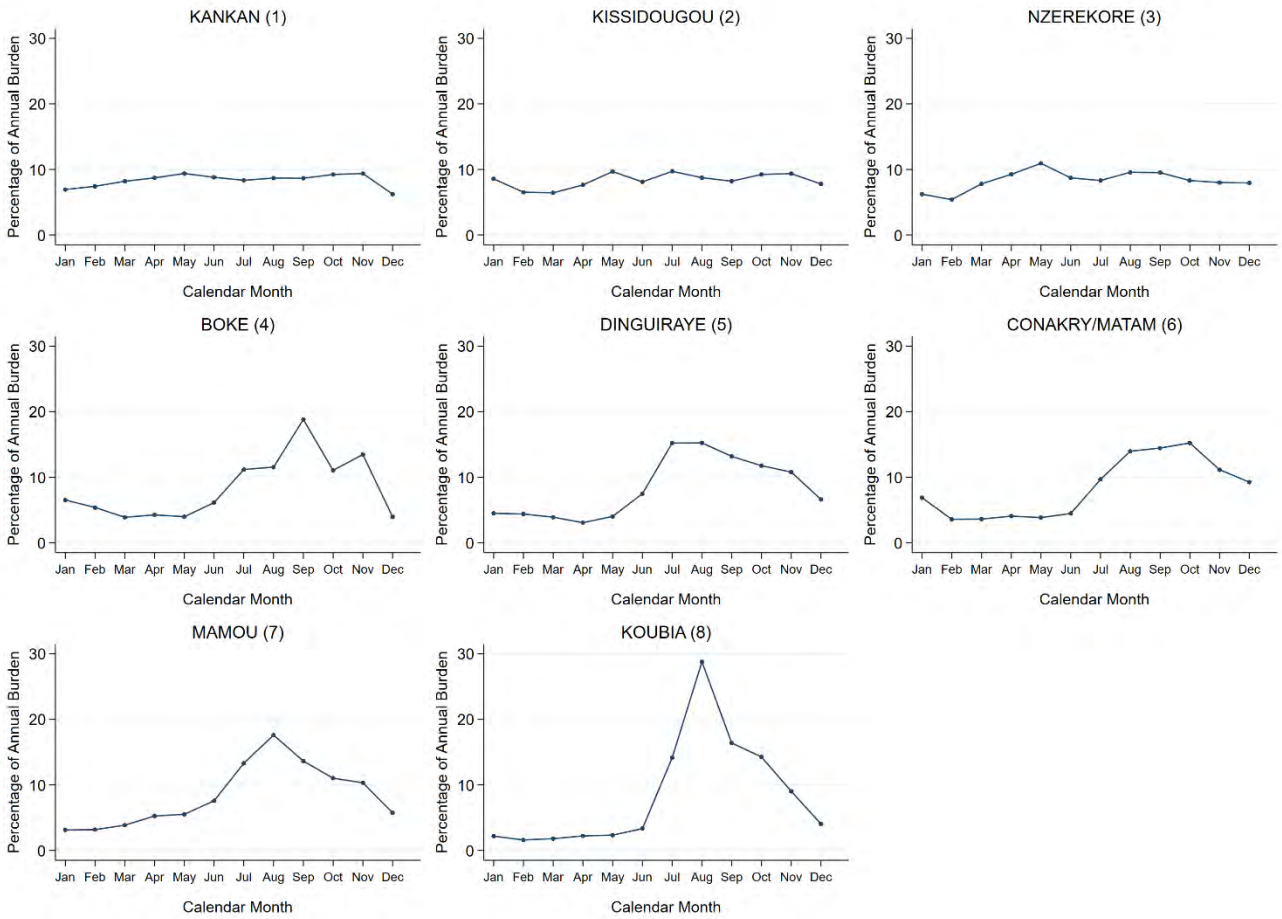

Figure A7 Seasonality patterns used in the schedule modelling, based on data collected by the Guinea PNLP. Percentage of the annual burden in 2018 is shown, by calendar month.

Figure A8 shows the cumulative incidence by month for the cohort of children born between month 1 and month 12 after different vaccination programmes are introduced. Scenario 6 (Conakry/Matam) is used for illustration. The top three panels show results for vaccination strategies without SMC, and the bottom three panels for vaccination strategies in combination with SMC. The cumulative incidence in scenarios with no intervention and with SMC alone are shown in all panels, for reference.

When single intervention strategies were considered, with a maximum of four doses of vaccine, the cumulative incidence was lowest in the SMC alone (reflecting the sustained high efficacy of SMC up to five years of age). The difference in cumulative incidence between the three vaccination strategies at five years of age was not large, but slightly favoured SV. The advantage of Seasonal Vaccination increases in more seasonal scenarios and decreases in less seasonal scenarios (results not shown).

However, an important point is the relative performance of Seasonal Vaccination compared to EPI or Hybrid vaccination in the first 24 months (Figure A8B). Due to the delay in first vaccination for SV (explained in more detail in Figure A9), there is no benefit of SV until month 19: the SV alone line (blue dash) is the same as the no intervention line (solid grey) until this point. Conversely, the benefit of EPI vaccination and Hybrid vaccination is apparent from month 9 onwards, as children who have received vaccines at the age of 5, 6 and 7 months begin to benefit from vaccine protection. The potential for EPI or Hybrid strategies to have superior efficacy at young ages, due to younger age at first vaccination, could translate into differences in severe malaria cases and deaths and should be considered carefully as a potential advantage of these strategies over SV strategies.

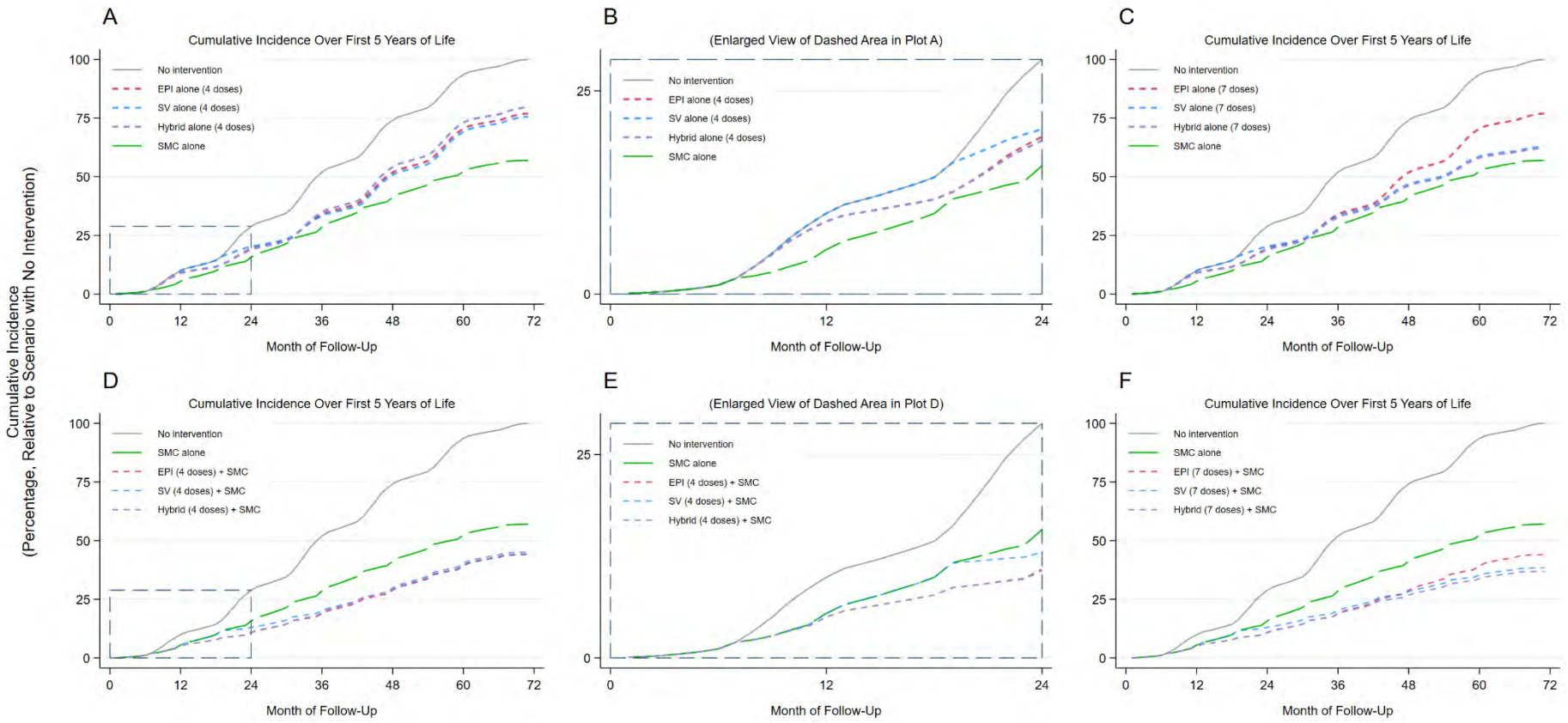

Figure A8 Cumulative incidence over the first five years of life under different vaccination schedules. Top Panels show cumulative incidence for single intervention strategies, expressed as a percentage of the cumulative incidence at 5 years in a scenario with no intervention. Panel A shows cumulative incidence up to 60 months for the birth cohort between month 1 and 12, for scenarios with no intervention, SMC alone, and vaccination strategies with up to 4 doses of RTS,S. Panel B shows an enlarged version of the hatched area in Panel A. Panel C shows the same as Panel A, but allowing up to 7 doses of RTS,S in vaccination strategies. Panel D shows cumulative incidence for no intervention, SMC alone, and vaccination strategies with up to 4 doses of RTS,S in combination with SMC. Panel E shows an enlarged version of the hatched area in panel D. Panel F shows the same as Panel D, i.e. vaccination in combination with SMC, but with up to 7 doses of RTS,S.

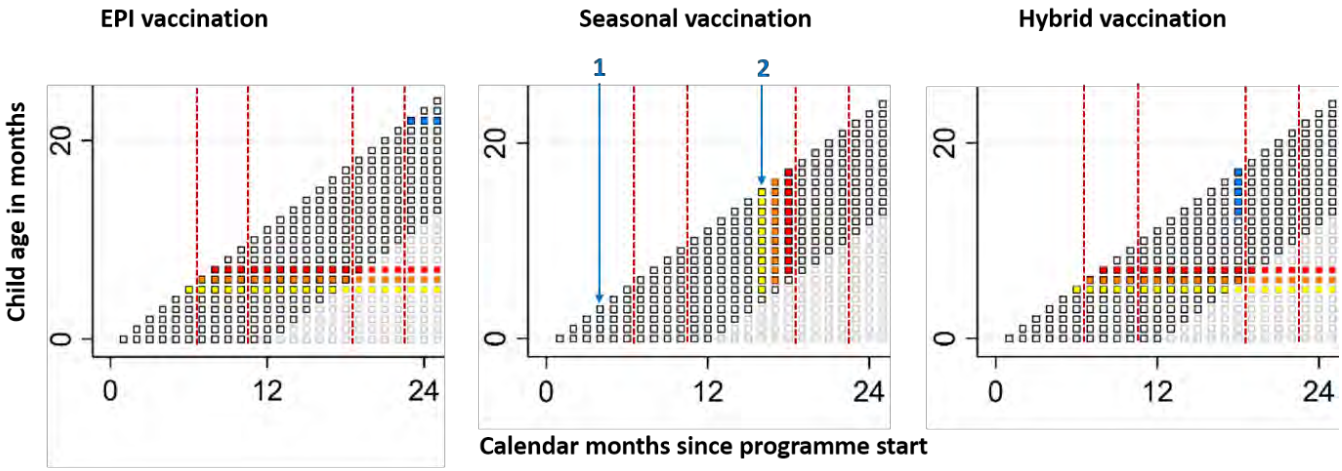

Figure A9 Dosing patterns in the first 24 months, among the birth cohort and differences between SV and EPI/Hybrid vaccination. The EPI and Hybrid strategies use EPI vaccination contacts for the primary series, so ensures the first dose of vaccine is given at five months of age (with the schedule used in the MVIP study in Malawi) or at 6 months of age (using the schedule used in Ghana and Kenya, not shown here). With SV, in month 4 (blue arrow, marked 1), when the three-monthly doses of the primary series would begin prior to the first rainy season, no children born since the programme began would have reached the age of five months, so no children from the birth cohort would be eligible for vaccination at that time. At the corresponding time the following year, month 16, (blue arrow, marked 2), most children from the birth cohort would have reached the age of 5 months and be eligible for vaccination. Children from the birth cohort born in December (month 12) would have reached only 4 months of age by the time of the pre-season vaccination (in month 16), so would not be eligible for first vaccination until the subsequent season (this would occur in month 28, not shown here).

Disaggregating impacts by age in the population model of EPI and SV to investigate this further we observed some disparities between EPI and SV. EPI had a greater impact in terms of reducing clinical cases and deaths in the first two years of life (children aged <24 months) compared to SV where impact was greater and sustained from age 2 onwards (Figure A10). This disparity resulted in a slightly higher number of deaths between approximately 10-20 months of age (reflecting the age range when all children would have received three doses under EPI, but not all children would have received three doses under SV). This is most marked when SV was compared to EPI in seasonal settings. In highly seasonal settings, the disadvantage of SV (due to higher age at vaccination) was offset somewhat by the higher effectiveness of SV (due to the shorter transmission season) (Figure A11).

We predict a shift in cases to older ages due to reduced malaria exposure leading to delays in the development of natural immunity (Figure A10, Figure A12). This effect is delayed with the introduction of a fifth dose in the SV schedule and is of similar magnitude across all vaccination scenarios and seasonality profiles. Despite this the overall cumulative impact of all schedules and intervention models remains positive over this 15-year horizon in all settings.

