

Annex B

Background on the RTS,S/AS01 malaria vaccine

Prepared for
Gavi Board and Committee Members

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This document draws on a background brief prepared in advance of a stakeholder meeting convened by WHO in October 2019 to discuss the RTS,S/AS01 malaria vaccine.

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This document is being provided as background information; it is not an official WHO publication.

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Annex B: Background on the RTS,S/AS01 malaria vaccine

This document provides an overview of the development and status of the RTS,S/AS01 malaria vaccine, including the latest data and other evidence. Based upon this information, it outlines the important role the vaccine could play—if recommended by the World Health Organization (WHO) for wider use—as an additional tool to reduce the burden of malaria in young children, those at highest risk of severe disease and death. As part of the evidence base provided, the document references some information and statements shared at a stakeholder meeting on RTS,S/AS01 convened by WHO in Geneva in October 2019.

Overview

Following 15 years of progress in bringing down malaria illness and death since 2000, progress has stalled, particularly in sub-Saharan Africa (see Figure 1). There is a consensus that new tools are needed—as well as more effectively targeted use of existing tools—to get malaria control back on track.¹

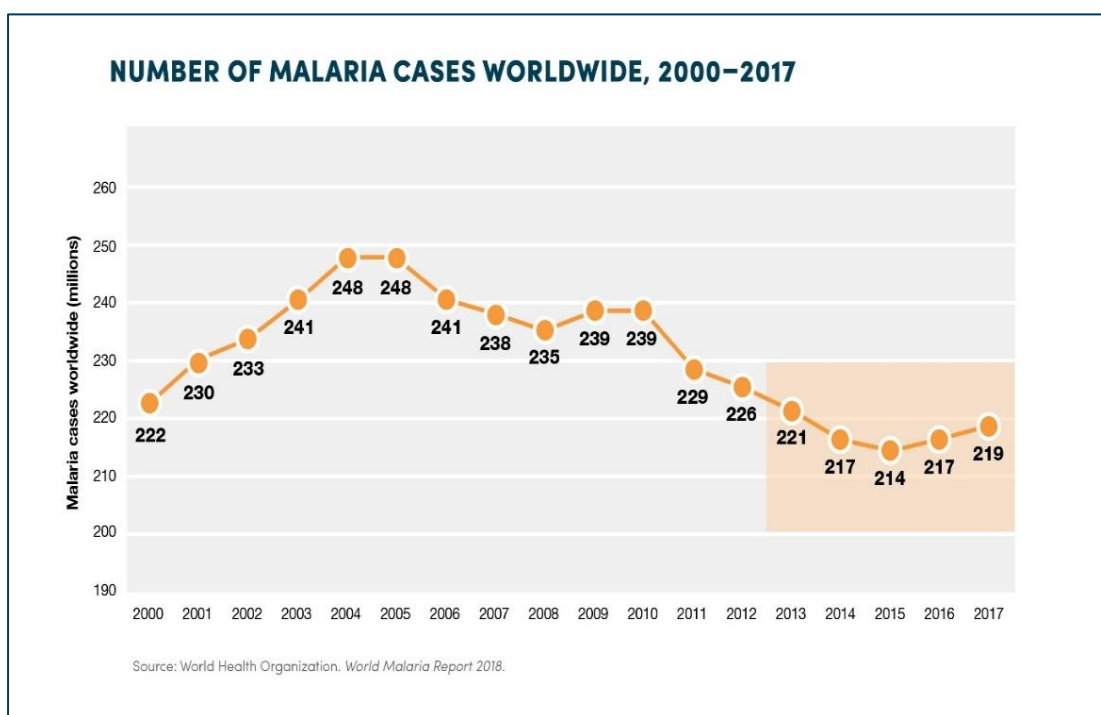


Figure 1. Number of malaria cases worldwide, 2000–2017.

The RTS,S/AS01 vaccine has successfully completed clinical evaluation and regulatory review and has been introduced in selected areas of Ghana, Kenya and Malawi as part of the Malaria Vaccine Implementation Programme (MVIP). The vaccine appears to have a similar efficacy to that provided by insecticide-treated mosquito nets (ITNs) and utilizes the successful childhood immunization delivery system—which can rapidly reach children across socioeconomic strata. Taking into account its demonstrated efficacy against clinical malaria, severe malaria, and hospitalization, the RTS,S/AS01 malaria vaccine has the potential to reduce illness and death considerably in areas with the greatest burden of the disease, and thereby has the potential to contribute to economic growth, equity, protection from catastrophic healthcare costs and poverty reduction. The addition of this vaccine to currently recommended malaria control tools could help accelerate the achievement of a number of the Sustainable Development Goals (SDGs), including SDGs on poverty, health and well-

being, equity, and economic growth (see [Appendix 1](#)). Data from the MVIP will inform a WHO policy recommendation on broader use of the vaccine, which may be considered as early as late 2021.

The disease

Malaria is a parasitic disease caused by the highly adaptable *Plasmodium* parasite. The deadliest malaria parasite for humans is *P. falciparum*, which is most prevalent and takes its greatest toll in sub-Saharan Africa. Worldwide, despite remarkable progress between 2000 and 2015 in bringing down the burden of disease, there are still more than 200 million cases and 400 000 deaths annually; more than half of deaths are among African children under 5 years of age.² As is the case with other health conditions, it is the poorest children—the most vulnerable population—who are at greatest risk of malaria illness and death, and whose families face the greatest economic hardships from a case of malaria, be it uncomplicated or severe.

The impact of imperfect tools, used imperfectly

For the prevention of malaria, WHO recommends the use of ITNs in all malaria-endemic settings or, where appropriate, the application of indoor residual spraying, and in specific population subgroups in sub-Saharan Africa, chemoprevention (i.e., pregnant women, children and other high-risk groups).³ ITNs are the cornerstone of malaria prevention efforts; they have been shown to reduce the frequency of uncomplicated and severe malaria episodes by 45%.⁴ In 2017, 72% of households in sub-Saharan Africa had at least one ITN, but only 50% of the population reported sleeping under an ITN (Figure 2).⁵ Despite continued efforts, ITN coverage has increased only marginally over the past 3 years and remains far from the target of universal coverage.⁶ Fewer people at risk of malaria are protected by indoor residual spraying (IRS), which reached 6.6% (64 million people) in the WHO Africa Region in 2017.⁷

Despite the moderate level of protection and the suboptimal levels of coverage achieved, ITNs were estimated to have been responsible for 68% of the reduction in malaria burden between 2000 and 2015.⁸ This is an example of how the imperfect application of an imperfect malaria control tool yielded unprecedented public health benefits.

The need for new tools

As malaria has reduced across sub-Saharan Africa, malaria burden has become more heterogeneous and it is evident that a “one size fits all” approach to malaria control is no longer appropriate. Use of ITNs has plateaued at 50%; reaching and maintaining levels of ITN use above 65% in any country is challenging. Moreover, while not yet well documented, marginal costs associated with achieving higher coverage are likely to increase.^{9,10} Efforts to increase ITN coverage must continue, together with employing more targeted or “tailored” approaches to the use of all malaria interventions. However, because the efficacy of ITNs is imperfect, at 45%, increasing ITN coverage alone will not be sufficient to reach the Global Technical Strategy for Malaria (GTS) goal of a 90% reduction in malaria case incidence and death rates by 2030.

In light of the stalling of progress in combatting malaria recorded over the past few years—particularly in sub-Saharan Africa—there is near-universal consensus that new tools are needed, together with more effectively targeted use of existing tools and increased financial resources, to get malaria control back on track.¹¹

The likelihood of other, new and transformative tools becoming available within the next decade was a topic of discussion at the October 2019 stakeholder meeting. Malaria experts noted the vibrant portfolio of tools under development, including attractive toxic sugar baits, house modifications, drugs, monoclonal antibodies and gene-drive products. They emphasized that development, evaluation and deployment of another new tool is at least 5 to 7 years away (assuming development is successful), and that it is likely that any new tools would also offer partial protection (see [Appendix 2](#)).

