Introduction

RTS,S/AS01 is the first and, to date, the only malaria vaccine to be recommended for use by the World Health Organization (WHO). On October 6, 2021, WHO recommended widespread use of the RTS,S/AS01 malaria vaccine for the prevention of Plasmodium falciparum malaria among children living in regions with moderate to high malaria transmission, as defined by WHO.\(^1\) The vaccine is to be provided as part of countries’ immunization and comprehensive malaria control strategies.

WHO’s recommendation was informed by a range of evidence, including two years of findings from pilot rollout of the vaccine in parts of Ghana, Kenya, and Malawi. Approval for use of the vaccine comes at a critical time. While scaled-up malaria control measures have contributed to a reduction in Africa’s malaria burden, nearly a half-million children continue to die annually from the disease.\(^2\)

With the RTS,S recommendation, endemic countries can consider whether and how to add a vaccine to existing malaria control tools to further reduce child illness and deaths from the parasitic disease. Since all malaria prevention tools provide partial protection, countries can achieve the greatest impact by identifying and using the appropriate mix of interventions for specific subnational settings. National malaria control programs will define the mix of interventions, based on a range of factors, including the local malaria epidemiology—transmission intensity, age patterns of severe disease, and insecticide resistance patterns, among other considerations.

Top: Women and children waiting for vaccination at an outreach clinic in Lilongwe, Malawi. Photo: PATH.
As with national decision-making for any new health intervention, countries will go through their own internal processes and consider a range of factors to determine whether they need the vaccine and to assess its applicability to their national and subnational contexts.

This document is meant to highlight some of the evidence and considerations relevant to country decision-making. It focuses on currently available data, information, and resources that countries may want to consider as they decide whether and how to adopt the new malaria tool. Among other areas, particular attention is paid to the following:

- The RTS,S/AS01 malaria vaccine
- Country decision-making and introduction considerations
- Phased introduction within the context of limited supply
- The vaccine as part of comprehensive malaria strategies
- Financing

The malaria vaccine

RTS,S/AS01 is a pediatric vaccine that acts against *P. falciparum*, the deadliest malaria parasite globally and the most prevalent in Africa. The vaccine is designed to prevent the parasite from infecting the liver, where it can mature, multiply, and infect red blood cells, which can lead to disease symptoms. The vaccine has been shown to significantly reduce malaria, including severe, life-threatening malaria, among children living in settings of moderate to high malaria transmission.

Vaccine presentation and schedule

The RTS,S vaccine is produced as a two-dose vial of lyophilized RTS,S powder clipped to a two-dose vial of liquid AS01 adjuvant suspension to be used for reconstitution. No preservative is included in either the RTS,S formulation or the AS01 adjuvant system, and a vaccine vial monitor is affixed to the AS01 vial.3 The shelf life of the vaccine is three years and it can be stored within the standard cold chain temperature range of 2°C–8°C. The vaccine should be reconstituted just prior to administration and the reconstituted vaccine discarded at the end of the vaccination session, or within six hours after opening. The reconstituted vaccine is administered intramuscularly.

WHO recommends that RTS,S be provided in a four-dose schedule to children from 5 months of age. The vaccine is administered in a three-dose primary schedule at a minimum interval of four weeks between doses, with a fourth dose provided approximately 12 to 18 months following the third dose to prolong the

---

**RTS,S EVIDENCE**

**Pilot implementation: 2019–2023**

- More than 1 million young children reached.
- Favorable safety profile; feasible to deliver; well accepted by caregivers and service providers.
- There were no reductions in use of other malaria tools.
- High impact in real-life setting: cases of deadly severe malaria reduced by 30%.

**Phase 3 trial: 2009–2014**

- 15,459 infants and young children enrolled.
- Malaria episodes reduced by 40%, and severe malaria by 30%, over four years.
- Efficacy varied by site, as did impact; for every 1,000 children vaccinated, 205 to 6,565 malaria episodes were averted.

**Seasonal RTS,S trial: 2017–2022**

- 6,000 young children enrolled.
- RTS,S has shown similar efficacy to SMC.
- Combined, SMC and RTS,S has had 60% to 70% greater impact on clinical malaria, severe illness, and death than either intervention alone.
duration of protection. According to WHO guidance, there can be flexibility in the schedule to optimize delivery. WHO recommends that children who begin their vaccination series complete the four doses.

Countries may consider seasonal deployment of RTS,S following a five-dose strategy. This strategy may be used in areas that experience either highly seasonal malaria transmission or perennial transmission with seasonal peaks.