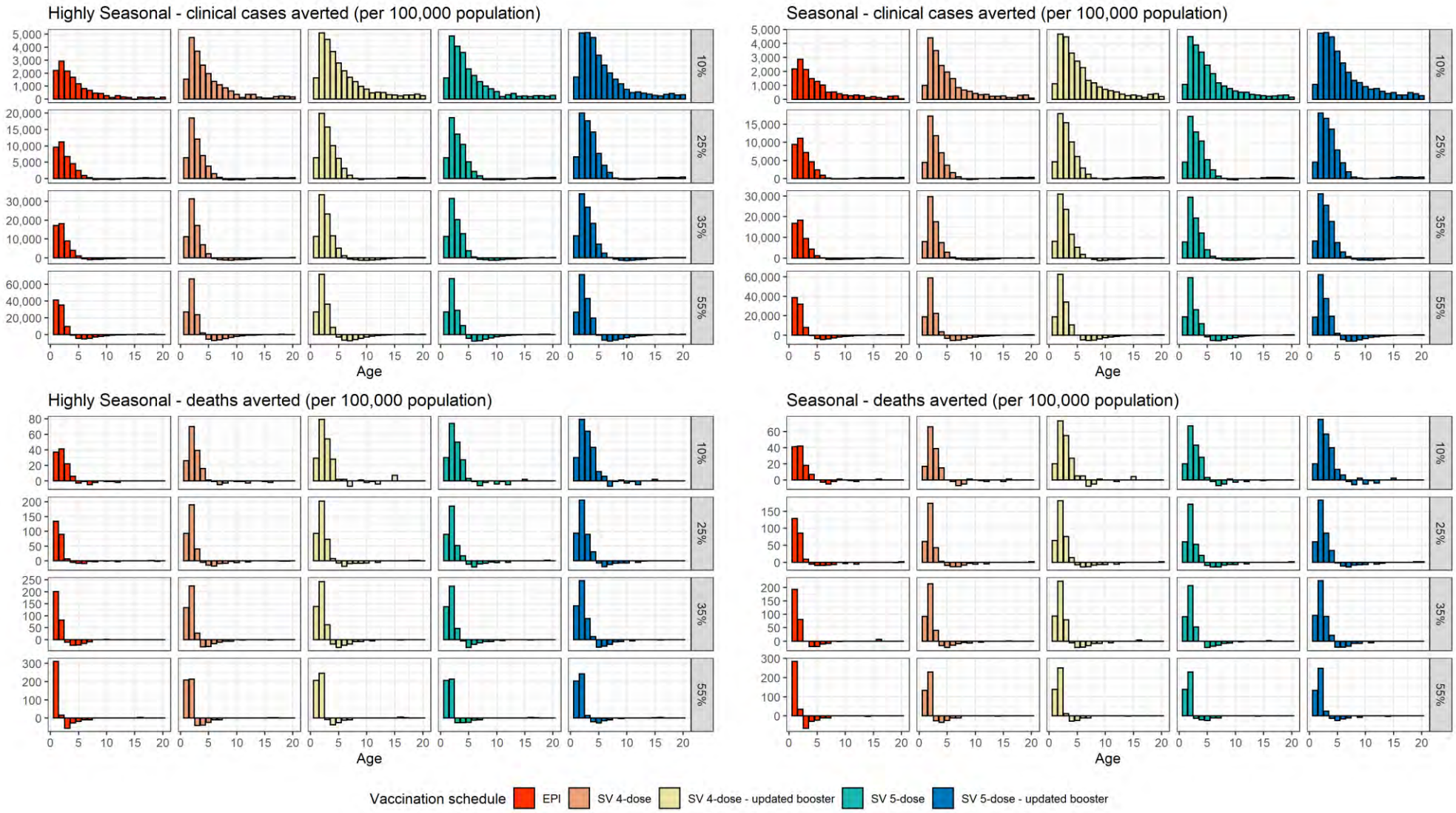

Figure A10 Cumulative number of clinical cases (top row) and deaths (bottom row) averted over 15 years for individuals up to 20 years old in 1-year age bands.The total cases averted are shown per 100,000 population for both seasonality settings. Results are presented for 4 transmission intensity levels.

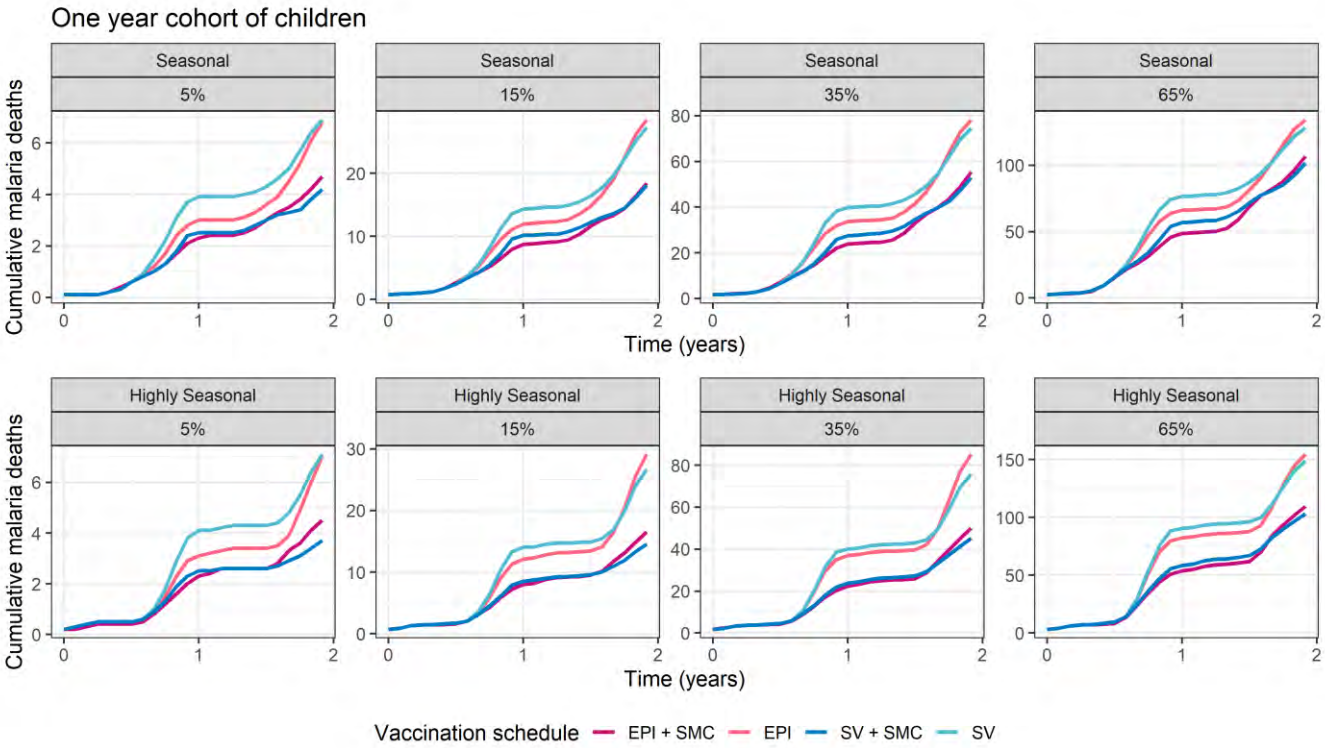

Figure A11 Deaths averted in a single one-year cohort of children. Columns represent four of of representative baseline $PfPR_{2\text{-}10}$ levels. All SV scenarios are represented by the blue line as impact is consistent following the primary series. Results are presented for a Seasonal setting (top row) and a Highly Seasonal setting (bottom row).

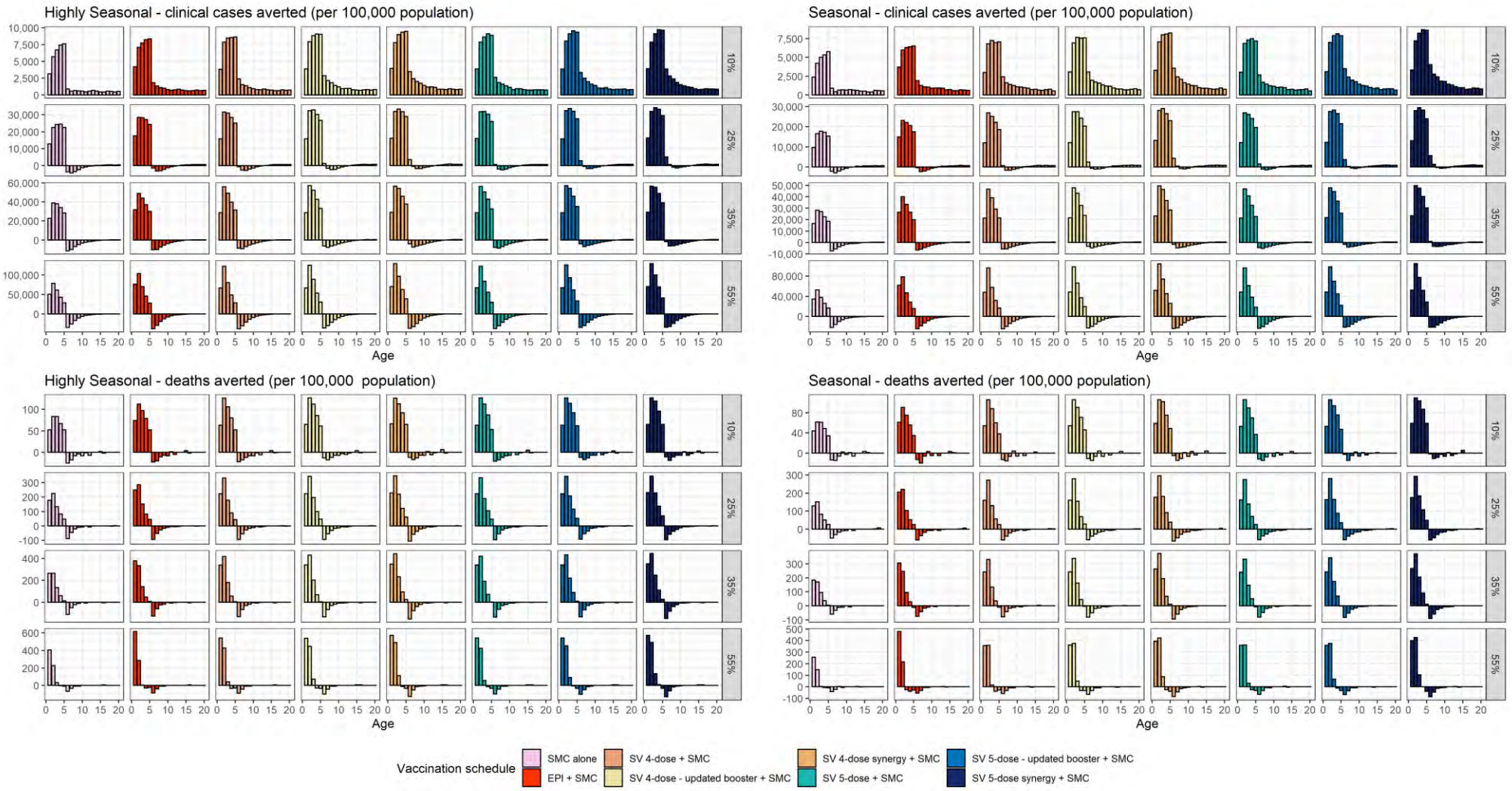

Figure A12 Cumulative number of clinical cases (top row) and deaths (bottom row) averted over 15 years for individuals up to 20 years old in 1-year age bands.The total cases averted are shown per 100,000 population for both seasonality settings. Results are presented for 4 transmission intensity levels.

Sensitivity analysis to vaccine coverage

Outputs per 100,000 fully vaccinated children remain consistent across the range of coverages (50%–90%) (Figure A13) as vaccine impact scales approximately linearly with vaccine coverage (Figure A13).

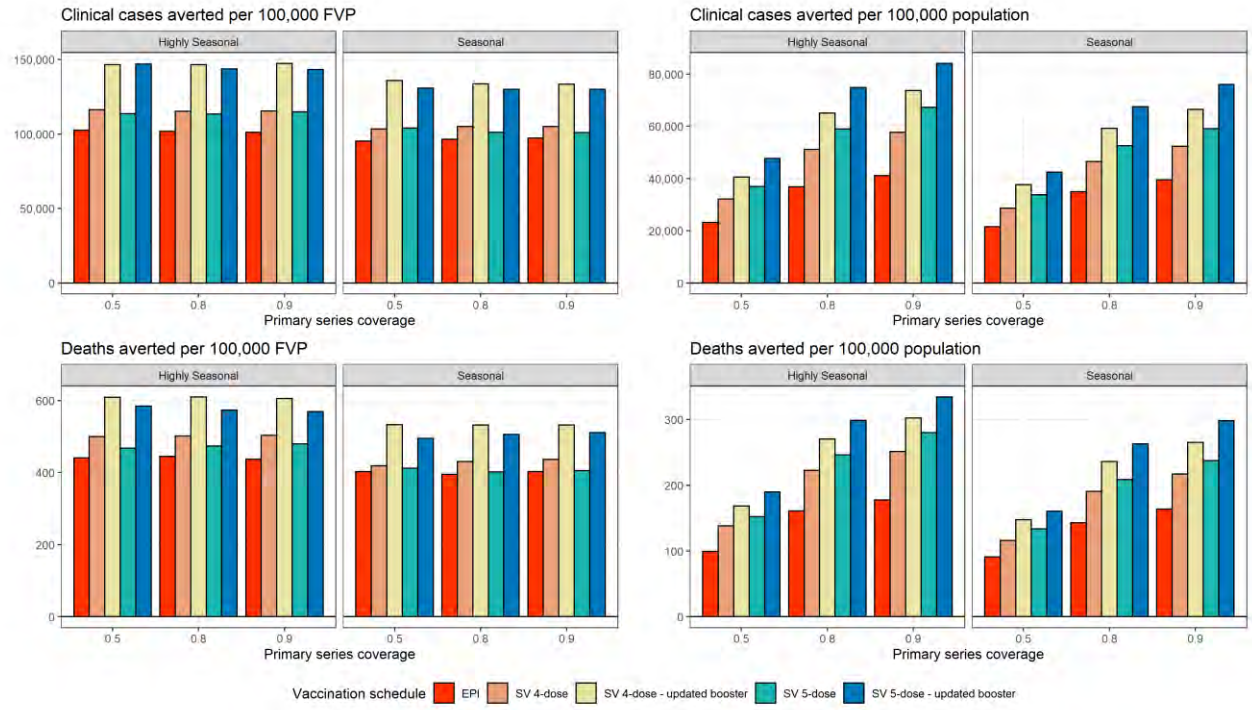

Figure A13 Impact of primary dose vaccine coverage on health outcomes. Outcomes are cumulative over 15 years and averaged over all baseline $PfPR_{2\text{-}10}$ (3%-65%). Coverage of the additional fourth and fifth doses was set to 80% of the primary series.