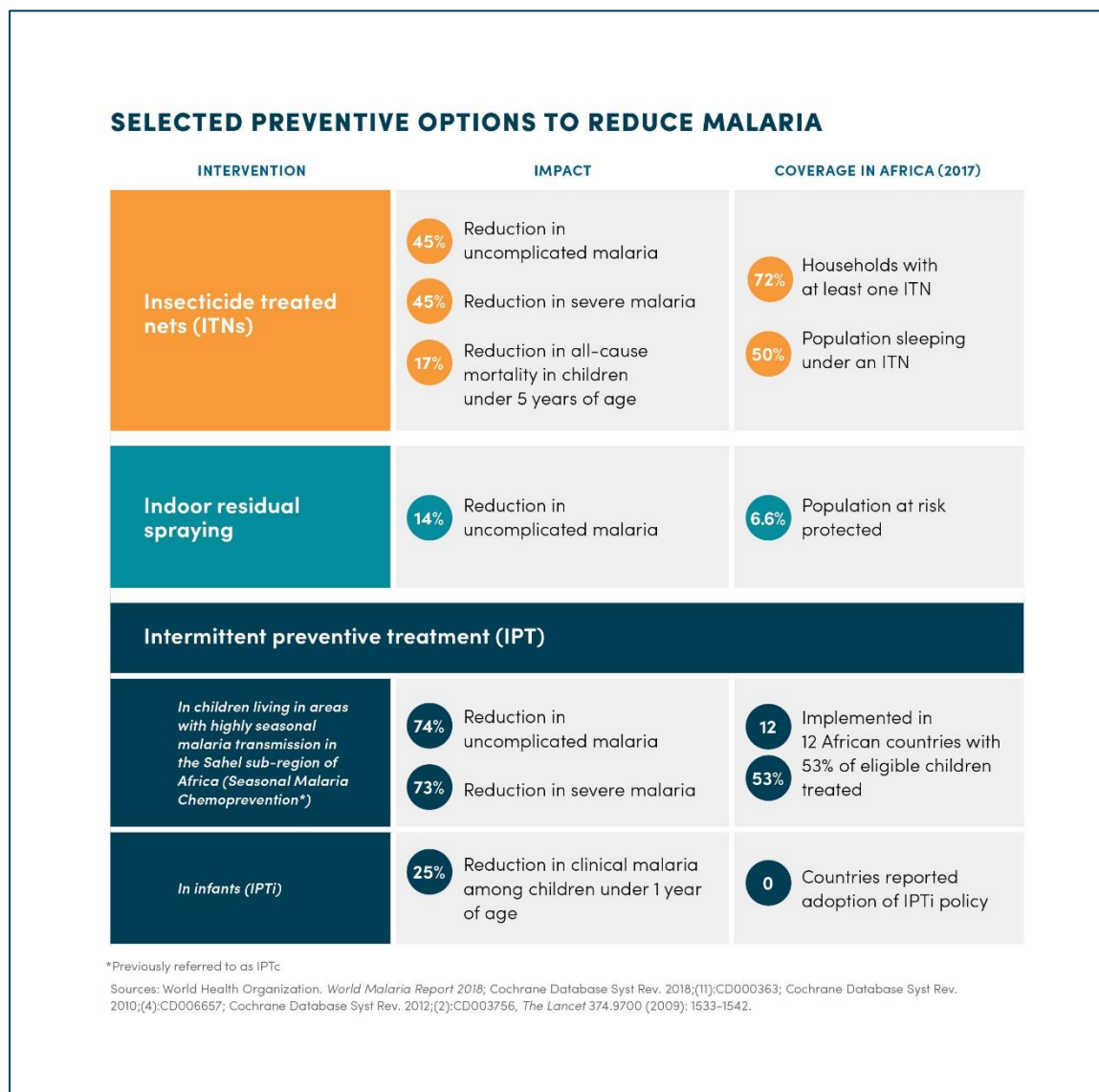


Figure 2. Selected preventive options to reduce malaria.

The vaccine

The RTS,S/AS01 malaria vaccine (often referred to as simply “RTS,S”)* is the first vaccine to successfully complete large-scale Phase 3 testing in the field, to be reviewed by a WHO-Listed (Regulatory) Authority (WLA), and to be recommended for pilot introduction by WHO. In this

* The letters in “RTS,S” represent the proteins or antigens that make up the RTS,S particle. The vaccine also contains GSK’s proprietary AS01 adjuvant system, and in scientific papers is usually referred to as RTS,S/AS01.

document, the term RTS,S/AS01 will be used to ensure clarity around references to the vaccine versus its components either the RTS,S antigen or AS01 adjuvant.

Current status of the RTS,S/AS01 malaria vaccine

The RTS,S/AS01 malaria vaccine, intended for use in children and rigorously tested in sub-Saharan Africa, is currently in pilot introduction in selected high-burden areas of Ghana, Kenya and Malawi. Ministries of health in the three countries are leading implementation of the vaccine through their routine immunization programmes, while WHO is responsible for overall coordination and technical oversight—including of the evaluation components that constitute the larger Malaria Vaccine Implementation Programme (MVIP).

The MVIP is designed to generate data and experience on the routine use of the vaccine to inform a WHO policy recommendation on future use of the vaccine and subsequent decisions on vaccine financing. It was designed to be a 6-year programme (2017–2023), with two funding phases to align with donor funding cycles. In 2016, Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid collaborated to provide US\$ 49.2 million for the first 3.5 years of the programme (2017–2020). Preparations for the pilot programme were initiated by WHO in 2017 and vaccinations started in 2019. Commitments of funding for 2021–2023 are needed by the end of 2019, or shortly thereafter, to ensure completion of the pilot implementations and evaluation components that will inform WHO policy recommendations.

The MVIP aims to vaccinate at least 1 million children in selected areas of the three countries to deliver data on safety and feasibility of the vaccine in the context of routine use. It will also generate data on impact before its completion in 2023. A recommendation on future use of the vaccine is possible as soon as late 2021, depending on how quickly safety data become available.

If data from the pilots are favourable, showing the vaccine to be safe and impactful, and WHO recommends RTS,S/AS01 for wider use across sub-Saharan Africa, it will be important that vaccine supply remain available in the pilot countries and be available for introduction in countries or areas where impact would be highest and children would most benefit.

Efficacy and safety

The Phase 3 programme

The Phase 3 programme to evaluate the RTS,S/AS01 malaria vaccine included a large-scale efficacy and safety trial conducted at 11 research centres in seven sub-Saharan African countries. This trial, conducted between 2009 and 2014, enrolled more than 15 000 infants and young children and provided an average of 3 and 4 years of follow-up, respectively, for each of the two age categories in the trial. As illustrated in Figure 3, in children aged 5 to 17 months at first vaccination, 4 doses of the vaccine were found to:

- prevent approximately 4 in 10 cases of malaria (39%);
- prevent approximately 3 in 10 (29%) cases of severe malaria, which untreated can kill up to half of children affected;¹²
- prevent 6 in 10 (61%) cases of severe malaria anaemia, and 3 in 10 (29%) of the blood transfusions required to treat life-threatening severe anaemia; and,
- significantly reduce overall hospital admissions (by 15%) and malaria-related admissions (by 37%).¹³

The Phase 3 data indicated that, although 3 or 4 doses of the vaccine resulted in a significant reduction in clinical malaria, a fourth RTS,S/AS01 dose, given 18 months after the third dose, provided significant incremental benefit (26% incremental efficacy) against clinical malaria and was needed for sustained vaccine efficacy against severe malaria in children aged 5–17 months.

