WHO Guidelines for malaria

Systematic reviews, background papers and other unpublished evidence considered in the development of recommendations

Prevention/Vaccine

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Title

Proposed framework for policy decision on RTS,S/AS01 malaria vaccine

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Framework for policy decision on RTS,S/AS01 Working Group

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This report was endorsed by the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) in April 2019. The report was used by the SAGE and the Malaria Policy Advisory Group (MPAG, formerly MPAC) to support the development of the recommendation included in the *WHO Guidelines for malaria*. It is being made publicly available for transparency purposes and information, in accordance with the *WHO handbook for guideline development, 2nd edition* (2014).

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.

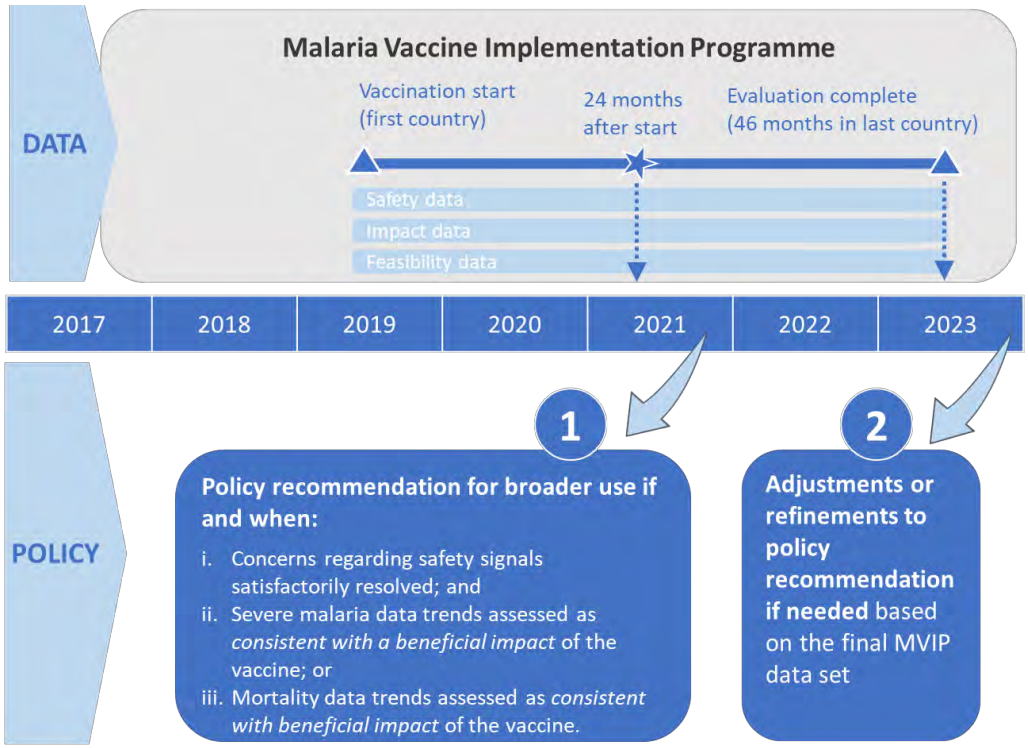
7) Expansion within MVIP countries should be synchronized with recommendation for broader use across sub-Saharan Africa.

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).