Annex 3 – Cost effectiveness

When considering vaccine introduction alone in seasonal settings, estimates of the incremental cost per clinical case or DALY averted were made in comparison to baseline no vaccination scenarios with standard levels of access to treatment and existing vector control. The vaccine alone scenario assumes no access to SMC. When considered in combination with SMC, cost-effectiveness estimates were made in comparison to baseline SMC delivery at 75% coverage and standard levels of access to treatment and existing vector control, so results are incremental to SMC. SMC cost estimates were informed by Gilmartin et al [4](Table A3). Data used for the cost-effectiveness analysis are presented in the tables below. Costs were aligned with the perennial estimates report ("An update to transmission modelling predictions of the RTS,S/AS01 malaria vaccine's public health impact and cost-effectiveness to include preliminary evidence on the cost of delivery from the Malaria Vaccine Implementation Programme").

Table A3 Costing data considered in this analysis. All data presented US$.

Cost per vaccine dose	Cost per vaccination including vaccine cost*	Cost of delivery per dose (economic, recurring)±			Total cost per dose		
		Mean	Min	Max	Mean	Min	Max
$2	$2.69	$1.62	$0.96	$2.67	$4.31	$3.65	$5.36
$5	$6.52	$1.62	$0.96	$2.67	$8.14	$7.48	$9.19
$10	$12.91	$1.62	$0.96	$2.67	$14.53	$13.87	$15.58

* Includes vaccines, injection and reconstitution syringes, safety boxes, freight, insurance and wastage as per Penny et al [5].

± The recurring cost of delivery excludes the initial set-up costs related to RTS,S introduction and delivery and may be more representative of the program costs in the long run. Reflect interim data from three MVIP countries averaged. The mean, min and max delivery cost values represent average, minimum and maximum values, respectively, across the three MVIP countries.

Table A4 Non-vaccine related costs

Intervention	Unit cost	Description
SMC with SP+AQ	$1.07 per child per monthly course [4]	Weighted average recurrent economic cost of administering four monthly SMC cycles during the ACCESS SMC program. Averaged over different delivery approaches, inflated to $US 2021.
Clinical malaria case management	$1.47 [5]	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.
Severe malaria case management	$22.41 [5]	

Figure A14A presents the incremental cost-per-case and cost-per-DALY averted for each vaccination schedule compared with no vaccination and standard levels of access to treatment for an assumed cost per dose of $5 over a range of baseline $PfPR_{2\text{-}10}$. Figure 14A assumes no access to SMC. Figure A14B presents the incremental cost-per-case and cost per-DALY averted for each vaccination schedule in

combination with SMC compared to SMC and standard levels of access to treatment. Figure 15 presents these same estimates for an assumed cost per dose of $2, $5 and $10.

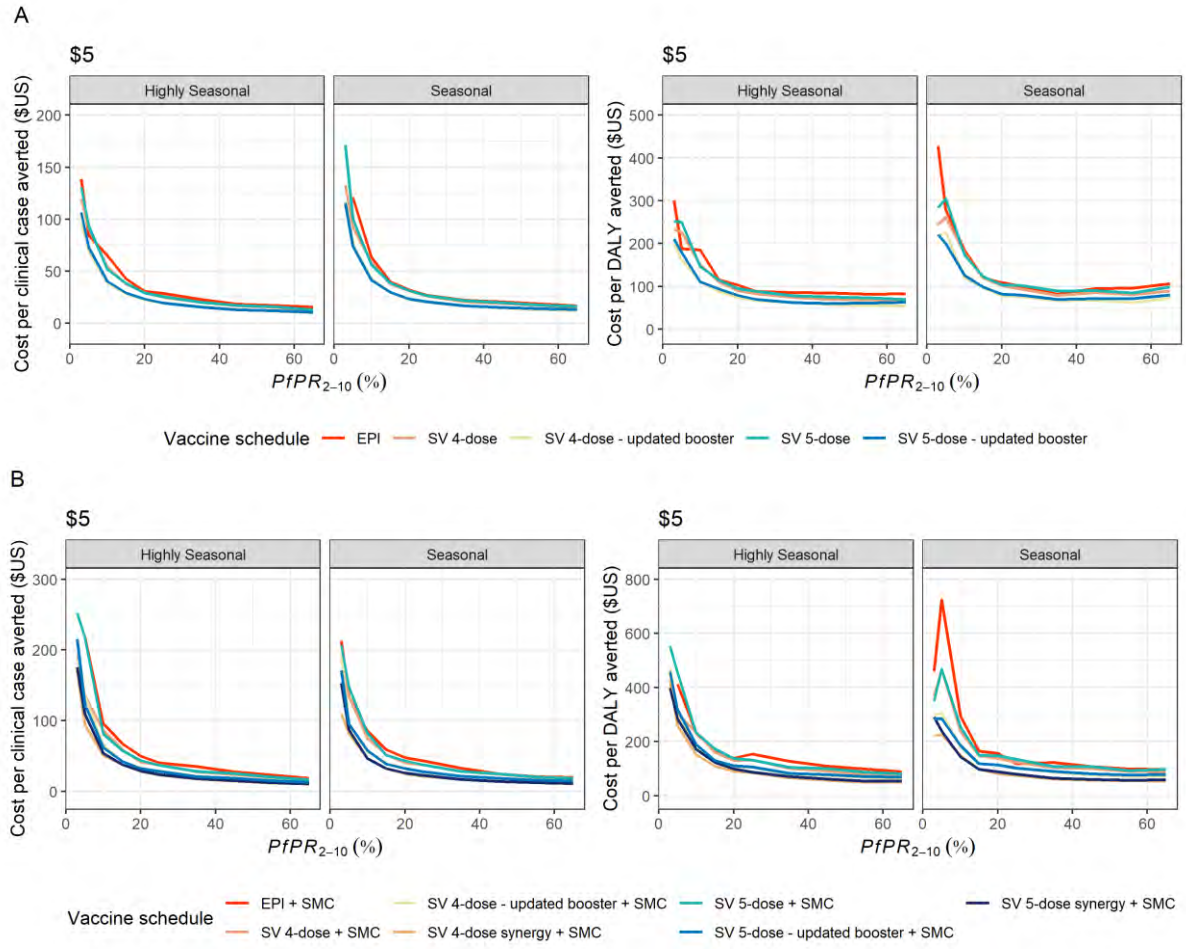

Figure A14 Summary of cost-effectiveness estimates for different RTS,S vaccination schedules A) when delivered alone ICERs relative to no-vaccination and B) when delivered with SMC ICERs relative to SMC. Cost-per-case and cost-per-DALY averted as a function of baseline *PfPR*$_{2-10}$ for a vaccine cost of $5. Lines represent model median estimates assuming a mean delivery cost of $1.62. SMC cost per child per monthly course of $1.01.

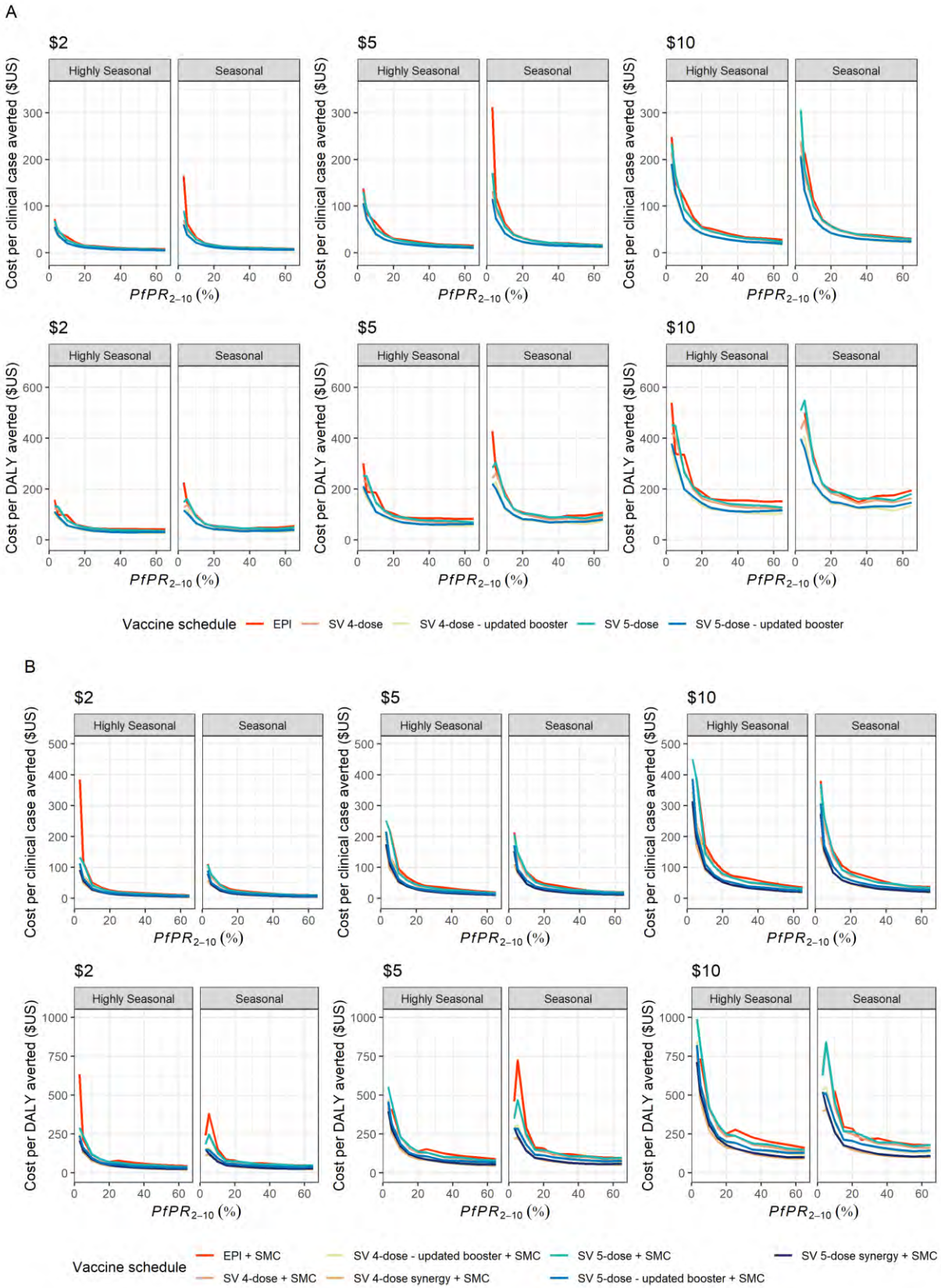

Figure A15 Summary of cost-effectiveness estimates for different RTS,S vaccination schedules A) when delivered alone, ICERs relative to no-vaccination and B) when delivered with SMC (bottom two rows), ICERs relative to SMC. as a function of baseline *PfPR*$_{2\text{-}10}$ for different vaccine costs of $2, $5, and $10. Lines represent model median estimates assuming a mean delivery cost of $1.62. SMC cost per child per monthly course of $1.01

Sensitivity of cost-effectiveness estimates to cost of delivery inputs

Table A5 Comparison of cost-effectiveness estimates across cost-of-delivery ranges for different vaccination schedules without SMC delivery after 15 years in regions with a $PfPR_{2-10}$ between 10-50%. Results are averaged across both seasonality profiles. ICERs are calculated relative to no-vaccination and standard levels of access to treatment and existing vector control.

	Interventions					
	EPI			SV (averaged over all models)		
	Min cost of delivery $0.96	Mean cost of delivery $1.62	Max cost of delivery $2.67	Min cost of delivery $0.96	Mean cost of delivery $1.62	Max cost of delivery $2.67
ICER per DALY averted						
$2 per dose	$48.59	$58.04	$73.06	$39.77	$47.63	$60.14
$5 per dose	$103.39	$112.84	$127.87	$85.39	$93.25	$105.76
$10 per dose	$194.83	$204.28	$219.31	$161.50	$169.36	$181.87
ICER per clinical case averted						
$2	$14.80	$17.66	$22.22	$11.73	$14.04	$17.71
$5	$31.43	$34.29	$38.85	$25.14	$27.44	$31.11
$10	$59.17	$62.03	$66.59	$47.50	$49.80	$53.48

Table A6 Comparison of cost-effectiveness estimates across cost-of-delivery ranges for different vaccination schedules combined with SMC delivery after 15 years in regions with a $PfPR_{2-10}$ between 10-50%. Results are averaged across both seasonality profiles. ICERs are calculated relative to SMC with standard levels of access to treatment and existing vector control.