It should be noted that the benefits seen in the Phase 3 trial were in addition to those already achieved through the use of ITNs (provided to all children participating to the trial at trial start and again 22 months later), and facilitated access to prompt diagnosis and effective antimalarial treatment. **(N.B.** The benefits were measured under ideal clinical trial conditions, rather than from real-world evidence, which likely limited the ability to measure an impact on mortality or severe malaria; the desire for evidence on impact of the vaccine on child mortality was among the factors cited by SAGE and MPAC in recommending large-scale pilot implementation).¹⁴

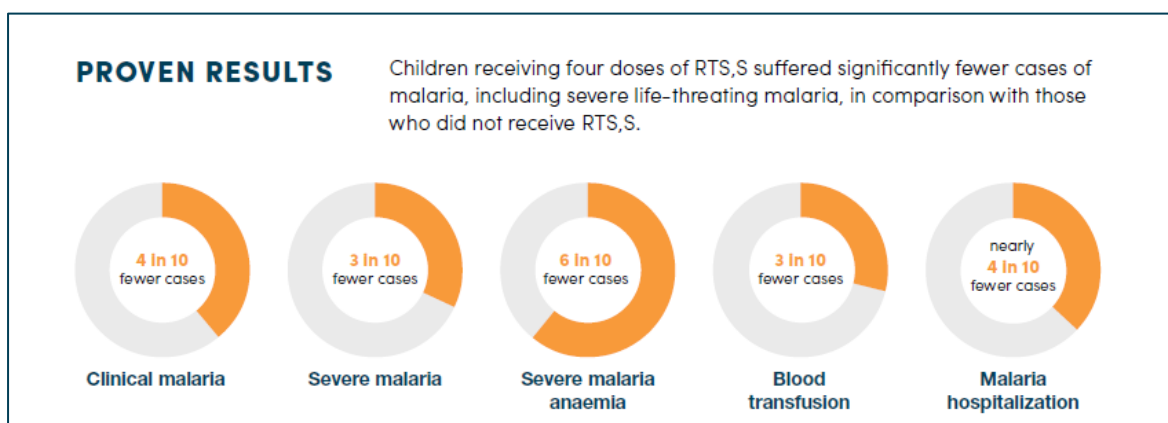


Figure 3. Proven results: Children aged 5 to 17 months at first vaccination who received 4 doses of RTS,S/AS01 experienced 61% fewer cases of severe malaria anaemia, over 4 years of follow-up.

The vaccine was found to be generally well tolerated, with adverse reactions comparable to those of other childhood vaccines, apart from a higher risk for febrile convulsions in the older age group within 7 days after a dose (with no long-term sequelae). Two potential risks were identified during the trial for which causality has not been established: meningitis (any cause) and cerebral malaria.¹⁵ A *post hoc* analysis showed that in the setting of low mortality due to facilitated access to care, there was a greater number of female deaths in those who received the vaccine compared with those who did not.

New information and insights since the 2016 WHO recommendation for pilots

Over the last several years—since the Phase 3 trial concluded in 2014 and the recommendation for pilots was adopted by WHO in 2016—further information on the long-term efficacy and safety of RTS,S has become available, as outlined below.

Following the conclusion of the pivotal Phase 3 efficacy and safety trial, a study conducted at 3 of the 11 research centres that participated in the trial sought to extend the period of follow-up from 4 years to 7 years, in part to address the question of whether a shift in malaria illness (or rebound) might occur as vaccine efficacy waned. The potential for such a shift in malaria illness to older age groups has been demonstrated with other malaria interventions after the intervention is no longer used (or in the case of a vaccine like RTS,S/AS01, when efficacy wanes). The results of the extended follow-up study, published in 2019, found sustained protection against malaria during the 7-year period in children who received 3 or 4 vaccine doses, and no imbalances in safety signals during the extended follow-up period.¹⁶

New information and insights since 2016

The following **new findings** since the end of the Phase 3 trial and the 2016 WHO recommendation for pilot implementation are reflected in a new “Framework for Policy Decision” (see page 12):

- **Efficacy positive for at least 7 years.** At 3 of 11 Phase 3 trial sites, children were followed for an additional 3 years (7 years total); vaccine efficacy remained positive for children who received 3 or 4 vaccine doses.
- **Reassuring on rebound.** The extended follow-up indicated that the period of rebound observed during the Phase 3 trial among children who received only 3 doses of vaccine resolved without an overall excess in severe malaria cases; no rebound was observed after 4 doses.
- **Review of trial data also shows rebound resolved during the Phase 3 trial.** The Phase 3 trial data (all 11 sites combined) are consistent with the extended follow-up findings. By the end of the Phase 3 trial, the risk of severe malaria was very low in all three study arms (i.e., receiving 3 doses or 4 doses of RTS,S/AS01, or the comparator vaccine), presumably due to acquired immunity. The vaccine supported children through the period of highest risk for malaria.
- **Policy decision need not be predicated on attaining high coverage, including coverage of the fourth dose.** Because children who receive 3 vaccine doses are not at increased risk of severe malaria through rebound, and because there is a benefit from 3 or 4 vaccine doses, a policy decision does not have to be predicated on attaining high vaccine coverage (including with the fourth dose). **However, a full evaluation, through 2023, is essential to understand incremental value of the fourth dose** (see pages 12 and 13).
- **Fourth dose: modelled estimates.** While the Phase 3 trial results showed a 26% incremental benefit of the fourth dose against clinical malaria over the 4-year follow-up period, mathematical models predict that when follow-up is extended to 10–15 years, over 90% of impact achieved is through the administration of the first 3 vaccine doses, with small incremental benefit of the fourth dose. **Again, the pilot implementations will assess the added benefit of the fourth dose.**
- **Safety data reassuring.** Safety data from an ongoing study of RTS,S/AS01 have shown no signals of concern and complement data being collected through the MVIP.

The data indicate that the period of rebound observed during the Phase 3 trial among children who received only 3 vaccine doses resolved without an overall excess in severe malaria cases, and no rebound was observed after 4 doses. These findings provide further reassurance that if there is a period of increased risk for severe malaria following RTS,S/AS01 vaccination (compatible with “rebound”), vaccination would still result in an overall positive effect in immunized children. Importantly, these results indicate that although the fourth dose would provide optimal benefit, children benefit from either 3 or 4 doses of the vaccine and that benefit is seen for at least 7 years after vaccination.

With respect to the meningitis safety signal, an ongoing trial of RTS,S in highly seasonal transmission settings (Burkina Faso and Mali) has not recorded any cases of meningitis in approximately 4 000 children who have received RTS,S (during more than 2 years of follow-up). The absence of meningitis

cases is reassuring, and the findings will complement data being collected through sentinel hospital surveillance in the pilot areas to establish whether meningitis is causally associated with the vaccine, or whether it could be a “chance finding”, as was noted in the European Medicines Agency’s Public Assessment Report (published in January 2015).

Safety monitoring is an integral element of the evaluation component of the MVIP, and GSK’s Phase 4 programme (Risk Management Plan) is focused primarily on following safety, including using more intensive techniques to detect any unusual health conditions, should they arise during the course of the programme (see Appendix 3).

A vaccine designed to reduce malaria illness and death

A point of discussion at the October 2019 stakeholder meeting was the fact that the long-term goal of malaria eradication and near-term reductions in malaria-specific child morbidity and mortality are both global priorities, on a continuum, contrary to the perceived tension between the two. The RTS,S/AS01 vaccine, as it is currently being delivered through childhood immunization programmes in the three implementing countries, is not a tool for elimination and eradication, but it could be a very important addition to current tools to help drive down malaria morbidity and mortality in African children. RTS,S/AS01 was developed for this purpose and had the greatest impact (during the Phase 3 trial) in areas with high malaria disease burden (and is cost-effective in areas of moderate-to-high malaria transmission). This is in contrast to a vaccine that might be developed for use in elimination and eradication efforts, as such a vaccine would target reducing malaria infection (including asymptomatic infection) in all age groups and would be used primarily in areas with low malaria incidence and relatively few cases (i.e., closer to elimination).

A similar perceived tension was noted between investments in research and development and those in program implementation. Again, it was stressed that the product development pipeline or investments in research and development should not be pitted against the need to bring existing tools to scale.

Potential public health impact

Clinical trial results and modelling point to the potential health impact of the malaria vaccine that is additional to those provided by other interventions. In the Phase 3 efficacy trial, during 4 years of follow-up in children who received 4 doses of RTS,S/AS01 from 5 months of age, thousands of cases of clinical malaria were averted per 1000 children vaccinated (range across sites 205–6565). Because children in areas of moderate-to-high parasite transmission (as measured by parasite prevalence) suffer multiple malaria episodes each year, the impact in terms of cases averted was greatest in areas with highest malaria burden: one site in western Kenya recorded more than 6500 malaria cases averted per 1000 vaccinees over the 4-year follow-up period.