RTS,S may be co-administered with most of the monovalent or combination vaccines used in routine childhood immunization programs in Africa. These include diphtheria, tetanus, whole cell pertussis, acellular pertussis, hepatitis B, Haemophilus influenzae type b, oral poliovirus, measles, rubella, yellow fever, rotavirus, and pneumococcal conjugate vaccines. No co-administration studies have been conducted with RTS,S and meningococcus A, typhoid conjugate, cholera, Japanese encephalitis, tick-borne encephalitis, rabies, mumps, influenza, or varicella vaccines.⁴

Evidence on the RTS,S vaccine

Evidence from RTS,S pilots in Ghana, Kenya, and Malawi and from clinical testing informed the 2021 WHO recommendation for wider use of the vaccine. Overall, the vaccine has been found to be safe and to reduce malaria, including deadly severe malaria, in children.⁴ Mathematical modeling has shown the vaccine to be a cost-effective addition to other recommended malaria interventions, including in areas with high bednet coverage and areas using seasonal malaria chemoprevention (SMC).⁵

Evidence from the pilots

More than 1 million children have received RTS,S vaccination through the routine immunization programs in Ghana, Kenya, and Malawi since the pilots began in 2019.⁶ The pilot data have shown that delivery of the RTS,S vaccine is feasible, with high uptake and equitable coverage of the vaccine through routine immunization systems, even when additional visits to clinics are required. A qualitative study led by PATH, in collaboration with research consortia in the three countries, demonstrated high community demand and indicated that trust in the malaria vaccine has grown as caregivers have seen the benefits of vaccination for their children.⁷

The pilots have also shown that equity in access to malaria prevention in vaccinating areas has increased. All three countries have had equitable coverage across socioeconomic groups, regardless of gender, and more than two-thirds of children in the implementing areas who had not been sleeping under a bednet had received the vaccine. Layering the malaria tools has resulted in more than 90 percent of children in the vaccinating areas benefiting from at least one preventive intervention. In addition, pilot data have shown that malaria vaccination has had no negative impact on uptake of bednets, other childhood vaccinations, or health care–seeking behavior for febrile illness.⁷

The pilots are scheduled to continue through 2023 to provide further understanding of the added value of the fourth vaccine dose, and to measure the impact of vaccine implementation on lives saved.

Evidence from clinical studies

In addition to the pilots, RTS,S has been rigorously tested and evaluated through a series of clinical trials.⁶⁹ The pivotal Phase 3 efficacy and safety trial, conducted between 2009 and 2014, involved 15,459
infants and young children and was conducted by 11 clinical research centers in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania). The trial demonstrated that among children who received four doses, the vaccine reduced one in four cases of malaria episodes and one in three severe malaria cases over a four-year period. The study also showed that at the trial site with the highest disease burden, more than 6,500 clinical malaria episodes were averted for every 1,000 children fully vaccinated with four vaccine doses.

A study of the longer-term impact of the vaccine, with a focus on severe malaria, was completed in December 2016. The study followed children who participated in the Phase 3 trial at three of the 11 research centers for an additional three years—a total of seven years of follow-up. Results showed that the incidence of severe malaria decreased as children got older, regardless of whether they received the vaccine; there was no evidence of rebound of severe malaria following the recommended four doses of the vaccine.

**Evidence on use in seasonal settings**

An additional Phase 3 study, conducted between 2017 and 2022, compared the efficacy of RTS,S to that of SMC, which is the standard treatment for children in areas with highly seasonal malaria transmission. Results from the first three years of the study showed that RTS,S was comparable to SMC in preventing malaria, and that combining the two interventions had significantly greater impact than the use of each intervention alone. Use of the two interventions together resulted in an approximately 70 percent further reduction in malaria deaths and hospitalizations, and a 60 percent reduction in uncomplicated malaria over use of SMC alone.

**Country decision-making and introduction considerations**

In considering whether and how to adopt the RTS,S malaria vaccine, countries are expected to work through nationally established review structures and processes and assess a range of global and local data. Data to be considered include the following: national and subnational malaria parasite prevalence; disease burden; existing malaria interventions; immunization system performance and appropriateness; availability of financial support; and health sector priorities, such as the potential of malaria and immunization programs to reach under-served populations and advance goals for equity and inclusion.

The quality of data and evidence used to support the decision-making process can enhance a country’s confidence in its decisions on whether and where to introduce the malaria vaccine. Each country will decide which types of evidence they need to gather locally for their decisions, and which other types of evidence—for example, cost-effectiveness estimates and acceptability data—may come from other sources.