	Interventions					
	EPI + SMC			SV (averaged over all models) + SMC		
	Min cost of delivery $0.96	Mean cost of delivery $1.62	Max cost of delivery $2.67	Min cost of delivery $0.96	Mean cost of delivery $1.62	Max cost of delivery $2.67
ICER per DALY averted						
$2 per dose	$68.43	$81.58	$102.40	$50.23	$60.09	$75.80
$5 per dose	$144.52	$157.63	$178.50	$107.52	$117.39	$133.10
$10 per dose	$271.48	$284.59	$305.46	$203.11	$212.98	$228.69
ICER per clinical case averted						
$2	$22.06	$26.30	$33.02	$15.14	$18.18	$22.82

$5	$46.58	$50.80	$57.51	$32.34	$35.31	$40.03
$10	$87.45	$91.67	$98.39	$61.05	$64.01	$68.73

Acknowledgements

The authors thank Professor Brian Greenwood and Dr Daniel Chandramohan of the London School of Hygiene and Tropical Medicine, Dr Jean-Bosco Ouedraogo of the Institut de Recherche en Sciences de la Sante, Burkina Faso and Dr Alassane Dicko of The Malaria Research and Training Center, University of Science, Technology and Techniques of Bamako, Mali for sharing the seasonal malaria vaccination Phase 3b clinical trial clinical trial results for the model validation process and for their helpful discussions surrounding this process. We also would like to thank Professor Paul Milligan of the London School for Hygiene and Tropical Medicine, Dr Eugene Kaman Lama, Coordinator of the National Malaria Control Programme in Guinea, Dr Kovana Marcel Loua of the Universite Abdel Gamal Nasser, Conakry, Guinea for providing data on the seasonality patterns of Malaria in Guinea used for the simplified modelling work in Annex 2.1.

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Annex 9: GRADE and Evidence to Recommendation tables on RTS,S/AS01 malaria vaccine

Content:

Annex 9a: GRADE table

Annex 9b: Evidence-to-recommendations table

Annex 9c: Risk of bias assessment (for studies included in the GRADE)

Annex 9a: Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Evidence summary table

Author(s): Villanueva G, Henschke N, Hamel C, Buckley B (Cochrane Response)

Question: Should a minimum of 4 doses of RTS,S/AS01 be provided to reduce malaria disease burden in children >= 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission?

Population: Children ≥ 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission

Intervention: A minimum of 4 doses of RTS,S/AS01 (given as a 3-dose initial series; first dose should be provided between 5 and 17 months of age) with a minimal interval between doses of 4 weeks

Comparison: Malaria interventions currently in place without malaria vaccination

Setting: countries in sub-Saharan Africa with moderate to high malaria transmission

Outcome	№ of studies	Certainty assessment						№ of patients		Effect		Certainty	Comments
		Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RTS,S/AS01	No vaccination	Relative (95% CI)	Absolute (95% CI)		
CLINICAL MALARIA (Efficacy, important outcome)	Clinical malaria episodes (from month 0 to end of study; median follow-up: 48 months) (modified ITT analysis) (assessed with: Illness in a child brought to a study facility with a measured temperature of 37·5°C and P. falciparum asexual = parasitaemia at a density of > 5000 parasites per cubic millimetre or a case of malaria meeting the primary case definition of severe malaria. Severe malaria primary case definition = P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one)												
	1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	not serious	none	R3R: N=2976; 6616 episodes	C3C: N=2974; 9585 episodes	VE: 36.3% (31.8 to 40.5)	-	⊕⊕⊕⊕ HIGH	PP analysis VE: 39% (95% CI 34.3 to 43.3)
	Clinical malaria events (at 3 years) (assessed **with: measured temperature ≥ 37.5 °C, or a history of fever within the past 48 hours, and P. falciparum parasitemia ≥ 5,000/m**m3 in children presenting at a study health facility)												
	1 [2] (Chandramohan)	*RTS,S/AS01 vs SMC alone*											
		randomised trials	not serious	not serious	not serious	not serious	none	Incidence: 278 (264.6 to 292.4)/1000 PYAR; 1540 events over 5535.7 PYAR	Incidence: 305 (290.5 to 319.8)/1000 PYAR; 1661 events over 5449.9 PYAR	HR 0.92 (99% CI 0.82 to 1.04)	-	⊕⊕⊕⊕ HIGH	"The 90, 95, and 99% CI for the HR all excluded the pre-specified non-inferiority margin of 1.20."
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	not serious	none	Incidence: 113 (104.7 to 122.5)/1000 PYA); 624 events over 5508 PYAR	Incidence: 305 (290.5 to 319.8)/1000 PYAR; 1661 events over 5449.9 PYAR	PE: 62.8% (58.4 to 66.8)	-	⊕⊕⊕⊕ HIGH	

SEVERE MALARIA (Efficacy, critical outcome)	Severe malaria episodes (from month 0 to end of study) (modified ITT analysis) (assessed with: P. falciparum asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity and without diagnosis of a coexisting illness. Markers of severe disease were prostration, respiratory distress, a Blantyre coma score of 2 (on a scale of 0 to = 5, with higher scores indicating a higher level of consciousness), two or more observed or reported seizures, hypoglycaemia, acidosis, elevated lactate level, or haemoglobin level of < 5 g per decilitre. Coexisting illnesses were defined as radiographically proven pneumonia, meningitis established by analysis of cerebrospinal fluid, bacteraemia, or gastroenteritis with severe dehydration)											
1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	not serious	none	R3R: N=2976; 116 episodes	C3C: N=2974; 171 episodes	VE: 32.2% (13.7 to 46.9)	-	⊕⊕⊕⊕ HIGH	PP analysis VE 28.5% (6.3 to 45.7)
Hospitalization due to severe malaria												
1 [2] (Chandramohan)	*RTS,S/AS01 vs SMC alone*											
	randomised trials	not serious	not serious	not serious	very serious [b]	none	37 events; 6.7 (4.8 to 9.2) per 1000 PYAR	37 events; 6.8 (4.9 to 9.4) per 1000 PYAR	PE: -0.4% (-65.8 to 25.7)		⊕⊕◯◯ LOW	Most cases of severe malaria were severe malaria anaemia (vaccine: 25/37; SMC: 31/37)
	SMC + RTS,S/AS01 vs SMC alone											
	randomised trials	not serious	not serious	not serious	serious [c]	none	11 events; 2.0 (1.1 to 3.6) per 100 PYAR	37 events; 6.8 (4.9 to 9.4) per 1000 PYAR	PE: 70.5% (41.9 to 85.0)		⊕⊕⊕◯ MODERATE	Most cases of severe malaria were severe malaria anaemia (vaccine + SMC: 10/11; SMC: 31/37)
Severe malaria (from month 0 to 24 months)												
1 [3] (MVPE)	pilot implementation study*	not serious [d]	not serious	not serious	serious [e]	none	-	-	IRR 0.70 (0.54 to 0.92)	-	⊕⊕⊕◯ MODERATE	
SEVERE ANEMIA (Impact, important outcome).	**≥1 episode of incident severe malaria anaemia (from month 0 to end of study)** (modified ITT analysis) (assessed with: a documented haemoglobin < 5·0 g per decilitre identified at clinical presentation to morbidity surveillance system in association with a P. falciparum parasitaemia at a density of > 5000 parasites per cubic millimetre)											
1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	serious [c]	none	R3R: 23/2976 (0.8%)	C3C: 44/2974 (1.5%)	VE 47.8% (11.6 to 69.9)	-	⊕⊕⊕◯ MODERATE	
WHO-defined severe malaria anaemia												
1 [2]	*RTS,S/AS01 vs SMC alone*											

	(Chandramohan)	randomised trials	not serious	not serious	not serious	very serious [b]	none	25 events; 4.52 (3.05 to 6.68) per 1000 PYAR	31 events; 5.69 (4.00 to 8.09) per 1000 PYAR	PE: 18.4% (-39.3 to 52.2)	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	serious [c]	none	10 events; 1.82 (0.977 to 3.37) per 1000 PYAR	31 events; 5.69 (4.00 to 8.09) per 1000 PYAR	PE: 67.9% (34.1 to 84.3)	-	⊕⊕⊕◯ MODERATE	
BLOOD TRANSFUSION (Impact, critical outcome)	Blood transfusion (from month 0 to end of study) (modified ITT analysis)												
	1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	serious [c]	none	R3R: 78/2976 (2.6%)	C3C: 109/2974 (3.7%)	VE 28.5% (3.5 to 47.2)	-	⊕⊕⊕◯ MODERATE	
	Blood transfusion (at 3 years)												
	1 [2] (Chandramohan)	*RTS,S/AS01 vs SMC alone*											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	21 events; 3.79 (2.47 to 5.82) per 1000 PYAR	23 events; 4.22 (2.80 to 6.35) per 1000 PYAR	PE: 8.27% (-67.6 to 49.8)	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	serious [c]	none	8 events; 1.45 (0.726 to 2.90) per 1000 PYAR	23 events; 4.22 (2.80 to 6.35) per 1000 PYAR	PE: 65.4% (22.9 to 84.5)	-	⊕⊕⊕◯ MODERATE	
CEREBRAL MALARIA (safety, critical outcome)	Possible cerebral malaria												
	1 [1] (RTS,S/AS01)	randomised trials	very serious [f]	not serious	not serious [g]	serious [c]	none	R3R: 19/2976 + R3C: 24 /2974	C3C: 10/2974	IRR: 2.15 (95% CI 1.1 to 4.3)	-	⊕◯◯◯ VERY LOW	
	WHO defined cerebral malaria												
	1 [2] (Chandramohan)	*RTS,S/AS01 vs SMC alone*											
		randomised trials	not serious	not serious	not serious	serious [h]	none	4 events; 0.723 (0.271 to 1.93) per 1000 PYAR	0 events	-	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											

		randomised trials	not serious	not serious	not serious	serious [h]	none	1 event; 0.182 (0.026 to 1.29) per 1000 PYAR	0 events			⊕⊕◯◯ LOW	
	Hospital admission with cerebral malaria (month 0 to month 24) (positive for P.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, excluding cases with probable meningitis)**												
	1 [3] (MVPE)	pilot implementation study*	not serious [d]	not serious	not serious	serious [i]	none	-	-	IRR: 0.77 (95% CI 0.44 to 1.35)	-	⊕⊕⊕◯ MODERATE	The 95% confidence intervals for pooled estimates obtained during this evaluation exclude an effect of the magnitude observed in Phase III trial, after allowing for the levels of uptake of the vaccine[†]
HOSPITAL ADMISSION (impact, critical outcome)	All-cause hospital admission (month 0 to study end) (modified ITT analysis)												
	1 [1] (RTS,S/AS01)	randomised trials	not serious [a]	not serious	not serious	not serious	none	R3R: 644/2976 (21.6%)	C3C: 771/2974 (25.9%)	VE 16.5% (7.2 to 24.9)	-	⊕⊕⊕⊕ HIGH	
	All-cause hospital admission (excluding external causes and surgery)												
	1 [2] (Chandramohan)	*RTS,S/AS01 vs SMC alone*											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	73 events; 13.2 (10.5 to 16.6) per 1000 PYAR	60 events; 11.0 (8.55 to 14.2) per 1000 PYAR	PE: -22.3% (-74.4 to 14.3)	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	very serious [b]	none	49 events; 8.90 (6.72 to 11.8) per 1000 PYAR	60 events; 11.0 (8.55 to 14.2) per 1000 PYAR	PE: 18.7% (-19.4 to 44.7)	-	⊕⊕◯◯ LOW	
	All-cause hospital admission (month 0 to month 24) A stay in hospital/inpatient facility for at least one night, (and patients who were admitted but died before an overnight stay was completed)												