Four modelling groups, working under the guidance of WHO, concluded in late 2015 that—based upon the Phase 3 trial results—the vaccine would be highly cost-effective in medium-to-high transmission settings, and could play an important complementary role in the reduction of malaria illness and death.¹⁷ They concluded that an average of 116 500 cases of clinical malaria disease and 484 deaths would be averted for every 100 000 children vaccinated with 4 doses of RTS,S/AS01. Thus, for every 200 children fully vaccinated, 1 death and 233 cases of clinical malaria that would occur in the absence of the vaccine, would be averted (over a period of 15 years).

In 2018, Gavi assessed RTS,S as a comparator to other vaccines which were being considered for investment as part of the Vaccine Investment Strategy (VIS) 2018. It was estimated that, over a period of 15 years, 49–142 million additional malaria cases would be prevented and 254 000–516 000 additional child deaths averted if the RTS,S/AS01 vaccine were added to currently used malaria control tools.¹⁸ These estimates are based upon a total projected demand of 60–80 million doses of vaccine annually, following introductions over a timeframe of 5–10 years and assuming no supply constraints. Of this estimated long-term demand, 15–20 million doses would be needed annually by Nigeria (see Figure 6 on page 11).

At the October 2019 stakeholder meeting, the results of modelling updated with the findings of the long-term (7-year) follow-up study were also shared. The mathematical models developed by Imperial College London and the Swiss Tropical and Public Health Institute suggest that the fourth dose may provide minimal added benefit and that the impact is more dependent on parasite prevalence and coverage with the first 3 doses of the vaccine.¹⁹ (Specifically, the modelling suggests that when vaccine impact is viewed over a 10–15 year time horizon, more than 90% of the impact achieved would be through the administration of the first 3 vaccine doses, with the fourth dose providing small incremental benefit.) As noted further below, more data on the public health impact of the fourth dose is expected by the time the MVIP is completed in 2023 and will inform any subsequent refinements to the WHO policy recommendation currently anticipated as soon as late 2021 (see the section on the policy pathway, starting on page 11).

Increased coverage and reach, including to the poorest children

In general, childhood vaccines have high and broad reach across socioeconomic strata. Although the RTS,S vaccine is delivered outside the current childhood vaccine schedule, we will learn about uptake through the pilot implementations. This reach suggests that while the malaria vaccine can provide added protection to individuals using ITNs or covered by IRS, it also has the potential to reach children who have not yet been reached by other malaria control interventions. These are often children who face the greatest obstacles to care and, as a result, are at highest risk of malaria. Vaccines also tend to rapidly achieve high coverage, including among the poorest children (see Figure 4).

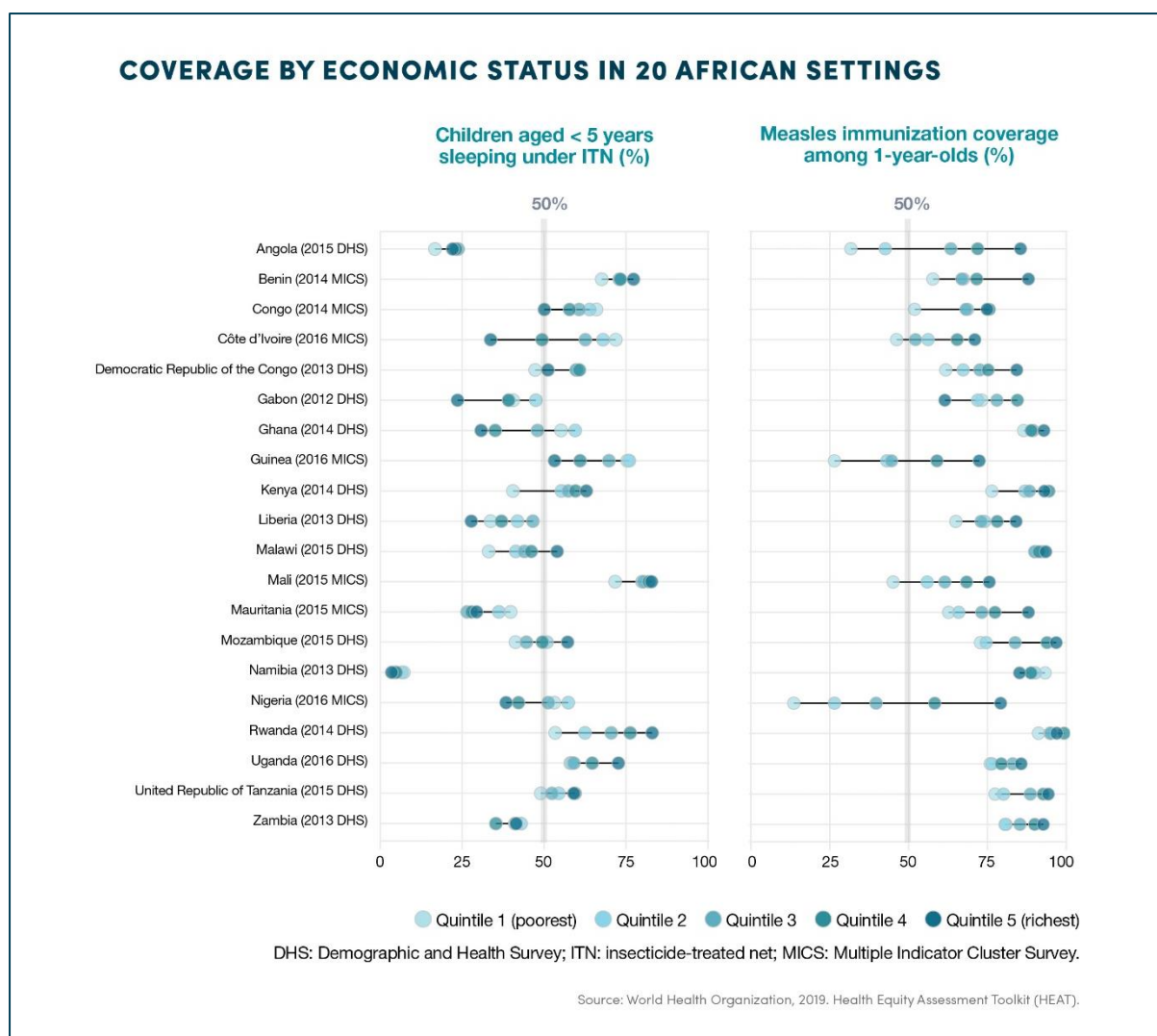


Figure 4. Coverage of insecticide-treated nets and measles immunization by economic status in 20 African settings.

Cost-effectiveness/economic evaluation

Vaccines are considered among the most impactful public health tools available, and vaccines and malaria control tools are among the most cost-effective interventions in public health. In addition to the research cited above, a paper published in 2017 predicted that the vaccine would substantially reduce malaria burden in children and would be highly cost-effective in most countries (based upon a price of US\$ 5.00 per dose [range of US\$ 2–10]).^{20,21} In the 2018 Vaccine Investment Strategy, Gavi assessed RTS,S as providing value for money in comparison with other vaccines; for a future Gavi investment decision regarding whether to support broader use of RTS,S it will be important to establish the cost-effectiveness of RTS,S relative to other malaria interventions and to update projections of financial implications.²² At the October 2019 stakeholder meeting, it was also noted that the vaccine would remain cost-effective even at double or more the price assumed by modelers.

Modelling has also shown the vaccine's cost-effectiveness to compare favourably with other recommended malaria prevention tools, as illustrated in Figure 5. The four modelling groups mentioned above concluded that the cost-effectiveness ranges for the vaccine (cost per disability-adjusted life year averted) overlapped with the cost-effectiveness ranges for other malaria control interventions, such as bed nets and indoor residual spraying.