In addition to identifying and reviewing the required data and information for malaria vaccine decisions, countries will need to identify appropriate decision-making review structures and processes. The clarity of the decision-making processes and structures used to review the vaccine can also enhance public confidence in the decisions regarding the malaria vaccine, and as a result, the effectiveness of the vaccine introduction process. Country considerations for these review and decision-making processes and structures could include the following:

- Use of national advisory bodies to determine whether to adopt the vaccine.
- Close collaboration between the national malaria and immunization programs and other relevant ministry of health departments throughout the decision-making, planning, and implementation phases.
- Incorporation of the vaccine into immunization guidelines and comprehensive malaria control strategies, as outlined in the WHO recommendation.
- Development of plans for phased vaccine introduction in accordance with the *WHO Framework for the allocation of limited malaria vaccine supply* (the Framework).
Joint malaria and immunization review and adoption decisions

Collaboration among relevant ministry of health departments—in particular, cooperation between the immunization and malaria control programs—is an essential feature of national decision-making for RTS,S. Should there be a decision to adopt the vaccine, early alignment between the malaria and immunization programs can help support the vaccine’s implementation as a strategic element of each of these national programs. Integration of the vaccine into each program’s strategy can also allow for the harmonization of cross-cutting activities, such as advocacy, communication, and social mobilization, and the alignment of other priorities, including training and supervision of health personnel, service delivery, and monitoring and evaluation.

Lessons from the pilot countries show that active participation of the national malaria control program in vaccine introduction and implementation activities can help ensure that malaria control perspectives are incorporated. Establishment of malaria vaccine technical working groups, with participation from the malaria and immunization programs and other internal and external partners, can sharpen technical guidance and provide a forum for alignment.

Phased introduction within the context of limited supply

Demand for the RTS,S malaria vaccine is expected to outstrip supply in the initial years of introduction. A recent global malaria vaccine market study, commissioned by WHO, found that vaccine supply might be insufficient through the medium term, with a constrained supply potentially during the first four to six years following expected first introductions in 2023. Efforts to ensure long-term, sustainable supply of the vaccine include the transfer of antigen manufacturing to Bharat Biotech of India. WHO, PATH, and partners are also working to accelerate the increase of supply, including through expanded manufacturing capacity for the vaccine (both antigen and adjuvant) and by facilitating the development of other first-generation and next-generation malaria vaccines.

WHO coordinated development of the Framework to manage expected supply shortfalls in the medium term—to guide where initial doses of vaccine will be deployed. The aim is to prioritize supply for use in areas of greatest need until supply meets demand.

The Framework outlines a mechanism for prioritizing the global and national allocation of the vaccine, based on best available scientific evidence, shared values, input by expert advisors, and broad consultation with affected countries and communities and other malaria vaccine stakeholders.

In applying the Framework, countries will be asked to identify the areas of greatest need within their borders. To do this, they will consider a range of data, including levels of \textit{P. falciparum} parasite prevalence and all-cause mortality rates in children under 5 years of age.

ALLOCATION OF INITIAL VACCINE SUPPLIES

Principles for allocating initial supplies include the following:

- Allocate the malaria vaccine where populations are in greatest need, where the disease burden is highest, and where the risk of progression to severe disease or death is also highest.
- Allocate the malaria vaccine to countries for use in areas where the expected health impact is greatest—that is, where the most lives can likely be saved with the limited available doses.
- Allocate the malaria vaccine to countries that commit to fairness in addressing the needs of marginalized individuals and communities in their malaria vaccination programs.
- Acknowledge burdens or risks that communities have assumed in helping to research and develop this vaccine.
Estimates of need for the vaccine are expected to be developed within the context of the subnational application of different malaria interventions. Countries introducing the malaria vaccine during the initial years of availability will be expected to plan and introduce it in a phased, subnational manner, starting in areas of greatest need.

The Framework also seeks to acknowledge the past contributions of communities during the development of the vaccine, by ensuring that if two countries score equally, based on the primary ethical principles, the one with a prior contribution to the vaccine’s development could be accorded priority.

Developed through an inclusive and consultative process, the Framework emphasizes the shared responsibility of all global stakeholders—including decision-makers in malaria-endemic countries, partners, and donors—to adhere to its principles as they consider financial and technical support. The Framework also emphasizes solidarity as a foundational value, by stipulating that if there are unmet vaccine requests for the areas of greatest need across multiple countries, no single country should receive more than 20 percent of the total available supply.