	1 [3] (MVPE)	pilot implementation study*	not serious [d]	not serious	not serious	serious [j]	none	-	-	PE 8.0% (-3.0 to 17.0)	-	⊕⊕⊕◯ MODERATE	
	Hospital admission (with a positive malaria test) (month 0 to month 24)												
	1 [3] (MVPE)	pilot implementation study*	not serious [d]	not serious	not serious	not serious	none	-	-	PE: 21% (7.0 to 32)	-	⊕⊕⊕⊕ HIGH	
ALL-CAUSE MORTALITY (impact and safety, critical outcome)	All-cause mortality (month 0 to study end) (modified ITT analysis)												
		All population											
		randomised trials	not serious [a]	not serious	not serious [g]	very serious [b]	none	R3R: 61 (13 malaria)/2976 + R3C: 51 (17 malaria)/2972	C3C: 46 (13 malaria)/2974	-	-	⊕⊕◯◯ LOW	
		Girls only (safety assessment)											
	1 [1] (RTS,S/AS01)	randomised trials	see above	see above	see above	see above	see above	R3R: 35 (9 malaria)/1467 + R3C: 32 (8 malaria)/1500	C3C: 17 (4 malaria)/1503	IRR: 2.0 (95% CI 1.2 to 3.4)	-	see above	Female/male risk ratio (95% CI) 1.50 (1.03 to 2.18)
		Boys only (safety assessment)											
		randomised trials	see above	see above	see above	see above	see above	R3R: 26 (4 malaria)/1509 + R3C: 19 (9 malaria)/1472	C3C: 29 (8 malaria)/1471	IRR: 0.8 (95% CI 0.5 to 1.2)	-	see above	
	All-cause mortality (excluding external causes and surgery)												
		RTS,S/AS01 vs SMC alone											
		All population											
	1 [2] (Chandramohan)	randomised trials	not serious	not serious	not serious	very serious [b]	none	22 events; 3.97 (2.62 to 6.04) per 1000 PYAR	25 events; 4.59 (3.10 to 6.79) per 1000 PYAR	PE: 12.1% (-55.7 to 50.4)	-	⊕⊕◯◯ LOW	
		Girls only (safety assessment)											

	randomised trials	see above	see above	see above	see above	see above	11 events; 4.15 (2.30, 7.49) per 1000 PYAR	9 events; 3.42 (1.78, 6.57) per 1000 PYAR	HR (95% CI) 1.23 (0.51 to 2.96)		see above	Gender Interaction parameter [$] (95% CI) 1.80 (0.56 to 5.79)
	Boys only (safety assessment)											
	randomised trials	see above	see above	see above	see above	see above	11 events; 3.82 (2.11, 6.89) per 1000 PYAR	16 events; 5.68 (3.48, 9.27) per 1000 PYAR	HR (95% CI) 0.68 (0.32 to 1.47)		see above	
	SMC + RTS,S/AS01 vs SMC alone											
	All population											
	randomised trials	not serious	not serious	not serious	serious [c]	none	12 events; 2.18 (1.24 to 3.84) per 1000 PYAR	25 events; 4.59 (3.10 to 6.79) per 1000 PYAR	PE: 52.3% (4.99 to 76.0)	-	⊕⊕⊕◯ MODERATE	
	Girls only (safety assessment)											
	randomised trials	see above	see above	see above	see above	see above	2 events; 0.75 (0.19, 3.01) per 1000 PYAR	9 events; 3.42 (1.78, 6.57) per 1000 PYAR	HR (95% CI) 0.22 (0.05 to 1.02)		see above	Gender Interaction parameter [$] (95% CI) 0.35 (0.06, 1.98)
	Boys only (safety assessment)											
	randomised trials	see above	see above	see above	see above	see above	10 events; 3.51 (1.89, 6.52) per 1000 PYAR	16 events; 5.68 (3.48, 9.27) per 1000 PYAR	HR (95% CI) 0.62 (0.28 to 1.37)		see above	
All-cause mortality (excluding deaths due to injury) (month 0 to month 24)												
1 [3] (MVPE)	*All population*											
	pilot implementation study*	not serious [d]	not serious	not serious	serious [k]	none	-	-	Mortality ratio 0.93 (0.84 to 1.03)	-	⊕⊕⊕◯ MODERATE	
	Girls only (safety assessment)											

		pilot implementation study*	see above	see above	see above	see above	see above	-	-	Mortality ratio 0.98 (0.87 to 1.09)	-	see above	Gender interaction: (female:male ratio of mortality ratios): 1.08 (0.93, 1.25); p = 0.321 Excludes interaction of the magnitude observed in the Phase 3 trial after allowing for uptake of the vaccine in the pilots (1.4)
		Boys only (safety assessment)											
		pilot implementation study*	see above	see above	see above	see above	see above	-	-	Mortality ratio 0.91 (0.80 to 1.04)	-	see above	
MENINGITIS (safety, critical outcome)	Meningitis (month 0 to study end) (mITT analysis)												
	1 [1] (RTS,S/AS01)	randomised trials	serious [l]	not serious	not serious [g]	serious [c]	none	R3R: 11/2976 + R3C: 1/2972	C3C: 1/2974	IRR: 10.5 (95% CI 1.41 to 78.0)	-	⊕⊕◯◯ LOW	
	Meningitis (confirmed by lumbar puncture)												
	1 [2] (Chandramohan)	*RTS,S/AS01 vs SMC alone*											
		randomised trials	not serious	not serious	not serious	very serious [m]	none	0 cases	0 cases	-	-	⊕⊕◯◯ LOW	
		SMC + RTS,S/AS01 vs SMC alone											
		randomised trials	not serious	not serious	not serious	very serious [m]	none	0 cases	0 cases	-	-	⊕⊕◯◯ LOW	
	Hospital admission with meningitis												

	1 [3] (MVPE)	pilot implementation study*	not serious [d]	not serious	not serious	serious [n]	none	-	-	IRR: 0.81 (95% CI 0.43 to 1.55)	-	⊕⊕⊕◯ MODERATE	Excludes effect of the magnitude observed in the phase 3 trial, after allowing for uptake of the vaccine in the pilots.††

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Abbreviations

CI: Confidence interval; IRR; incidence rate ratio; ITT: intention-to-treat; PE: protective efficacy; PYAR: person years at risk; VE: vaccine efficacy

R3R: 3× RTS,S plus booster RTS,S; R3C: 3× RTS,S plus comparator vaccine; C3C: controls (comparator vaccines)

Explanations

* Pilot implementation study designed to be analyzed as cluster randomised controlled trial

† To be able to rule out an association with cerebral malaria of the magnitude seen in the phase 3 trial we would therefore want to be able to exclude rate ratios of about 2.2 (1.6 allowing for 60% coverage and 5% contamination) or more

†† To be able to rule out an association with meningitis of the magnitude seen in the phase 3 trial we would therefore want to be able to exclude rate ratios of about 10.5 (4.5 allowing for coverage and contamination) or more.

$ Interaction parameter and 95% CI indicates evidence for effect modification by gender (1 indicates no effect modification)

a. Study was rated as unclear risk of bias due to heavy involvement of the funder within the project; however, it has not been downgraded for ROB as this was the only concern and the study is otherwise well conducted.

b. Downgraded two levels due to imprecision: few events and a very large confidence interval that incorporates the possibility of benefit and harm

c. Downgraded one level due to imprecision: few events and large confidence interval

d. Not downgraded for risk of bias despite being an open-label study because the findings from the household survey suggest there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behavior, or health worker behavior in testing and treating for febrile illness.

e. Downgraded one level for imprecision: large confidence interval that incorporates the possibility of benefit and little to no effect.

f. Downgraded two levels for risk of bias: unclear risk of bias due to heavy involvement of the funder within the project. In addition, this was a post-hoc analysis based on an imprecise algorithm, followed by record review and expert panel review. Cerebral malaria is a difficult diagnosis to make in real time, and worse through record review.

g. For this safety outcome we have reported the combined results for children receiving 3 or 4 doses of the vaccine; however, it has not been downgraded for indirectness.

h. Downgraded two levels due to imprecision: very few events and 0 events in the control arm

i. Downgraded one level due to imprecision: large confidence interval that incorporates the possibility of benefit and harm. Study was powered for a pooled analysis only, country estimates vary but confidence intervals are wide and consistent with pooled effect.

j. Downgraded one level due to imprecision as the large confidence interval incorporates de posibiliity of benefit and harm. Not downgraded a second level despite being powered for a pooled analysis only, country estimates vary but confidence intervals are wide and consistent with pooled effect.

k. Downgraded one level for imprecision: analysis not powered at this time point to assess impact of vaccine introduction on mortality, but the pooled point estimate for mortality is consistent with the expected impact (3% - 8% depending on the proportion of deaths attributable to malaria.

l. Downgraded one level for risk of bias: unclear risk of bias due to heavy involvement of the funder within the project. In addition, this outcome was not pre-specified in the protocol (post-hoc analysis).

m. Downgraded two levels for imprecision: no events reported in either group.

n. Downgraded one level due to imprecision: large confidence interval that incorporates the possibility of benefit and harm. It was only downgraded by 1 level because the result excludes an effect of the magnitude observed in the phase 3 trial, after allowing for uptake of the vaccine in the pilots.

References

1. RTS, S Clinical Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet; 2015.

2. Chandramohan D, Zongo I,Sagara I,Cairns M,Yerbanga RS,et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. New England Journal of Medicine; 2021.

3. P Milligan and K Moore, Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced. V1.3 Aug 2021.

Annex 9b: Malaria Policy Advisory Group (MPAG) and Strategic Advisory Group of Experts (SAGE) on Immunization - Evidence to recommendations framework

Question: Should a minimum of 4 doses of RTS,S/AS01 be provided to reduce malaria disease burden in children >= 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission?

Population: Children >= 5 months of age living in countries in sub-Saharan Africa with moderate to high malaria transmission

Intervention: A minimum of 4 doses of RTS,S/AS01 (given as a 3-dose initial series; dose 1 should be provided between 5 and 17 months of age) with a minimal interval between doses of 4 weeks

Comparison(s): Malaria interventions currently in place without malaria vaccination

Outcome: Clinical malaria, severe malaria, anaemia, blood transfusion, cerebral malaria, hospital admission, all-cause mortality, safety (AE, SAE, AEFI, AESI), tolerability

Background:

WHO estimated in the 2020 World Malaria Report that, in 2019, approximately 229 million cases and 409 000 deaths were attributable to malaria, with 94% of these deaths occurring in sub-Saharan Africa. Most malaria deaths in Africa occur in children younger than 5 years. 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.

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.

However, between 2015 and 2019 the annual case incidence decreased by less than 2%, indicating a slowing of the rate of decline since 2015.[4] 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. [iii] There is general agreement that to get malaria control back on track, new tools are needed alongside efforts to increase uptake and use of current malaria control tools.

The Malaria Vaccine Implementation Programme (MVIP) was developed in response to the 2015 joint recommendation by SAGE and MPAC to introduce the RTS,S/AS01 (RTS,S) malaria vaccine in phased introductions in 3-5 African countries. Recognizing the potential of the vaccine to reduce clinical and severe malaria in African children, the pilots were designed to answer outstanding questions on safety, impact in routine use, and feasibility of reaching children with the recommended 4-dose schedule. The ministries of health (MoH) of the three pilot countries, Ghana, Kenya and Malawi, are delivering the RTS,S vaccine in selected areas through their child immunization services. Data are collected through the Malaria Vaccine Pilot Evaluation (MVPE) to inform WHO recommendations on the broader use of RTS,S in sub-Saharan Africa.

In 2019, the SAGE and MPAC endorsed the Framework for WHO recommendation on RTS,S/AS01[1] which outlines a step-wise approach for review and WHO recommendation on broader use of RTS,S based on emerging pilot data. In the Framework it was agreed that a WHO policy recommendation on the use of RTS,S/AS01 beyond the pilot countries could be made if and when (i) concerns regarding the safety signals observed in the Phase 3 trial are satisfactorily resolved, and (ii) severe malaria or mortality data trends are assessed as consistent with a beneficial impact of the vaccine. The 2019 Framework further states that a recommendation could be made in absence of data showing vaccine impact on mortality (impact on severe malaria is an acceptable surrogate); a recommendation need not be predicated on attaining high coverage, including coverage of dose 4; and cost effectiveness estimates should be regularly refined as data become available for increasingly precise calculation, and presented at appropriate time points.

The rate of events in the malaria vaccine pilot evaluations allowed for sufficient data availability to conduct the primary analysis per the statistical analysis plan (SAP) on safety and impact on hospitalized severe malaria 24 months after the start of RTS,S vaccination in the first pilot country(end of April 2021).

[1] Framework for Recommendation on RTS,S, April 2019: https://www.who.int/malaria/mpac/proposed-framework-for-policy-decision-on-rtss-as01-malaria-vaccine.pdf

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies by setting* ☐	Despite considerable efforts and the use of multiple interventions, combined as appropriate according to the setting, malaria continues as a major public health problem. In areas of high transmission, malaria remains a major cause of child morbidity and mortality, even where insecticide treated net (ITN) coverage is high. This includes areas of highly seasonal transmission, where seasonal malaria chemoprevention (SMC) is provided monthly through the high transmission season. WHO estimated that in 2019, approximately 229 million cases and 409 000 deaths were attributable to malaria, with 94% of these deaths occurring in sub-Saharan Africa. Most malaria deaths in Africa occur in children younger than 5 years.[i] Most malaria deaths in Africa occur in children younger than 5 years. Furthermore, the last four WHO World Malaria Reports have indicated that progress in malaria control has stalled, with very little reduction in the past 5 years despite continued efforts to increase coverage and access to current interventions. In some sub-Saharan African countries, cases are increasing.[2] All of our current malaria control interventions are either insecticide or drug based, and are threatened by emerging resistance[3].	Notably, the malaria control situation is different than when the RTS,S vaccine was considered for by WHO in 2015. At that time, malaria cases had been declining year-on-year as a result of ITNs and introduction of highly effective artemisinin-containing therapy.

[2] World Malaria Report 2020. 2020, World Health Organization: Geneva, Switzerland
[3] Global plan for insecticide resistance management in malaria vectors. Geneva: World Health Organization; 2012 (http://apps.who.int/iris/bitstream/10665/44846/1/9789241564472_eng.pdf, accessed 10 March 2015)
WHO, Roll Back Malaria Partnership. Global plan for artemisinin resistance containment. Geneva: World Health Organization; 2011 (http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf, accessed 10 March 2015

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Modeled estimates from the Swiss TPH and Imperial College were updated in 2021 utilizing the underlying model structure and vaccine parameterization from the 2015 analysis and more comprehensive coverage and cost of delivery data that have been informed by MVIP. In moderate to high transmission settings, median predictions from the two models were 417 and 448 deaths averted per 100 000 fully vaccinated children (defined as having received at least 3 doses) and the range of model predictions at 80% level were 205-540 and 315-534 respectively. The models estimated 9.2% to 18.6% of all malaria deaths averted in vaccinated children < 5 years. Modest vaccine efficacy has potential translate into significant public health impact on morbidity and mortality. In large Phase 3 trial (2009-2014) participants who received 4-dose schedule at 5-17 months of age, vaccine efficacy (VE) against clinical malaria was 39% (95% CI 34.3,43.3) and VE against severe malaria up to the end of the trial was 31.5% (95%CI 9.3, 48.3). From month 0 to study end, 1774 cases of clinical malaria per 1000 children (95% CI 1387-2186; range across sites 205-6565) were averted.[4] This VE and impact observed were on top of existing interventions (i.e. insecticide treated nets) and was observed both where ITN use was high and in the two sites where ITN use was not high. Secondary objectives of the Phase 3 trial included the measurement of VE against severe malaria and against all-cause mortality. Vaccine efficacy against severe malaria was significant (as above), but because of the low mortality rate among children enrolled in the Phase 3 trial in which children had improved access to care, data derived from trials were insufficient to draw conclusions on of the impact of the vaccine on mortality. Extended follow up study (7-years follow-up total) of subset of children at 3 trial sites, showed that among trial participants given 4-dose and 3-dose schedules at 5-17 months, VE against severe malaria was 37% (95%CI15 to 53; p=0·0028) and 10% (95%CI −18, 32; p=0·44) respectively. VE against clinical malaria was 24% (95% CI: 16; 31) in 4-dose group and 19% (95% CI: 11; 27) in 3-dose group.[5] The evaluation of the Malaria Vaccine Pilot Implementation Programme in Ghana, Malawi and Kenya, after 2 years, demonstrated that high coverage of the vaccine was achieved, (in household surveys, 62% of children 12-23 months had received 3 doses of RTS,S/AS01 in Malawi, and 67% in Ghana; in	The SAGE and MPAG endorsed Framework for WHO Recommendation states that a WHO recommendation for broader use could be made in absence of data showing a vaccine impact on mortality. Impact on severe malaria is an acceptable interim surrogate indicator if assessed as consistent with a beneficial impact. The MVPE household survey showed equitable delivery of the RTS,S/AS01 vaccine with respect to gender, socio-economic status, and ITN use.