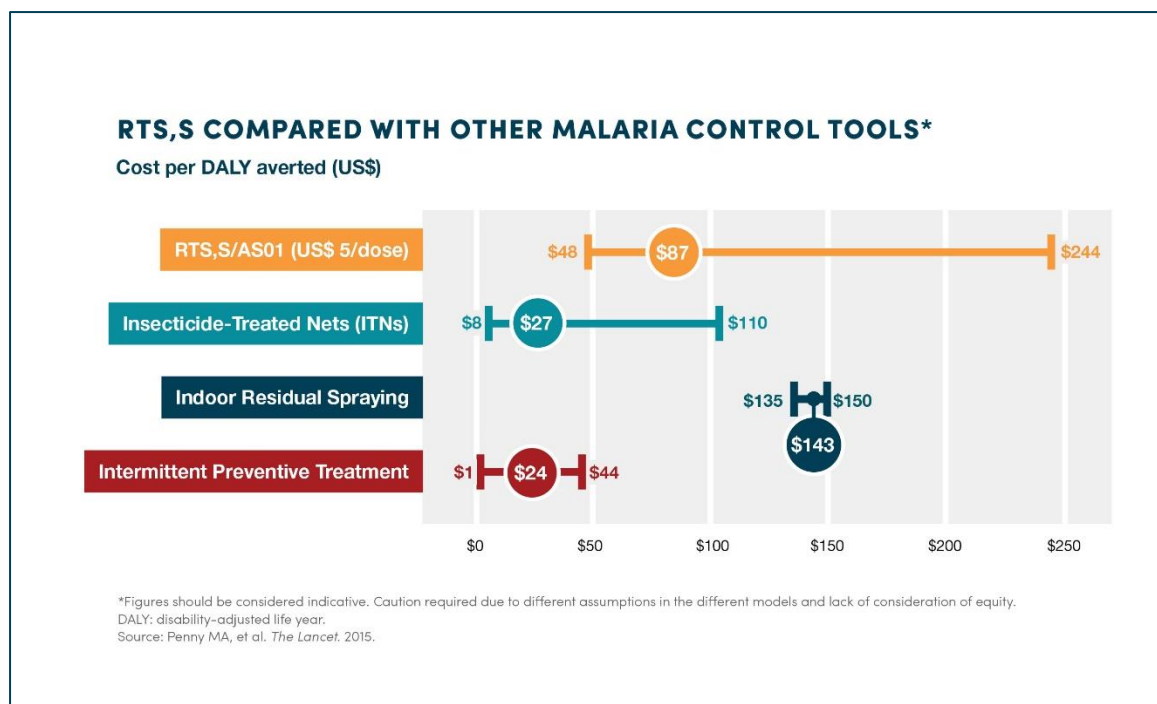


Figure 5. RTS,S/AS01 compared with other malaria control tools: cost-effectiveness ranges overlap, using a hypothetical price of US\$ 5.00 per dose.

Potential demand for the vaccine

There are approximately 15–20 million infants who live in areas of moderate-to-high malaria transmission (defined as *Plasmodium falciparum* parasite prevalence above 10%), which translates into a long-term potential demand of 60–80 million doses annually (based on a 4-dose schedule and 2017 disease burden estimates), as illustrated in Figure 6.²³ This demand forecast assumes no change in malaria epidemiology in the long term, although it is important to note that demand is greatly influenced by the definition of population at risk and the sequence of country introductions. It is estimated that 10 countries would make up approximately 80% of the demand for RTS,S/AS01. The potential demand for the vaccine will also need to factor in the introduction of other new malaria interventions and/or demographic changes.

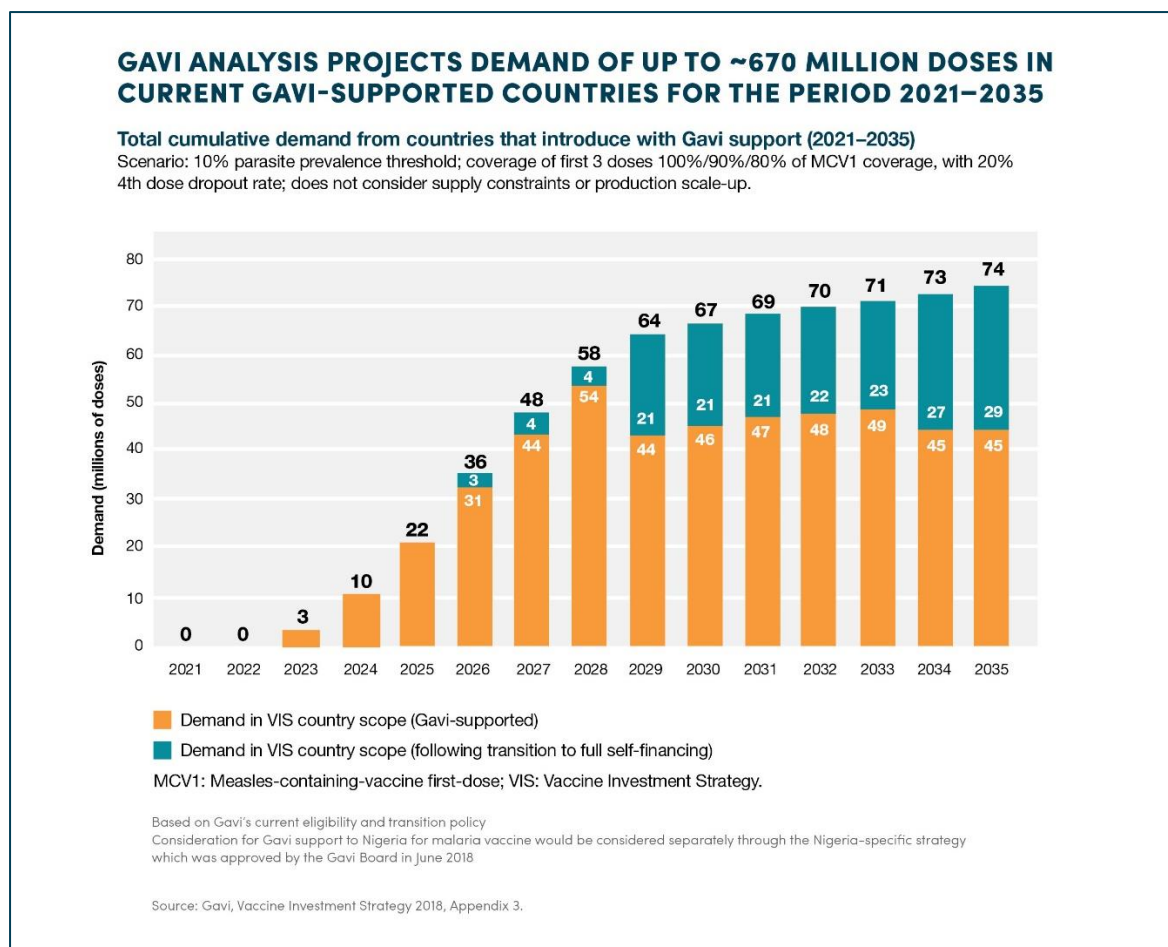


Figure 6. Gavi analysis projects demand of up to ~670 million doses in current Gavi-supported countries for the period 2021–2035.

Pathway to access and related challenges

In the event of a WHO policy recommendation supportive of wider vaccine use, access to RTS,S could be expected to follow the typical vaccine financing and procurement pathway to availability in endemic regions in sub-Saharan Africa. However, given that the anticipated timing of policy, financing and supply decisions for the vaccine will not be fully aligned, key decisions for public health goals may need to be taken in the absence of full information.

Regulatory status and 2016 WHO recommendation for pilots

In July 2015, the European Medicines Agency (EMA) provided a positive scientific opinion under Article 58 (a formal EMA procedure to evaluate vaccines not intended for use in Europe), stating that the vaccine is likely to be beneficial and that its benefits outweigh potential risks, and that "...the benefits of vaccination may be particularly important among children in high-transmission areas in which mortality is very high." Following the EMA decision, WHO's advisory committees for malaria and for immunization—the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC)—jointly called for a pilot implementation of the vaccine in settings of moderate-to-high malaria parasite transmission in sub-Saharan Africa.²⁴ WHO officially adopted the SAGE/MPAC recommendation in January 2016, recognizing the considerable public health potential of the vaccine while also acknowledging the need for further evaluation before considering its widescale deployment.²⁵ Following a joint review coordinated by WHO, regulatory

authorities in the three implementing countries (Malawi, Ghana and Kenya) approved the vaccine for use in the context of the MVIP.

As part of the 2015 review process for RTS,S/AS01, the Joint Technical Expert Group (JTEG), comprised of MPAC and SAGE members, advised WHO to monitor emerging data from the MVIP, noting that “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.” 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.” There also was no guidance as to how impact data should be incorporated into the policy decision.