The vaccine as part of comprehensive malaria strategies

In developing plans for the introduction and implementation of the RTS,S vaccine, countries will need to incorporate the vaccine, together with other malaria prevention and control interventions, into comprehensive malaria control strategies. These comprehensive strategies will take into consideration the principles of phased, subnational introduction as outlined in the Framework, as well as the appropriate mix of other recommended malaria interventions for different subnational settings. WHO’s Global Malaria Programme has developed guidance for countries on the subnational tailoring of malaria interventions, including the use of local data and contextual information to determine the appropriate mix of malaria interventions for a given area, with the goal of achieving optimum impact on malaria transmission and burden of disease.\(^8\)

Countries will also be expected to include the vaccine in national malaria strategic plans, either as an addendum to their current plans or within updated plans, as a complementary tool to existing malaria control interventions. WHO, PATH, and other partners can provide technical assistance to countries for the required data review and layering of information to develop the tailored, subnational mix.\(^8\)

Financing

Following the December 2021 approval of a malaria vaccine program by the Board of Gavi, the Vaccine Alliance, initial funding is being provided by Gavi to support the introduction, procurement, and delivery of the RTS,S malaria vaccine for Gavi-eligible countries in sub-Saharan Africa through 2025. Gavi’s malaria vaccine program, which began in 2022, will follow its general requirements for vaccine support, including funding eligibility, review by an independent review committee, co-financing according to Gavi’s co-financing policy (a revision of which is expected in December 2022), and prioritization of equity.

Gavi launched its vaccine funding guidelines in July 2022,\(^19\) with the scheduled close of the initial application window for non-pilot countries in January 2023. Subsequent application windows will close on

---

\(^8\) The WHO Guidelines for Malaria include additional information on recommended malaria interventions, including the malaria vaccine, WHO anticipates issuing guidance on the incorporation of the malaria vaccine into subnational packages of malaria interventions in Quarter 3 of 2022.
a regular basis thereafter. Countries that are interested in applying during the initial funding windows are asked to submit an expression of interest to Gavi by September 13, 2022. Funding applications will be reviewed by Gavi’s independent review committee. Although Gavi anticipates approximately 12 to 18 months between receipt of the applications and approved vaccine introduction, there are ongoing efforts by Gavi and its partners to accelerate this process.

Countries applying for Gavi support for introduction of the malaria vaccine will be expected to meet the general Gavi application requirements, including the following:\textsuperscript{20}

- Description of the epidemiological rationale and target population (e.g., summary of review by the National Immunization Technical Advisory Group or other appropriate body).
- Description of the implementation plan, including timing, projected coverage, and geography.
- Confirmation of cold chain readiness.
- Confirmation of financial readiness (e.g., sign-off from the ministry of finance).
- Description of preparatory activities, such as training and social mobilization.
- Link to other relevant interventions (e.g., comprehensive disease control plans and a strategy for co-delivery of interventions).
- Explanation of schedule choice and delivery modalities.
- Consideration of technical assistance needs.

In addition, country applications for introducing the malaria vaccine will need to demonstrate the following:\textsuperscript{19}

- Confirmation of the country’s decision to introduce the malaria vaccine (minister of health sign-off, as well as, for example, National Immunization Technical Advisory Group meeting minutes and Immunization Inter-agency Coordination Committee minutes).
- Existence of a joint immunization-malaria coordination mechanism (e.g., the establishment of a working group with joint expanded program on immunization/national malaria control program participation).
- Plans to use the malaria vaccine together with other appropriate malaria interventions, based on local data and context.
- Integrated and multisectoral approaches where, as much as possible, the deployment of the malaria vaccine utilizes existing health systems, including the existing routine immunization systems.
- Strong community engagement to ensure vaccine acceptance and resilient demand. Community engagement should incorporate community education on the vaccine, including its efficacy and the need to continue use of other malaria control interventions even after rollout of the vaccine.

Additional requirements are specified in the \textit{Gavi Vaccine Funding Guidelines}.\textsuperscript{19}

In addition, The Global Fund to Fight AIDS, Tuberculosis and Malaria is revising its guidance to include the malaria vaccine. Countries eligible for Gavi support in the rollout of the vaccine will need to include the vaccine in both their national malaria strategic plans and their national immunization plans. For its part, the Global Fund will support malaria program reviews and subnational tailoring for countries updating malaria strategic plans. The Global Fund will also provide funding for the coordination of various activities aimed at reducing the malaria burden. Global Fund investments will support countries as they try to meet the requirements of Gavi malaria vaccine funding.
PATH's role in vaccine development and introduction

PATH leverages decades of hands-on experience to develop, introduce, and improve vaccines and immunization technologies. To accomplish its objectives, PATH works through multisector partnerships, that include countries and manufacturers, to advance and sustain country goals for immunization equity and vaccination coverage.

Specifically, PATH’s Center for Vaccine Innovation and Access accelerates development and delivery of vaccines for the most vulnerable children and communities. The team’s expertise spans all stages—from preclinical research and pivotal evaluations of vaccine candidates to innovative approaches for introducing vaccines and for strengthening immunization systems.

As a key aspect of this work, PATH’s Policy, Access, and Introduction team partners with countries to advance and sustain vaccination coverage and equity. The PATH team builds strong relationships with immunization program managers, ministries of health, and other stakeholders to understand needs, respond to priorities, and to work together as partners.

References