[4] RTS,S Clinical Trial Partnership, *Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial.* Lancet, 2015. **386**(9988): p. 31-45.

[5] Tinto, H., et al., Long-term incidence of severe malaria following RTS,S/AS01 vaccination in children and infants in Africa: an open-label 3-year extension study of a phase 3 randomised controlled trial. Lancet Infect Dis, 2019. 19(8): p. 821-832.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Benefits of the intervention Are the desirable anticipated effects large? (continued from page 3)					Kenya, 69% had received 3 doses based on administrative data), and in pooled analysis of data from the three countries, introduction of RTS,S/AS01 was associated with a 30% reduction in the incidence of hospital admission with severe malaria (incidence rate ratio (IRR) 0.70, 95%CI 0.54, 0.92), a 21% reduction in hospitalization with a positive malaria test (IRR=0.79, 95% CI 0.68, 0.93), a 8% reduction in hospital admission for any cause (IRR=0.92, 95%CI 0.83, 1.03), and a 7% reduction in mortality due to any cause excluding injuries (IRR=0.93, 95% CI 0.84, 1.03). The impact on severe malaria was consistent with the impact that would be expected if the effectiveness of three doses of RTS,S/AS01 was equal to the efficacy observed in the Phase 3 trial, given the level of uptake of the vaccine in the pilot implementation. 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. The household survey shows that the vaccine was provided equitably across socio-economic status and gender. Vaccine introduction did not negatively impact ITN use. Moreover, the vaccine improved equitable access to malaria control interventions, with 69-75% of children who did not sleep under an ITN the prior night having received at least one dose of RTS,S/AS01. In a 3-year study, conducted in settings of highly seasonal malaria, where seasonal malaria chemoprevention (SMC) is WHO-recommended as a highly efficacious means to reduce malaria during peak transmission season, trial participants were randomized to 3 arms; to receive SMC alone, to receive RTS,S/AS01 alone just before peak season with annual doses, or to receive SMC + seasonal RTS,S/AS01. At 3 years, a protective efficacy against clinical malaria of 62.8% (95% CI 58.4, 66.8) and 59.8% (95% CI 54.7, 64.0), were shown in the SMC + RTS,S/AS01 group compared with the SMC-alone or compared with the RTS,S/AS01 alone group, respectively. Importantly, RTS,S/AS01 alone provided seasonally was non-inferior to SMC alone.[6]	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	In the large Phase 3 trial (2009-2014), one identified known safety risk was noted: febrile seizures within 7 days of vaccination and all cases resolved without sequalae. Three safety signals were identified, which were unexplained and without known causality: an excess of meningitis cases in RTS,S/AS01 recipients; an excess of cerebral malaria cases in a post-hoc analysis; and, also in a post-hoc analysis, an excess of deaths among girls who received RTS,S/AS01 but not among boys. In a 7-year follow-up study of a subset of children from three Phase 3 trial sites, no imbalance in safety signals was observed during the additional 3 years of follow-up. In addition, VE remained positive throughout the study period. In 2018, MPAC concluded these data provide further	

[6] Chandramohan et al, 2021. Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention. New England Journal of Medicine. https://www.nejm.org/doi/full/10.1056/NEJMoa2026330

	CRITERIA	JUDGEMENTS		RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Harms of the intervention (continued from page 5)			reassurance on the absence of a rebound effect after dose 4 or of a persistent rebound effect after only 3 doses. This was based on the assessment that the previously observed apparent rebound of severe malaria among children who received only 3 doses of RTS,S/AS01 was time limited, with very few severe malaria cases after 4 years of follow up, and no further imbalance in safety signals or death and was seen as giving further reinforcement of the safety profile of the vaccine and its apparent benefit in children who receive either 3 or 4 doses. [7] The malaria vaccine pilot evaluation was well-powered when pooled across countries to detect adverse effects of the magnitudes observed in the Phase 3 trial if they occurred. -There was no evidence that RTS,S/AS01 introduction increased incidence of hospital admission with meningitis: incidence rate ratio (vaccinating: comparison areas) was 0.81 (95%CI 0.43, 1.55). -There was no evidence that RTS,S/AS01 introduction increased incidence of hospital admission with cerebral malaria: incidence rate ratio (vaccinating: comparison areas) was 0.77 (95% 0.44, 1.35). --There was no evidence that the effect of RTS,S/AS01 introduction on all-cause mortality differed between girls and boys: relative mortality ratio (the mortality ratio between vaccinating and comparator areas, for girls, relative to the mortality ratio for boys), was 1.08 (95%CI 0.93, 1.25). Further evidence on vaccine safety was obtained from the following studies, in which no malaria vaccine associated increase in meningitis, cerebral malaria or female deaths was observed: the Phase 3 trial of RTS,S/AS01 with SMC (N~6000, ~4000 children received RTS,S/AS01 dose 1)[6] and the Phase 3 fractional dose trial (N=1500; 1200 children received RTS,S/AS01 dose 1), or pooled Phase 2 RTS,S/AS clinical trials (N~2000).[8] Routine pharmacovigilance in the 3 pilot countries, where over 2 million doses of RTS,S/AS01 have been administered through the routine EPI clinics, and over 710 000 children have received at least 1 RTS,S/AS01 vaccine dose, did not show an imbalance in the safety signals identified in the Phase 3 trial, nor did it reveal any new safety signals. The European Medicines Agency (EMA) has maintained a positive scientific opinion under article 58, stating that benefits outweigh risks and the vaccine has an acceptable safety profile.[9] Data from the pilot and other studies listed support the EMA conclusion that the safety signals observed in the Phase 3 trial were likely chance findings.	

[7] Framework for Recommendation on RTS,S, April 2019: https://www.who.int/malaria/mpac/proposed-framework-for-policy-decision-on-rtss-as01-malaria-vaccine.pdf
[8] Vekemans, J., et al., *Pooled analysis of safety data from pediatric Phase II RTS,S/AS malaria candidate vaccine trials.* Hum Vaccin, 2011. **7**(12): p. 1309-16.
[9] *Mosquirix: Opinion on medicine for use outside EU*. [cited 2021 July 1]; Available from: https://www.ema.europa.eu/en/mosquirix-h-w-2300.

	CRITERIA	JUDGEMENTS					RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Balance between benefits and harms	*Favours inter-vention*	*Favours com-parison*	~~*Favours both*~~	*Favours neither*	*Unclear*	In the large Phase 3 trial, the vaccine was shown to protect against clinical and severe malaria, severe malaria anemia, blood transfusions, hospitalization due to malaria, and all-cause hospitalizations. Benefits against malaria-related mortality and all-cause mortality are unknown, but severe malaria is a sufficient proximal marker of malaria mortality. In pilot introductions, with vaccine provided through the routine system, relatively high coverage levels of the first 3 vaccine doses were obtained over a relatively short period and during the Covid-19 pandemic (surveys assessed coverage of 3 doses in children 12-23 months as 62% in Malawi and 67% in Ghana . During the first 24 months of vaccine introduction, a statistically significant 30% reduction in hospitalized severe malaria and a 21% reduction in hospitalization with malaria was observed. There was no indication of a reduction in use of ITNs or a change in health seeking behavior or diagnosis and treatment of febrile illness was observed with malaria vaccine introduction. The vaccine is generally well-tolerated, with an identified risk of febrile convulsions within 7 days of vaccination. The MVPE was well powered to detect the safety signals of the magnitude observed in the Phase 3 trial. The safety signals observed during Phase 3 trial were not observed in the pilot implementations. No additional concerns were raised through the routine national pharmacovigilance, the Phase 3 post-authorization safety analysis by GSK, the trial of seasonal RTS,S/AS01 with or without SMC, nor the pooled Phase 2 trial safety analysis. Concerns about potential excess risk of severe malaria should a child not receive dose 4 were not borne out in the extended follow-up study of 3 sites in the Phase 3 trial, in the modeling study, nor in re-assessment of the Phase 3 trial data, which showed reductions in severe malaria among children who received 3 vaccine doses prior to the end of the Phase 3 trial.	*2019 Framework:* Recommendation on use of RTS,S/AS01 could be made if and when: - concerns regarding safety signals observed in the Phase 3 trial (related to meningitis, cerebral malaria, and sex-specific mortality) satisfactorily resolved - either severe malaria or mortality data trends are assessed as consistent with a beneficial impact of the vaccine; *2019 Framework:* WHO recommendations for broader use of RTS,S need not be predicated on attaining high coverage (including coverage of dose 4). The overall benefit/risk in context of what can be implemented is positive. Judgment options defined by the Working Group as: - "Favours intervention:" RTS,S/AS01 plus other malaria control interventions - "Favours comparison" other malaria control interventions - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable
		☒	☐		☐	☐		

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☐ *High* ☒ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Mod-erate* ☒ *High* ☐	The certainty of the evidence ranged from very low to high; however, most outcomes have been rated as either **moderate or high certainty**.	The main reason for downgrading the certainty of the evidence was imprecision, mostly for safety outcomes, due to the small number of events. In the Phase 3 trial there were 22 cases of meningitis; 53 cases of cerebral malaria; 156 deaths in girls, and 150 deaths in boys (notably far fewer than included in the analysis for the MVPE). The safety signals observed in the Phase 3 trial were rare, unexplained events. A significant risk difference was 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 (both outside of the meningitis belt); and, there was inconsistency in etiology, with cases of bacterial, mycobacterial, viral, and those with no pathogen isolated. It was also unclear whether 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 compared with boys 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 (N ~ 2000, Vekemans et al).

Desirable	Study	Effect	Certainty
Clinical malaria	Phase 3 trial –RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC Pilot Evaluations (MVPE) - RTS,S vs control	Favours RTS,S No difference Favours RTS,S + SMC Not reported	High High High -
Severe malaria	Phase 3 trial –RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,Ss No difference Favours RTS,S + SMC Favours RTS,S	High Low Moderate Moderate
Severe malaria anaemia	Phase 3 trial – RTS,S vs control Chandramohan[a] -RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,S No difference Favours RTS,S + SMC Not reported	Moderate Low Moderate -
Blood transfusion	Phase 3 trial – RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,S No difference Favours RTS,S + SMC Not reported	Moderate Low Moderate -
Hospital admission	Phase 3 trial – RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours RTS,S No difference No difference No Difference	High Low Low Moderate
Undesirable			
Cerebral malaria	Phase 3 trial – RTS,S vs control Chandramohan - RTS,S vs SMC Chandramohan[b] - - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours comparison Probably no diff 4 vs 0 events Probably no diff 1 vs 0 events No difference	Very low Low Low Moderate
All-cause mortality	Phase 3 trial – RTS,S vs control Chandramohan[a] - RTS,S vs SMC Chandramohan[b] - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Girls - Favours comparison Boys - No difference Girls - No difference Boys - No difference Girls - No difference Boys - No difference Girls - No difference Boys - No difference	Low Low Low Low Moderate Moderate Moderate Moderate
Meningitis	Phase 3 trial – RTS,S vs control Chandramohan[a] - RTS,S vs SMC Chandramohan[b] - RTS,S + SMC vs SMC MVPE – RTS,S vs control	Favours comparison No cases in either group No cases in either group No difference	Low Low Low Moderate