To clarify the expectations and relative contribution of the collected data (feasibility, safety, impact) to a future policy recommendation, MPAC and SAGE endorsed, during their April 2017 meetings, the establishment of a working group to develop a “Framework for Policy Decision for RTS,S/AS01 Malaria Vaccine.” The working group[†] reviewed the data and other information that led to the 2016 WHO recommendation for pilots, and the information that has emerged since then (as outlined above). They also reviewed policy positions taken by WHO on other vaccines and malaria interventions, to ensure that consideration of RTS,S/AS01 aligned with the approach taken previously. The group presented the Framework to SAGE and MPAC in April 2019, and it was endorsed by both groups.

Future WHO policy recommendation

Based on the April 2019 SAGE/MPAC endorsement, WHO has concluded that a recommendation on future use of the vaccine could be made as soon as late 2021, depending on how quickly safety data from the pilots become available (see Figure 7). A

A framework for WHO policy decision

In April 2019, SAGE and MPAC endorsed a policy decision framework clarifying how and when data from the MVIP will be used to inform a future WHO policy recommendation for broader use of RTS,S/AS01, and WHO subsequently adopted the framework. The framework outlines a stepwise approach: a policy recommendation could be considered as soon as concerns regarding safety signals observed in the Phase 3 trial are satisfactorily resolved and data trends in either severe malaria or mortality are assessed as consistent with a beneficial impact of the vaccine. Refinements to the policy recommendation could be made following the completion of the pilots in 2023, based upon data regarding the incremental public health value of the fourth dose and the vaccine’s impact on mortality.

This stepwise approach ensures that a policy decision is made as soon as the risk-benefit of the vaccine in routine use can be established with the necessary level of confidence and that the vaccine would not be unnecessarily withheld from countries in need, if it is found to be beneficial. SAGE and MPAC stressed the importance of the pilots being completed to establish the public health value of the fourth dose and assess the vaccine’s impact on mortality.

[†] Working group members: Quique Bassat (Immunization and vaccines related implementation research advisory committee [IVIR-AC]), Gabriel Carrasquilla (MPAC), Umberto D’Alessandro (MPAC), Eusebio Maçete (MVIP Programme Advisory Group [PAG]), Kim Mulholland (MVIP PAG), Terry Nolan (SAGE member until October 2018), Melissa Penny (Modelers), Peter Smith (Chair, MVIP PAG), Fred Were (SAGE).

positive WHO recommendation in 2021 for broader vaccine use in sub-Saharan Africa, if accompanied by a funding decision, would signal the need for vaccine supply.

Refinements to the policy recommendation for the malaria vaccine could be made following completion of the pilots in 2023, based upon data regarding the incremental public health value of the fourth dose and the vaccine's impact on mortality. High coverage is not considered a pre-condition for a positive recommendation, as vaccine coverage increases over time and reaching high vaccine coverages typically take years to achieve.

Country adoption decisions

In the event of a positive WHO recommendation endemic countries would start the process of deciding whether to introduce the vaccine, in line with their national policymaking and regulatory processes. Such decisions will need to be coordinated with the EPI and malaria control programmes, considering factors such as levels of malaria transmission, the use and coverage other malaria control interventions, and in what context the vaccine could best complement other tools as part of a package of interventions, as well as the priorities and strength of the national immunization programmes. Positive decisions would also require appropriate national planning, including financial planning. Final adoption decisions by countries would likely take place following a global level financing decision. Although not a concrete signal of demand, it is worth noting that 10 countries expressed interest in participating in the pilot programme and several countries have already expressed their continued interest in the vaccine. The potential demand for the vaccine on the part of African endemic countries was also in evidence at the October 2019 stakeholder meeting.

Global financing decisions

As noted above, in the event of a positive WHO recommendation, global-level vaccine financing and procurement mechanisms would consider supporting the vaccine's availability in endemic regions of sub-Saharan Africa. Since 2013, Gavi has included the malaria vaccine in its vaccine investment strategy and is expected to review the modalities of its potential funding support for broader vaccine roll-out following a WHO policy recommendation and in coordination with other agencies with malaria investments, such as the Global Fund and Unitaid. (Discussions among Gavi, Global Fund and Unitaid regarding future direction have begun, in keeping with the intent of the Global Action Plan for Healthy Lives and Well-being for All, launched in September 2019.)

Vaccine supply

GSK restarted the dedicated manufacturing facility that produces the RTS,S vaccine antigen to donate up to 10 million doses of vaccine for use in the MVIP.[‡] These doses are expected to fulfil vaccine demand in the pilot countries through the completion of the pilots in 2023 and (in the event of a positive policy recommendation in late 2021) allowing for expansion into comparator and other areas of the three countries. Depending on the timing of funding decisions and other factors, additional vaccine doses could be needed in the pilot countries as soon as 2023, and in additional countries as soon as 2024. GSK has already committed to supply up to 15 million doses of vaccine per year, at a price of cost plus a mark-up of no more than 5%, to the end of 2028 (assuming demand) if a WHO recommendation and subsequent adoption and financing decisions are positive.

[‡] The donation doses are part of global access commitments agreed between PATH and GSK prior to the provision of funding to support the Phase 3 efficacy and safety trial and other Phase 3 studies (this funding was provided by the Bill & Melinda Gates Foundation to PATH).

In addition, to enable long-term sustainable supply, GSK has committed to transfer the product—including bulk antigen production, filling, lyophilization, and packaging, as well as the product license—to another vaccine manufacturer, excluding GSK’s proprietary adjuvant necessary for the vaccine, which GSK has agreed to supply at a price of cost plus a mark-up of no more than 5% through 2042. The process of identifying another vaccine manufacturer, working through the product transfer, and meeting associated technical and regulatory milestones will take several years. GSK, PATH and WHO are already working to identify this manufacturer, concurrent with the pilot programme.

The current manufacturing strategy calls for GSK to provide the vaccine until 2028, with the future manufacturer (product transfer recipient) taking over by 2028.

Key challenges to access

Challenges in planning for timely supply of the vaccine have arisen in a situation where a policy recommendation is pending and, therefore, demand is uncertain. This situation has resulted in a mismatch of timing between financing decisions and manufacturing/supply decisions. Figure 7 illustrates the various timelines and the resulting uncertainty for vaccine supply.