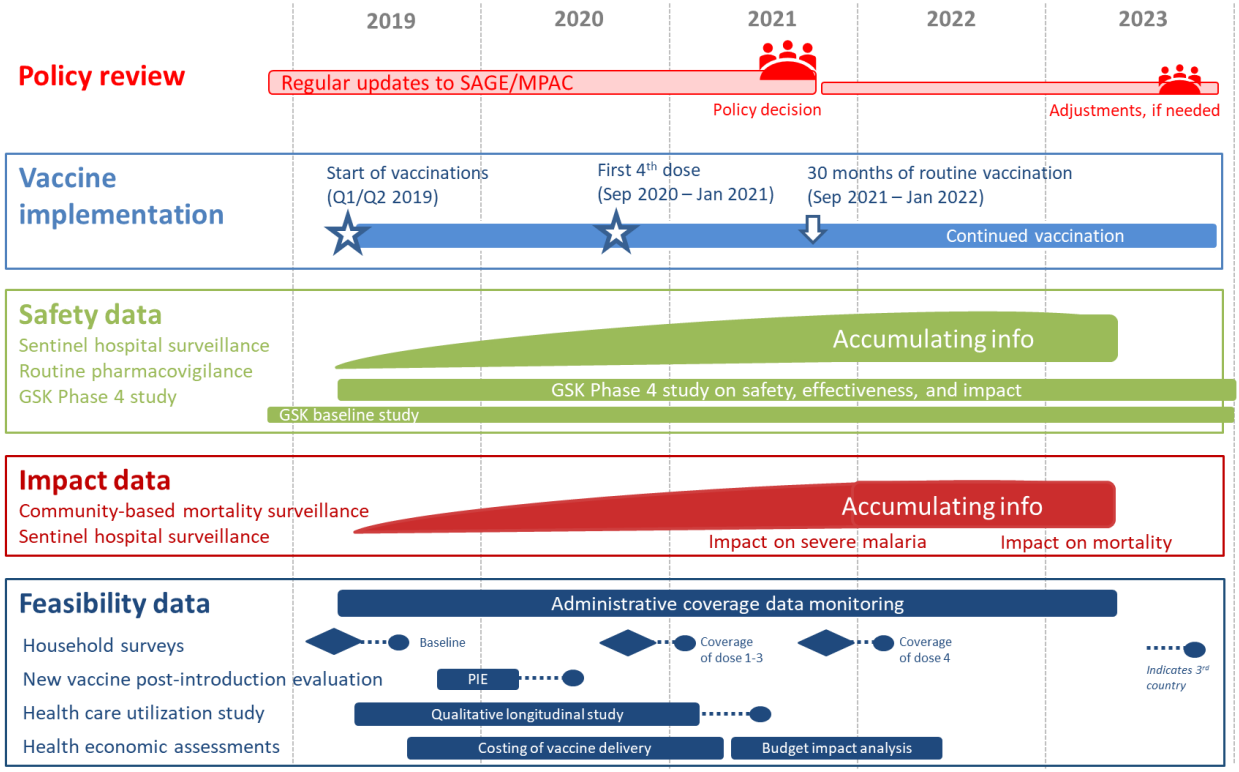
3) GSK-sponsored Phase 4 study

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.

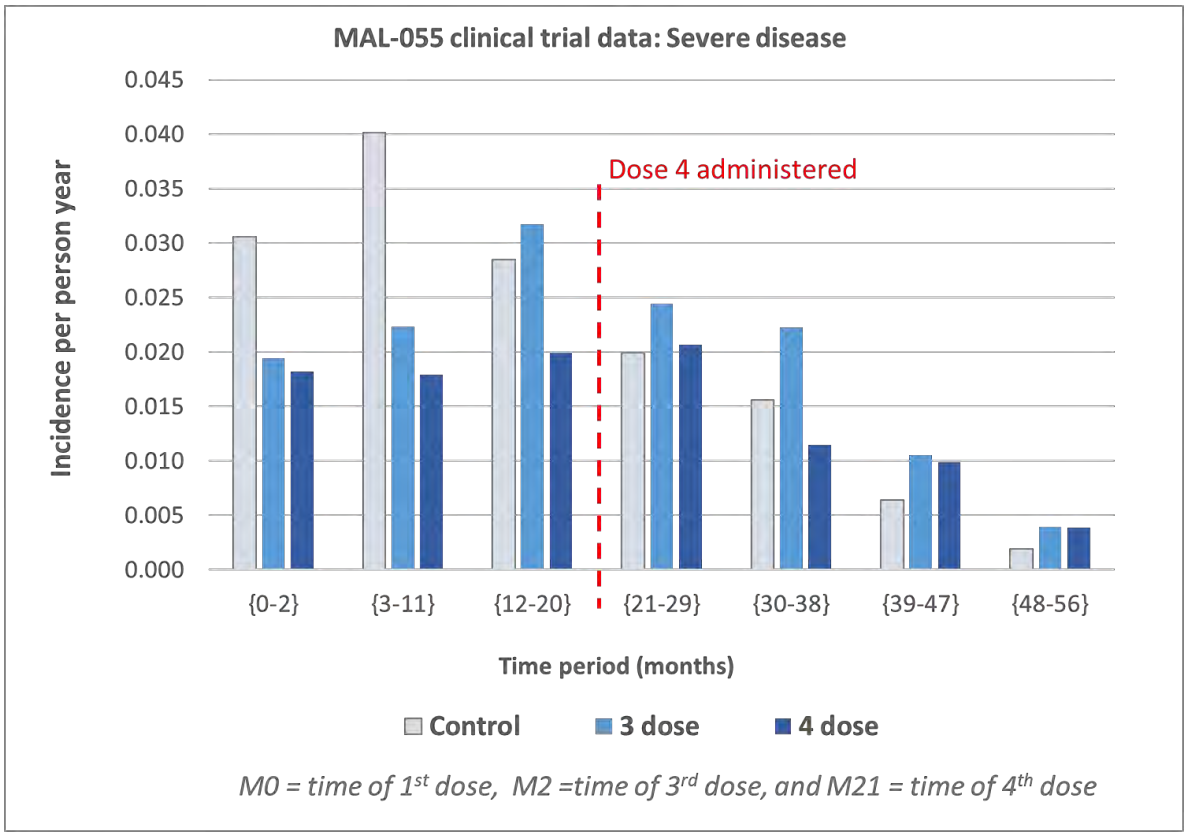
Further analysis of MAL-076 and MAL-055 data

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).