	CRITERIA	JUDGEMENTS					RESEARCH EVIDENCE	ADDITIONAL INFORMATION
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐	*Possibly important uncertainty or variability* ☐	*Probably no important uncertainty or variability* ☐	*No important uncertainty or variability* ☒	*No known undesirable outcomes* ☐	In the MVIP, severe malaria was reduced by 30% during the first 24 months of vaccine introduction, when the vaccine was delivered by the MoH through the routine childhood immunization programme, achieving high impact in a real-life situation on top of current malaria control interventions. Hospitalization with malaria infection was reduced by 21%. Additionally, the Phase 3 trial conducted between 2009 and 2014 demonstrated a 40% reduction in malaria cases presenting at the health facility or hospital. The seasonal malaria vaccination trial[6] showed how vaccine delivery can be optimized for higher efficacy and impact. Undesired effects include risk of febrile convulsions; reactogenicity - including fever after vaccination; and the requirement to administer a 4-dose schedule requiring new vaccine visits* Caregiver and health worker interviews and statements from the MoH in the pilot countries indicate that the relative importance of the desirable outcomes over the undesirable outcomes is high.	Malaria remains a primary cause of childhood death in sub-Saharan Africa, with financial and societal repercussions. High value placed on reduction of uncomplicated and severe malaria, and malaria death. *Notably, most, if not all sub-Saharan African countries, recommend monthly child health visits until 5 years of age, so these should not be new health facility visits.
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☐	*Yes* ☒	*Varies* ☐	All 3 MVIP countries showed increasing utilization (coverage) of the vaccine, captured through both administrative and survey data, over 24-months of RTS,S/AS01 implementation. Midline household surveys estimated coverage rates of 79.7%, 79.5%, and 74.1% for dose 1 and 71.2%, 65.5% and 65.2% for dose 3, respectively for Ghana, Kenya, and Malawi (measured through available immunization cards). Survey results were consistent with coverage estimates from the administrative data and suggest acceptability by target population, caregivers, and health workers administering the vaccine. Midline surveys did not find any significant difference in vaccine coverage by the child gender, socio-economic status, or ITN use. These data indicate relatively rapid scale up for a new vaccine with a unique schedule; dropout between doses has been comparable to other vaccines. A qualitative study (HUS) conducted within the MVIP found the following: --Severity and frequency of malaria widely recognized among primary caregivers who expressed strong enthusiasm for a malaria vaccine regardless of individual concern/question about RTS,S --In all countries, uptake of RTS,S/AS01 doses 1-3 generally high, initially (dose 1) based on strong trust in government, health system, and vaccines and later (doses 2-3) shifting to specific trust in RTS,S/AS01 as caregivers observe absence of side effects and perceive direct benefits of the vaccine (malaria less frequent and severe). --When adequately informed about dose schedules, caregivers are motivated to attend additional visits for vaccinations, including RTS,S/AS01.	Household survey and administrative data from the MVPE indicate the value of vaccine and acceptability by target population, with relatively rapid scale up for a new vaccine with a unique schedule, and dropout between doses comparable to other vaccines. HUS data indicate high acceptance and desirability of the vaccine. Midline surveys and the second round of the qualitative study were conducted between provision of dose 3 and dose 4 and thus did not capture data on the uptake/coverage/ acceptability of dose 4.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
						--Almost all caregivers whose children received 3 RTS,S/AS01 doses were aware of dose 4 at 24 months and expressed commitment to taking the child. Post introduction evaluation (PIE) conducted in Malawi (non-representative sample) found that 83% of community members accepted the vaccine; 89% of community members were aware the vaccine provides partial protection and 83% were aware of potential side effects, such as fever.	
RESOURCE USE	Are the resources required small?	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☒	Additional resources are required for commodity procurement and for the health system provision of the new vaccine. Additional health system resources will be required for adding new vaccination visits (at least 1 for first 3 doses and additional visit for dose 4). The MVIP cost of delivery study found: Incremental non-vaccine cost of introducing and delivering a dose of RTS,S/AS01 ranges between $1.20-$2.50 (financial) and $2.07-$4.77 (economic) across MVIP countries. Cost of delivery is slightly lower if considering the first 3 doses, (range: $0.94- $1.97 (financial); $1.71-$3.86 (economic). Cost of delivery is likely slightly higher for dose 4: there is limited data to infer cost of delivery of dose 4 at the time of this analysis. Although not directly comparable, MVIP cost of delivery estimates are broadly consistent with previous cost projections of RTS,S/AS01 delivery[10,11]. The resources needed to deliver RTS,S/AS01 may be generally comparable with other new vaccines. The cost estimates of RTS,S/AS01 delivery during the pilot is relatively higher than the cost per dose for newly introduced vaccines such as PCV or Rotavirus $0.84 (range: $0.48 to $1.38, economic)[12], but comparable with the HPV vaccine pilot implementation which range between $1.74 and $2.24 (financial) and between $2.22 and $4.29 (economic).[8] Comparisons of the MVIP costing estimates to findings from the literature should be made cautiously, acknowledging that the methods and the delivery strategies are different, and these estimates are drawn from ongoing pilot studies rather than a full national introduction. GSK has committed to at-cost (plus 5%) pricing for the vaccine. GSK has also a product transfer agreement with Bharat Biotech Industries Ltd; the stated intention of this product transfer is to ensure the long-term, low-cost production of RTS,S.	Resources may not be small, but modelling indicates highly cost effective at US$ 5-10 per dose (other cost effectiveness studies had different costs associated). Resources required are likely comparable with other new vaccine introductions. Resource requirement is largely dependent on vaccine price and potential donor funding available to support vaccine purchase and introduction. The added benefit provided through the ability of the malaria vaccine to reach children not currently accessing ITNs or other malaria preventive measures should be considered. Likewise, the relatively rapid scale up to coverage levels that are higher than those reached for most other malaria interventions, and the delivery through an established platform are unique features for a malaria intervention that should be considered as part of the cost assessment and when considering the value of the vaccine. There are implied costs of vaccine introduction however the size of resources required depends on perspective and cost effectiveness. The magnitude is likely to vary depending how countries in sub-Saharan Africa integrate the vaccine within the available vaccine portfolio, malaria control efforts, and multiple other factors.

[10] Galactionova K, Bertram M, Lauer J, Tediosi F. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda: A generalizable approach drawing on publicly available data. Vaccine 2015; 33:6710–6718.
11 Sicuri E, Yaya Bocoum F, Nonvignon J, et al. The Costs of Implementing Vaccination With the RTS,S Malaria Vaccine in Five Sub-Saharan African Countries. MDM Policy Pract 2019; 4.
[12] Immunization Delivery Cost Catalogue. http://immunizationeconomics.org/ican-idcc-findings#anchor-top

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Predictions of RTS,S/AS01 cost-effectiveness per disability-adjusted-life year (DALY) averted are comparable with other new vaccines. In 2015, four mathematical models of the impact of RTS,S/AS01 predict a substantial additional public health impact in settings with prevalence of infection in those aged 2-10 years between 10% and 65%.[13] Predictions from two of the four models (Imperial College and Swiss TPH) were subsequently fit against the results on severe malaria from the follow up study in three of the Phase 3 trials sites. The model predictions were found to be consistent with the measured impact of the from the longer-term follow up study, supporting the validity of the earlier cost effectiveness estimates. Predictions from the Swiss TPH and Imperial College were updated in 2021 utilizing the underlying model structure and vaccine parameterization from the 2015 analysis and more comprehensive coverage and cost of delivery data that have been informed by MVIP. In moderate to high transmission settings, median predictions from the two models were 417 and 448 deaths averted per 100 000 vaccinees in a 4-dose schedule (where a fully vaccinated child is defined as any that has received at least 3 doses) , and the range of model predictions at 80% level were 205-540 and 315-534 respectively. The two models estimated 9.2% to 18.6% of all malaria deaths averted in vaccinated children < 5 years. Modelling predictions indicate a significant public health impact and high level of cost-effectiveness in those settings if implemented after achieving high bed net usage and high coverage of SMC, where latter intervention is appropriate. Predictions using the Swiss TPH model, at a price of $5 per dose, predicted the median cost-effectiveness ratio of $97 (range $81-$230) per DALY averted in various African countries. Predictions using the Imperial College model predicted the median cost-effectiveness ratio of $103 (range $86 - $151) per DALY averted at a price of $5 per dose program cost. Although summary statistics from the 2015 and 2021 analyses are not directly comparable, the cost per DALY averted and cost per clinical case averted predictions 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 RTS,S/AS01 is still predicted to be cost-effective compared with standard norms and thresholds. This result suggests that RTS,S/AS01, conditional on assumptions on price, coverage, and vaccine properties, is highly cost-effective across African countries.	The 2019 Framework for WHO recommendation states: Cost-effectiveness estimates should be regularly refined as data become available for increasingly precise calculations and presented at appropriate time points. The anonymized six African country analysis of CEA done in 2015 suggest the cost effectiveness of RTS,S introduction range between $92 - $282 per DALY averted across countries. These results are consistent with that observed in the transmission setting specific estimates.[14]

[13] Penny, M.A., et al., Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models. Lancet, 2016. 387(10016): p. 367-375.
[14] Galactionova K, Bertram M, Lauer J, Tediosi F. Costing RTS,S introduction in Burkina Faso, Ghana, Kenya, Senegal, Tanzania and Uganda: a generalizable approach drawing on publicly available data. Vaccine. 2015;33(48):6710–8

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
EQUITY	What would be the impact on health inequities?	*Increa-sed*	*Un-certain*	*Re-duced*	*Varies*	Household surveys in Ghana and Malawi showed that vaccine uptake was equitable, with similar coverage across socio-economic groups and in boys and girls. Vaccine introduction did not negatively impact ITN use, uptake of other childhood vaccines, or health seeking behavior. Introduction of the vaccine resulted in broadened access to at least one malaria preventive intervention (ITNs or malaria vaccine). 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 - 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.	**This criteria was considered in context of following questions:** Is the condition more common in certain disadvantaged group? • *Children under 5 years are most affected by malaria, pronounced in the rural and poor (low SES) populations (World Malaria Report. 2020)* Is its severity greater, in people from specific group or with a particular disability? • *Exposure to HIV and HIV infection has direct or indirect role on child health outcomes – malaria, anemia and nutrition (Dorsey G, et al ; Malaria J, 2012, Berkley et at 2009 and Hendrikensen et at 2012)* • *Chronic malnutrition is associated with severity of malaria (Das D, et al BMC 2018)* • *Malnutrition and being female was associated with increased mortality in children aged less than 10 years (Tshimanga M, et al, Pan Afr Med J 2017)* • *The vaccine has been shown to be safe and efficacious in malnourished children (MAL 055 clinical trial data) and in HIV infected children (Otieno, L et al, Lancet Infect Dis 2016)* • *Homozygous sickle cell disease does not confer protection for severe malaria* Are there significant differences resulting in varying levels of access to intervention or coverage levels? Is there a risk that discrimination could impact outcomes? • *In some (but not all) countries, access to malaria control measures differ by SES, rural/urban settings (WMR, 2020)*
		☐	☐	☒	☐		

	CRITERIA	JUDGEMENTS					RESEARCH EVIDENCE	ADDITIONAL INFORMATION
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health (MoH), Immunization Managers)?	*Inter-vention* ☒	*Com parison* ☐	~~*Both*~~	*Neit her* ☐	*Un-clear* ☐	MoH, through the support of the MVIP, promoted use of RTS,S/AS01 in the vaccine implementation areas. Other malaria preventive measures were supported by the MoH in all MVIP areas. The Malawi PIE conducted in mid-2021 (not necessarily representative samples) reported that: 100% of health workers accepted RTS,S/AS01 as an addition to the available vaccine portfolio and malaria intervention tools, 83% of district level respondents stated that the introduction of RTS,S/AS01 improved the routine immunization programs. 67% of health sector respondents said the introduction of malaria vaccine was successful; 57% said that vaccine introduction improved the EPI. Good uptake and coverage of the malaria vaccine (as noted through the administrative data and the household survey) provide further evidence of acceptability by MOH staff administering the vaccine. Health providers interviewed through the qualitative HUS study expressed positive perceptions of the vaccine as an intervention and a significant component of malaria control efforts. Consistent with findings from primary child caregivers, health providers also emphasized the positive responses from the caregivers and perceptions about the vaccine's benefits. Chief concerns from health providers were around operational challenges faced in introducing and delivering RTS,S/AS01 (i.e. increased workload, training, eligibility). The vaccine itself was not the subject of questions or challenges, suggesting antigen itself continues to be acceptable to providers.	Judgment options defined as: - "Intervention:" RTS,S/AS01 plus other malaria control interventions is an acceptable option - "Comparison" other malaria control interventions is only acceptable option - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable - Note: "Both" removed due to lack of clarity in meaning MVIP countries (Ghana, Kenya, and Malawi) have valuable lessons learned and guidance based on their experiences implementing the MVIP vaccine when it comes to vaccine launch, stakeholder engagement, communications, schedule considerations, and integration within existing MoH programmes. Coordination between the NMCP and EPI programmes at central, regional and local levels were considered important for successful implementation.
	Which option is acceptable to target group?	*Inter-vention* ☒	*Com parison* ☐	~~*Both*~~	*Neit her* ☐	*Un-clear* ☐	The MVIP midline survey found no impact on use of ITN in intervention areas following introduction of RTS,S/AS01—indicating both interventions are acceptable. Overall health seeking behavior for febrile illnesses was also found to be similar between intervention and comparison groups and between baseline and midline surveys. Good uptake and coverage (as noted through administrative data and household survey) provide further evidence of acceptability; modest drop-out rate and continued increases in uptake suggest that additional visits are seen as acceptable to target populations. Within the MVIP qualitative study, malaria was seen by the population as a significant health risk and RTS,S/AS01, together with other malaria control measures, was seen as an acceptable intervention. Caregivers perceived the vaccine as reducing the severity and frequency of malaria. Positive attitudes and trust among caregivers increased substantially between R1 and R2 interviews, driven mainly by their perception of vaccine's health benefits in their own children and the broader community. Early concerns about safety were replaced by widespread perception that adverse events following immunization (AEFI) are "normal" and similar to other vaccines. Most caregivers expressed their intent to take their children to receive dose 4, and many did so enthusiastically.	Judgment options defined as: - "Intervention:" RTS,S/AS01 plus other malaria control interventions is an acceptable option - "Comparison" other malaria control interventions is only acceptable option - "Neither" intervention nor the control are acceptable - "Unclear" if either intervention or control are acceptable - Note: "Both" removed due to lack of clarity in meaning

	CRITERIA	JUDGEMENTS						RESEARCH EVIDENCE	ADDITIONAL INFORMATION
FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*Varies*	As of June 2021, more than 2.1 million doses of RTS,S/AS01 had been administered and more than 740 000 children across Ghana, Kenya, Malawi had received dose 1 through childhood vaccination using the strategies routinely used for new vaccine introduction. Demand and uptake of all doses has been strong in all three countries despite the challenges brought about by the COVID-19 pandemic. While there was variation in performance observed, according to administrative data, all three countries reached at least 74% of their target populations with RTS,S/AS01 dose 1 and at least 63% with the RTS,S/AS01 dose 3. 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 dose 1. Administrative data indicate that dose 4 can reach children, with drop out between dose 3 and 4 at approximately 19% in Malawi and 31% in Ghana after approximately 9 months of introduction of dose 4. This level of drop out early after vaccine introduction is not unexpected. It is not yet known whether additional efforts will be needed to increase dose 4 uptake. Data on the perceptions and utilization of dose 4 from the qualitative study is currently pending and will provide a clearer reflection on the feasibility of the 4-dose schedule. However, qualitative interviews with health providers and other sub-national health sector staff, supported by evidence from child caregivers, suggest that with time, a 4-dose RTS,S/AS01 schedule is feasible to implement: Providers have positive attitudes about RTS,S/AS01 and perceive that child caregivers value it as well. Understanding of dose eligibility has generally improved over time, likely reflecting improved training materials and increased familiarity with the vaccine. This finding is consistent with improved understanding of eligibility among child caregivers.	Regarding RTS,S/AS01 provided seasonally, there is no programmatic evidence at this point in time to understand whether the seasonal vaccine administration is feasible. Other malaria control interventions have been provided intermittently, (SMC, Intermittent Preventive Treatment of malaria in infancy (IPTi), Intermittent Preventive Treatment of malaria in pregnancy (IPTp), indoor residual spraying (IRS). Administration mechanisms differ between these interventions and differ to vaccine administration. *2019 Framework:* Need not be predicated on attaining high coverage (including dose 4). High coverage frequently not attained until several years after start of implementation.
		☐	☐	☐	☐	☒	☐		

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒
Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐	
Recommendation (text)	**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.				