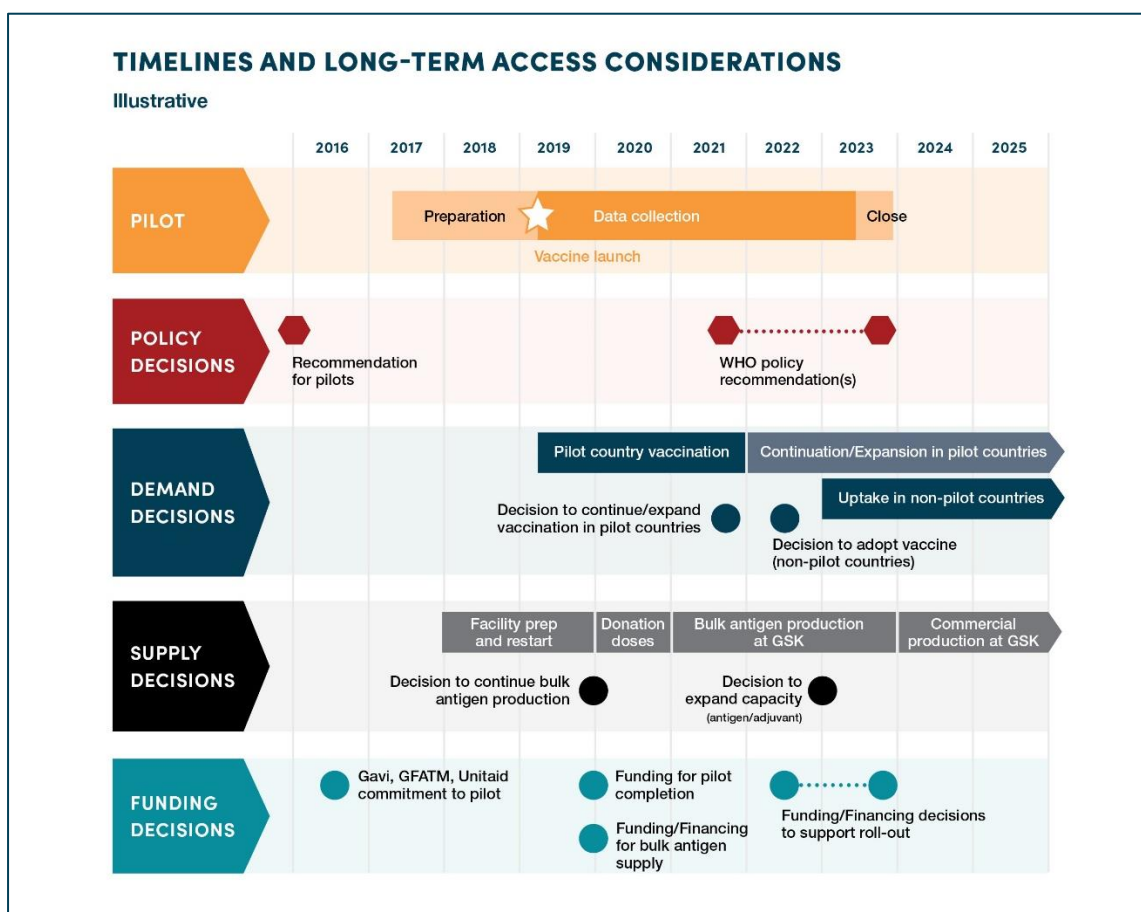


Figure 7. Timelines and long-term access considerations for the RTS,S/AS01 malaria vaccine (illustrative).

The malaria vaccine as a potential, complementary tool for added protection against malaria

The RTS,S/AS01 malaria vaccine is a new tool that could be delivered through national immunization programmes, and thereby has the potential to rapidly reach high levels of coverage, including reaching poorer children who are at highest risk of dying of malaria. At a time when emerging insecticide and drug resistance threaten current malaria prevention tools, the vaccine has the added benefit of being neither insecticide- nor drug-based. The independent Malaria Policy Advisory Committee (MPAC) advising WHO, adopted a statement in August 2019, that “A malaria vaccine such as RTS,S has the potential to help get malaria control back on track and may prove to be an important addition to current control tools.” (See [Appendix 2](#) for the full MPAC statement.)

Appendix 1. The RTS,S/AS01 malaria vaccine and its potential contributions to achievement of the Sustainable Development Goals and other internationally agreed goals

The addition of a new class of tools to the tool kit used against malaria could have powerful, positive impact, given the toll malaria takes on health, wealth and overall socioeconomic development. Here we outline some of the ways that the RTS,S/AS01 malaria vaccine could contribute to the achievement of internationally agreed upon goals.

Internationally agreed goal	Potential impact of a new tool: The RTS,S/AS01 malaria vaccine
Sustainable Development Goal (SDG) 1 No poverty	A reduction in clinical malaria will result in a reduction in associated direct and indirect costs to families, communities and nations. Preventing malaria protects household income from lost earnings and the costs of seeking care. A 10% reduction in malaria has been associated with a 0.3% rise in annual GDP and faster GDP growth. ²⁶ The impact is even greater in high-burden, low-income countries, where the same reduction was associated with a nearly 2% increase in GDP per capita. In 2015, the Roll Back Malaria Partnership calculated the benefits of achieving the 2030 malaria targets for reducing malaria illness and death at US\$ 4 trillion. ²⁷
SDG3 Good health and well-being	By reducing both clinical malaria and severe cases, child health would benefit directly from the addition of a vaccine to current control measures, while the overall well-being of families would benefit from the knowledge that their young children have added protection from this debilitating illness.
SDG 5 Gender Equality	In some communities, boys are more likely than girls to be brought for malaria treatment, while immunization programmes tend to be gender neutral.
SDG 8 Decent work and economic growth	Malaria negatively affects economic growth. Even children with uncomplicated malaria suffer days of high fevers, chills, severe muscle aches, and headaches, and frequently vomiting or diarrhoea. Parents miss work or older siblings miss school, which is a cause for some of the negative economic impact from malaria. Further prevention of malaria cases is expected to increase economic growth.
SDG 10 Reduced inequities	Malaria disproportionately affects the poor, who are the most likely to suffer from and die of malaria. The poorest people tend to have the least access to malaria preventive tools (including ITNs) and to treatment services. Because vaccines routinely reach high coverage, including relatively high coverage among the poorest children, the addition of the RTS,S/AS01 vaccine could help reduce inequities.

Internationally agreed goal	Potential impact of a new tool: The RTS,S/AS01 malaria vaccine
SDG 17 Partnerships for the goals	<p>The pilot introduction of the first malaria vaccine has fostered new and stronger partnerships. The MVIP brings together ministries of health, international organizations, academic and non-governmental organizations, and the corporate sector; it has benefited from an unprecedented collaboration among three major international funding bodies—Gavi, the Global Fund, and Unitaid—and it relies upon effective coordination between malaria and immunization programmes, within both health ministries and participating organizations. As such, the MVIP experience establishes networks that can serve future efforts to implement the Global Action Plan for Healthy Lives and Well-being for All.</p>
Global Technical Strategy for Malaria (GTS) Goal (2030): Reduce malaria incidence globally compared with 2015	<p>When added to currently recommended malaria control measures, RTS,S/AS01 could lead to significant reductions in the tens of millions of clinical malaria episodes that occur each year.</p>
GTS Goal: Reduce malaria mortality rates globally compared with 2015	<p>While the GTS target of a 40% reduction in malaria mortality by 2020 is not expected to be achieved, the malaria vaccine—if recommended for wider use as an additional malaria control tool—could help put efforts back on track for 2030.</p>
GTS Goal: Reduce antimicrobial resistance	<p>Malaria is the primary diagnosis for a majority of childhood visits to health facilities and a third of paediatric hospitalizations. A significant reduction in malaria febrile illness and associated health facility could have a marked impact on community-wide antimalarial and antibiotic use and thus on antimicrobial resistance. Malaria is a common comorbidity to other illnesses and a risk factor for non-typhoid salmonella, the most common cause of bacteraemia in sub-Saharan African hospitals. Ministries of health are now facing the emergence of multidrug resistance among non-typhoid salmonella, with only expensive broad-spectrum antibiotics available for treatment in many areas.²⁸</p>

Appendix 2. Statement by the Malaria Policy Advisory Committee (MPAC) on the RTS,S/AS01 malaria vaccine

Released on 26 August 2019

Globally, 219 million cases of malaria were reported in 2018, and an estimated 435 000 people, including 260 000 African children, died from malaria in 2017. Scale up of WHO-recommended preventive measures resulted in a substantial decline in malaria morbidity and mortality between 2000 and 2015. However, in 2015 and 2016, progress with malaria control stalled and started to reverse, with an upswing in malaria cases, particularly in sub-Saharan Africa. A malaria vaccine such as RTS,S has the potential to help get malaria control back on track, and may prove to be an important addition to current control tools. The RTS,S vaccine, with its reported level of efficacy, has been shown to provide substantial and significant added protection on top of that provided by optimal case management and high coverage of insecticide-treated mosquito nets (ITNs), reducing clinical malaria by 55% during the 12 months following primary vaccination, and by 39% over 4 years. Recent data from long-term follow-up are reassuring regarding its long-term efficacy and safety. The well-established Expanded Programme on Immunization can reach even the poorest children, who are generally at highest risk of malaria, and suffer the highest mortality rates.

The opportunity to evaluate the feasibility of delivery, safety and effectiveness of the RTS,S vaccine, through pilot implementation in three countries, comes at a critical time in malaria control: no other malaria vaccine has entered phase 3 clinical trials. Additional preventive tools are in the development pipeline, and MPAC looks forward to reviewing their potential to reduce the malaria burden. However, the development, evaluation and deployment of these new tools is expected to take several years. Moreover, it is likely that they will also offer only partial protection.