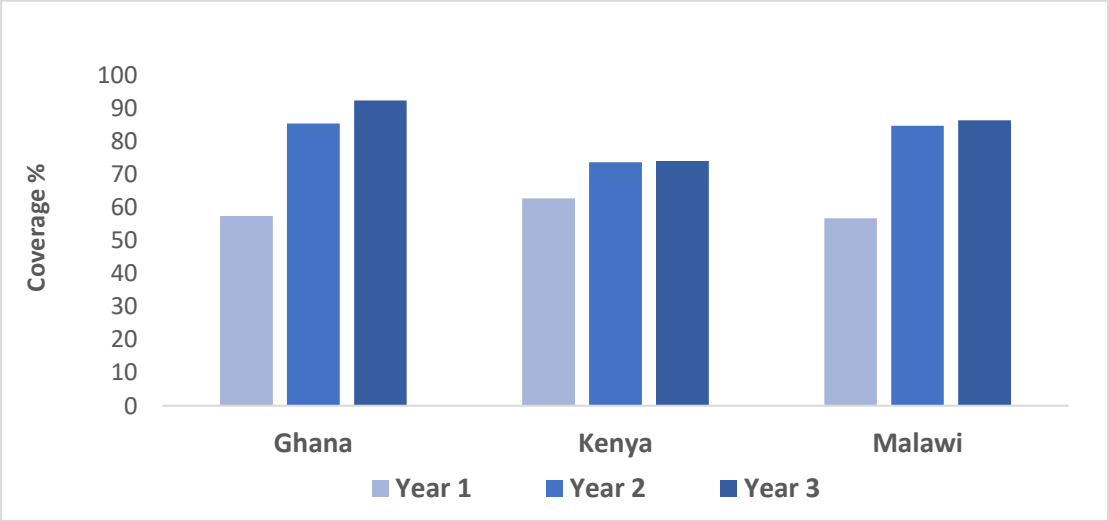


Figure 1a. Average WHO/UNICEF (as of 15 July 2018) estimated first year of life vaccine coverage in Ghana, Kenya, and Malawi during first 3 years following introduction, including the year of introduction (**third dose pneumococcal vaccine, Haemophilus influenza type b vaccine, and second dose rotavirus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

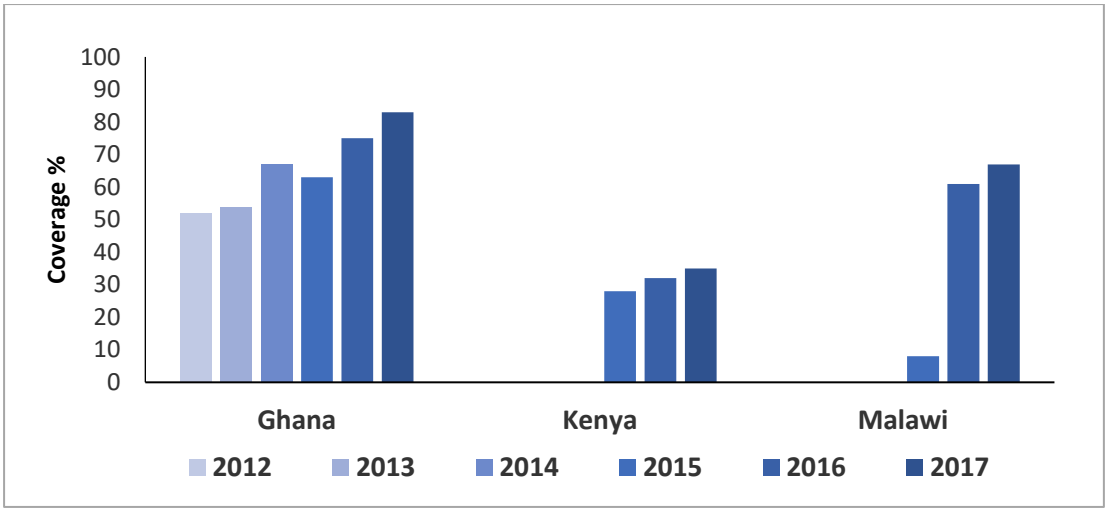


Figure 1b. **Second dose measles-containing vaccine** WHO/UNICEF estimated coverage (as of 15 July 2018) in Ghana, Kenya and Malawi, 2012-2017. The first year shown for each country is the year of introduction.

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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