Recommendation (continued)	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 dose 1, vaccination should be started before 18 months of age. A dose 4 should be given between about 12 and 18 months after dose 3 (i.e., at around 18 months to 2 years of age), however there can be flexibility to optimize delivery. The minimal interval between doses 3 and 4 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 dose 1 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 dose 4 (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 dose 4 can be made at the end of the pilots.

Implementation considerations	• Flexibility in dosing schedules is encouraged. Countries may want to provide dose 1 slightly earlier than 5 months of age and may want to provide the first 3 doses monthly. The pilot uncovered situations where the 6,7,9 month schedule caused some confusion. Likewise, MoH officials have expressed an interest in providing dose 4 at the same time as the meningococcal A (MenA) conjugate vaccine or the second dose of measles and rubella (MR), e.g. both at 18 months of age. • Data on seasonal vaccination supports its use in the Sahel and sub-Sahel region, and it may be appropriate for areas outside of the Sahel region where malaria transmission varies substantially by season. A seasonal strategy may optimize vaccine efficacy in other areas with moderate to high transmission and seasonality. • Vaccination should continue in the MVIP areas implementing RTS,S/AS01, and expand to the pilot evaluation comparison areas as soon as feasible.
Monitoring and evaluation	• 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. • MVIP will continue to monitor for or collect data on safety and impact, and on the value of dose 4, 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 dose 4. • Monitoring and evaluation around flexible schedules and implemented strategies are encouraged; this includes strategies for seasonal vaccination of RTS,S/AS01. • Vaccine effectiveness studies following widespread introduction.
Research priorities	The following research are recommended for the following areas, with the Working Group 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. • Through the MVIP, collect additional information on how best to achieve coverage of dose 4, 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. • Further evaluation 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.

Research priorities (continued)	• 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.

Annex 9c: Risk of bias assessment (for studies included in GRADE)

Author(s): Villanueva G, Henschke N, Hamel C, Buckley B (Cochrane Response)

[1]RTS,S Clinical Trials Partnership -2015

1. RTS, S Clinical Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. The Lancet; 2015.

ROB Domain	Judgement	Text supporting judgement
1. Was the allocation sequence adequately generated?	Low risk	In supplementary appendix: "Participating children from each age category were randomized into one of three study groups according to a 1:1:1 ratio (R3R, R3C or C3C) using a randomization algorithm with SAS version 9.1."
2. Was allocation adequately concealed?	Low risk	The treatment allocation at the investigator site will be performed using a central randomization system on Internet (SBIR).
3. For cluster RCTs, was there bias arising from the timing of identification and recruitment of participants? (see Figure 1)	n/a	Participants were individually randomized.
4. Was knowledge of allocated intervention adequately prevented during study? (i.e., blinding of participants and personnel)	All outcomes: Low risk	"Data were collected in a double-blinded (observer-blind) manner; the vaccinated children and their parent(s)/guardian(s) as well as those responsible for the evaluation of study endpoints were unaware of whether RTS,S/AS01 or a comparator vaccine had been administered to a particular child. The vaccines used in this study were of different appearance. The content of the syringe was, therefore, masked with an opaque tape to ensure that parent(s)/guardian(s) were blinded. The only members of study staff who knew of the vaccine assignment were those responsible for preparation and administration of vaccines; these staff played no other role in the study except screening or collection of biologic specimens."
5. Was knowledge of allocated intervention adequately prevented during the study from outcome assessors?	All outcomes: Low risk	See above.

Risk of bias assessment: RTS,S/AS01 malaria vaccine

ROB Domain	Judgement	Text supporting judgement
6. Were incomplete outcome data adequately addressed?	All outcomes except AEs: Low risk	A modified ITT analysis was used which included all children who received at least one dose.
7. Are reports of the study free of suggestion of selective reporting?	Low risk	There are 65 outcomes listed in the trial registry. All the results are reported in the trial registry.
8. Was the study apparently free of other problems that could put it at high risk of bias?	Unclear risk	The study was funded by GSK, the manufacturer of the interventional vaccine. "GSK Biologicals SA were involved in the study design, and coordinated data collection, data analysis, data interpretation, and writing of the report."
Outcomes: Clinical malaria, Severe malaria, Anemia, Blood transfusion, Hospital admission, All-cause mortality, Safety	**Overall risk**: Low risk	No details on allocation concealment and heavy involvement of the funder within the project.

Domains highlighted in blue are outcome specific.

Risk of bias assessment: RTS,S/AS01 malaria vaccine

[2]Chandramohan 2021

2. Chandramohan D, Zongo I,Sagara I,Cairns M,Yerbanga RS,et al. Seasonal malaria vaccination with or without seasonal malaria chemoprevention. New England Journal of Medicine; 2021.

ROB Domain	Judgement	Text supporting judgement
1. Was the allocation sequence adequately generated?	Low risk	Children were allocated randomly by an independent statistician. "The randomization list used permuted blocks after sorting by age, gender, area of residence and prior receipt of chemoprevention."
2. Was allocation adequately concealed?	Low risk	"Tablet PCs with the randomization list were accessible only to the chief pharmacist."
3. For cluster RCTs, was there bias arising from the timing of identification and recruitment of participants? (see Figure 1)	n/a	Individually randomized
4. Was knowledge of allocated intervention adequately prevented during study? (i.e., blinding of participants and personnel)	Low risk	The study registry (NCT03143218) states that it is triple blind (participant, care provider, investigator). "Syringes containing study vaccines were prepared by a chief pharmacist and masked with tape to blind the vaccine administrator, caretakers and children to the vaccine being given. The pharmacist and the vaccine administrator took no further part in the trial." "Drugs were pre-packaged by a pharmacist, who took no further part in the trial, in re-sealable enveloped labelled with the QR code. Each dose of SP+AQ or placebo was administered as directly-observed therapy by project staff at distribution points in study villages."
5. Was knowledge of allocated intervention adequately prevented during the study from outcome assessors?	Low risk	"All other investigators and study staff remained blind to treatment allocation."
6. Were incomplete outcome data adequately addressed?	Low risk	6861 children were randomized with 5920 children (86.3%) receiving at least one dose of study vaccine (no difference between the 3 groups).

Risk of bias assessment: RTS,S/AS01 malaria vaccine

ROB Domain	Judgement	Text supporting judgement
		"The primary analysis was by modified ITT. The mITT population included all eligible children whose parents consented and who received a first dose of study vaccine in April 2017." "Secondary outcomes were analysed only by mITT."
7. Are reports of the study free of suggestion of selective reporting?	Unclear risk	There are 14 outcomes reported in the trial registry. All primary and secondary outcomes are reported in the main report or supplementary appendix.
8. Was the study apparently free of other problems that could put it at high risk of bias?		The study registry was first posted on May 8, 2017 however the study began on April 17, 2017. Although this was retrospectively registered (by ~3 weeks), this would not affect any results. The trial was funded by non-profit agencies, however, the study drugs were donated by the pharmaceutical company. One of the authors is an employee of the GSK group of companies and has restricted shares in the GSK group of companies.
Outcomes: Clinical malaria, Hospital admission, death, malaria anemia	**Overall risk:** Low risk	

Risk of bias assessment: RTS,S/AS01 malaria vaccine

[3]MVPE surveillance data

3. P Milligan and K Moore, Statistical report on the results of the RTS,S/AS01 Malaria Vaccine Pilot Evaluation 24 months after the vaccine was introduced. V1.3 Aug 2021.

ROB Domain	Judgement	Text supporting judgement
1. Was the allocation sequence adequately generated?	Low risk	"To ensure the implementation and comparison areas were similar in all ways relevant to the evaluation, except the use of the vaccine, the following key factors, which may be associated with the endpoints being evaluated, were balanced in implementation and comparison areas: malaria transmission; vaccination coverage; number of hospitals and other health facilities; geographic location; population size in clusters. The approach used is technically referred to as a balanced (or constrained) randomization". "Each country team was requested to provide the data for the randomization. In parallel, the WHO HQ statistician developed a computer program, written in R, to generate the balanced options for each country. Once data was provided, the WHO statistician ran the code to identify the balanced options for each country." Country process: "The computer programme was developed to provide a long list of acceptable permutations of the ways the clusters could be assigned, with each option assigned a unique, sequential number. Once the list of options was produced for each country, a linkage analysis was performed (reports attached as annex 3) to check that an adequate set of balanced options was accurate. This included checking that balance criteria were not overly constraining and, for example, forcing that some clusters were always - or never - allocated together. Once this was confirmed the list of balanced options was provided to the country so that one option could be selected. In each country, pieces of paper, each with the number of one of the allocation options, were folded and placed in a container. One of the pieces of paper was pulled out of the container by the designated individual at the country's randomisation event." In-depth individual country reports of the randomisation outputs are provided in the protocol.
2. Was allocation adequately concealed?	Low risk	Randomisation process was done by (an external) WHO HQ statistician who developed a computer program to generate the balanced options for each country.

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ROB Domain	Judgement	Text supporting judgement
		"The computer programme was developed to provide a long list of acceptable permutations of the ways the clusters could be assigned, with each option assigned a unique, sequential number".
3. For cluster RCTs, was there bias arising from the timing of identification and recruitment of participants? (see Figure 1)	Low risk	Clusters (i.e. areas) appear to have been randomised before recruitment of participants. The total number of clusters required for the MVIP was determined by the need for statistical power to assess the vaccine's impact on mortality.
4. Was knowledge of allocated intervention adequately prevented during study? (i.e., blinding of participants and personnel)	Unclear risk	Open label study with cluster randomised areas. However, from the household survey (HHS) findings there is no evidence that the introduction of RTS,S/AS01 had a negative effect on uptake of other childhood vaccines, ITN use, care-seeking behavior, or health worker behavior in testing and treating for febrile illness.
5. Was knowledge of allocated intervention adequately prevented during the study from outcome assessors?	Low risk	Primary outcomes of interest (impact and safety) confirmed by laboratory testing, unlikely that assessors were aware of vaccination status. "Surveillance for severe malaria and other conditions is being maintained 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." According to the protocol, "for all cases with a diagnosis of meningitis, and a sample of non-meningitis diagnoses, an independent expert review, blinded to vaccine status, may be conducted on the patient's record". In the end, the assessment based on patient's record was not done as it was deemed to be unhelpful.
6. Were incomplete outcome data adequately addressed?	Low risk	Full results not available, this analysis based on power sufficient to test the safety signals identified in Phase 3 trial. No information about withdrawals and exclusions from analysis. Quote: "there were no withdrawals as we were not following patients longitudinally, however there were missing outcome data (e.g. if a lumbar puncture was not done we have missing data on their meningitis status). We noted no differences in missingness between vaccinating and comparison areas after adjustment using the age-ineligible group, so the statistical method used to calculate the rate ratios (using the age-ineligible group for adjustment) should have adequately addressed the problem of missing data if we assume that the data were missing at random."

Risk of bias assessment: RTS,S/AS01 malaria vaccine

ROB Domain	Judgement	Text supporting judgement
7. Are reports of the study free of suggestion of selective reporting?	Low risk	Trial registry and study protocols checked, all primary outcomes at this time point (24 months) analysed and reported.
8. Was the study apparently free of other problems that could put it at high risk of bias?	Low risk	This study was funded by WHO. Regarding the statistical analysis, the MVIP statistical team, contracted from London School of Hygiene and Tropical Medicine (LSHTM), developed a statistical analysis plan for the analysis of merged data from the MVPE. The MVIP data manager maintained a database for collecting and merging data from the evaluation partners and reporting to stakeholders. Since the start of surveillance (2019), safety and impact data are received and reviewed on a monthly basis by the data manager, statisticians, WHO, and the MVPE consortium in each country.
Outcomes: Safety (cerebral malaria, severe malaria, meningitis, mortality), impact (hospitalization)	**Overall risk:** Unclear risk	No details on role of the funder within the project. Open-label study. Limited information on missing data due to study not yet being published.

Risk of bias assessment: RTS,S/AS01 malaria vaccine

Figure 1. Suggested algorithm for reaching risk of bias judgements for bias arising from the randomization process in a cluster-randomized trial