At a time when the downward trend in malaria cases and deaths has stalled, when our current control efforts are threatened by resistance, and when no new intervention approaching the efficacy of RTS,S is available, MPAC looks forward to reviewing the results of the pilot implementations, in accordance with the Framework for Policy Decision on RTS,S/AS01 approved at the April 2019 MPAC and SAGE meetings. If these results are promising, the RTS,S vaccine, in combination with ITNs and other control measures, is likely to be an important additional tool to change the course of malaria incidence and reduce malaria deaths in African children.

The Malaria Policy Advisory Committee (MPAC) was established in 2011 to provide independent advice to WHO on developing policy recommendations to control and eliminate malaria. An independent advisory group bringing together the world's foremost experts on malaria, the MPAC provides strategic technical guidance to WHO Director-General as part of a transparent, responsive and credible policy-setting process on malaria.

More information on MPAC:

<https://www.who.int/malaria/mpac/background/en/>

More information on the pilot implementation of the malaria vaccine:

https://www.who.int/immunization/diseases/malaria/malaria_vaccine_implementation_programme/en/

Appendix 3. Additional information on the Malaria Vaccine Implementation Programme

The Malaria Vaccine Implementation Programme (MVIP) was established to support the pilot implementation of the RTS,S/AS01 vaccine through routine immunization programmes in selected areas of Africa. Data from the MVIP will inform a WHO policy recommendation on the vaccine's potential deployment on a broader scale.

In 2015, the WHO issued a call for expressions of interest for African Ministries of Health to collaborate: of the ten countries that applied, three were selected, based upon standardized criteria, which included having strong immunization and malaria control programmes.

Ministries of health in the pilot countries are leading vaccine introduction, supported by WHO and in collaboration with in-country and international partners, including PATH, a non-profit organization, and GSK, the vaccine manufacturer (see Figure 8). WHO is responsible for coordination and technical/scientific oversight of the MVIP and also supports ministries of health as they introduce the vaccine. PATH provides technical and project management support for the MVIP and is leading studies on healthcare utilization and the economics of vaccine implementation. GSK is donating up to 10 million doses of RTS,S/AS01 for use in the MVIP and is leading additional studies to continue monitoring the vaccine's safety and effectiveness in routine use.⁵ Financing for the MVIP has been mobilized through an unprecedented collaboration between three major global health funding bodies: Gavi, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

The MVIP's aim is to vaccinate approximately 360 000 children per year in the selected areas across the three countries, and is intended to evaluate:

- the feasibility of delivering the required four doses of the vaccine in routine settings;
- the vaccine's potential role in reducing childhood deaths; and,
- the vaccine's safety profile in the context of routine use.

The pilot studies will use sentinel hospital surveillance, community-based mortality surveillance and three household surveys to collect the data. The qualitative health assessment (Healthcare Utilization Study) and economic analyses are commissioned by PATH, and GSK is the sponsor of Phase 4 studies, which will continue to assess the safety, effectiveness and impact of the vaccine.

⁵ The donation doses are part of global access commitments agreed between PATH and GSK prior to the provision of funding to support the Phase 3 efficacy and safety trial and other Phase 3 studies (funding was provided by the Bill & Melinda Gates Foundation to PATH).

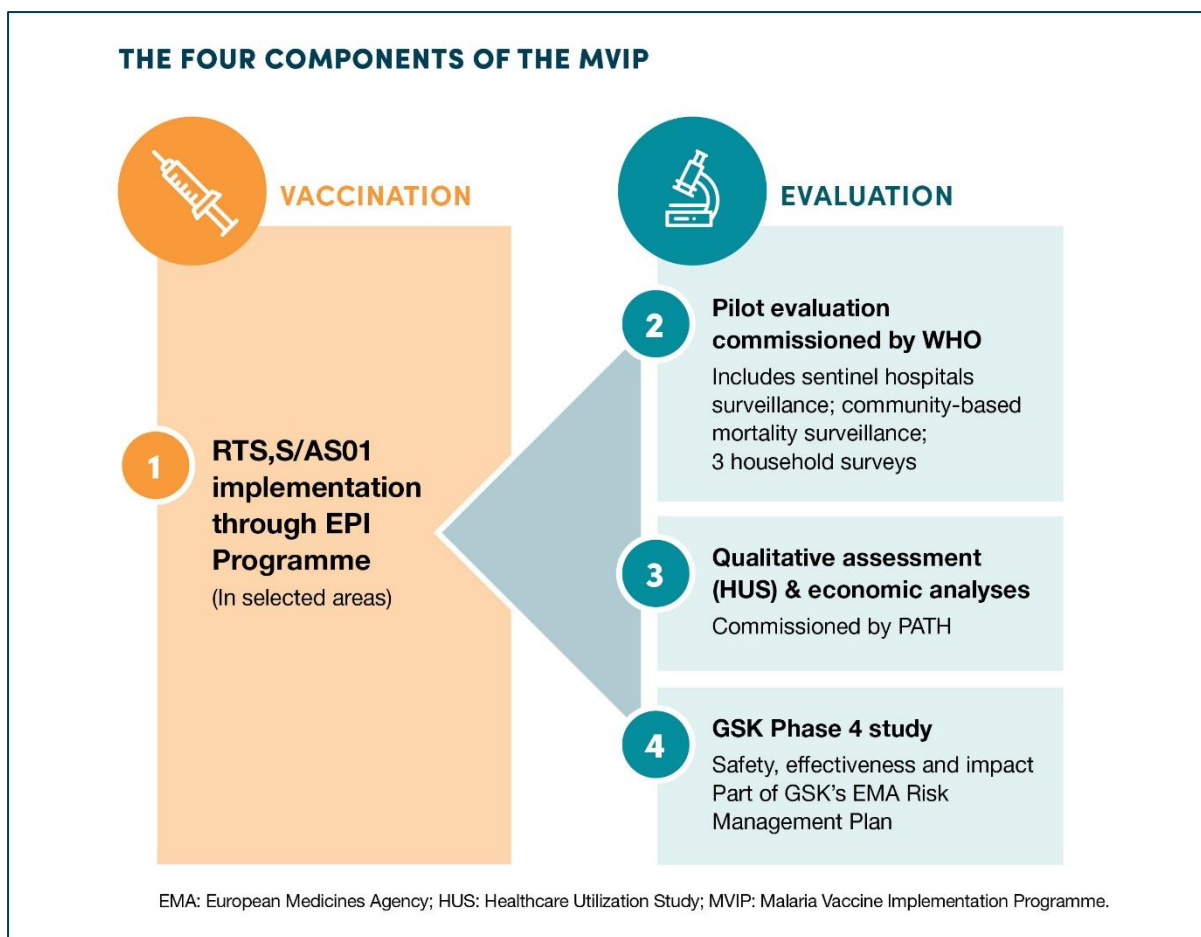


Figure 8. The four components of the Malaria Vaccine implementation Programme.

The vaccination schedule in each of the three pilot countries is illustrated in Figure 9 and shows how countries implementing countries are combining specific visits with the provision of other healthcare interventions, towards strengthening further health care provision during the second year of life.

Progress to date

Pilot introductions of the malaria vaccine by national immunization programmes in Ghana, Kenya and Malawi began in 2019 in selected areas with moderate to high malaria transmission. At this writing, the vaccine introduction has seen positive demand.

Vaccine/Intervention	Child Age											
	Birth	6 weeks	10 weeks	14 weeks	5 months	6 months	7 months	9 months	12 months	18 months	22 months	24 months
BCG	1											
Oral polio	0	1	2	3								
DTP-HepB-Hib (pentavalent)		1	2	3								
Pneumococcal conjugate		1	2	3								
Rotavirus		1	2									
Inactivated polio				1								
Meningococcal A conjugate										1		
Measles-Rubella								1		2		
Yellow Fever								1				
RTS,S in Ghana						1	2	3				4
RTS,S in Kenya						1	2	3				4
RTS,S in Malawi					1	2	3				4	
Vitamin A						1			2	3		4
Growth monitoring	●	●	●	●	●	●	●	●	●	●	●	●
Deworming												●

BCG: bacille Calmette-Guerin (tuberculosis vaccine); DTP-HepB-Hib: diphtheria, tetanus, pertussis, hepatitis B, Haemophilus influenzae type B (pentavalent vaccine).

Figure 9. Integration of RTS,S/AS01 into routine healthcare visits; some vaccinations are timed to coincide with the delivery of other healthcare interventions.

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