

RTS,S Frequently Asked Questions (FAQs)



What is RTS,S?

RTS,S/AS01 (RTS,S) is the first malaria vaccine shown to provide partial protection against malaria in young children, and the first to be provided to young children through national immunization programs in three sub-Saharan African countries—Ghana, Kenya, and Malawi. RTS,S is an injectable vaccine and, like vaccines generally, aims to trigger the body's own immune system to defend against disease, in this case, malaria caused by *Plasmodium (P.) falciparum*, the deadliest species of the malaria parasite globally and the most prevalent in Africa. Specifically, RTS,S is designed to prevent the malaria parasite from infecting, maturing, and multiplying in the liver, after which the parasite would normally re-enter the bloodstream and infect red blood cells, leading to disease symptoms.

The vaccine was recommended by the World Health Organization (WHO) in 2016 for pilot introduction in areas of moderate-to-high malaria transmission. Through the WHO-coordinated Malaria Vaccine Implementation Programme (MVIP), the vaccine is now being evaluated for use as a complementary malaria control tool that could be added to (not replace) the core package of WHO-recommended preventive, diagnostic, and treatment measures.

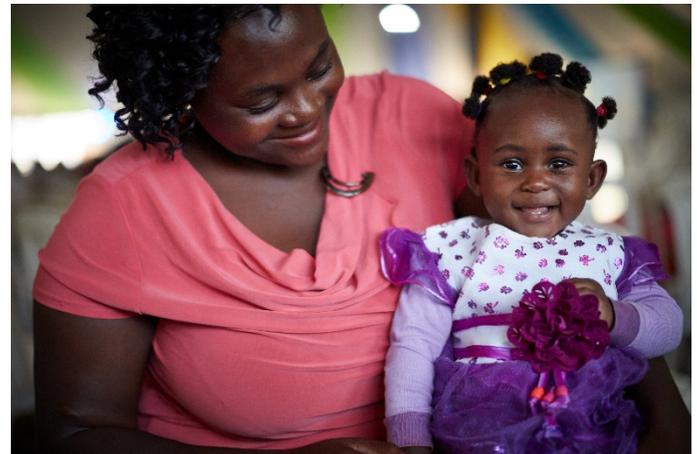
What makes RTS,S different from other malaria vaccines?

RTS,S is the first and, to date, the only vaccine to show a protective effect against malaria among young children in Phase 3 clinical trials. It is the first malaria vaccine being provided to young children through routine immunization programs as part of a large-scale pilot introduction.

Why, when existing interventions appear to be working, do we need a malaria vaccine?

Although existing interventions have helped to reduce malaria deaths significantly, a well-tolerated and effective vaccine could

add an important complementary tool for malaria control efforts. This could be particularly helpful in those areas most affected by malaria and where progress in controlling the disease has recently plateaued.¹ The RTS,S vaccine is intended to complement existing measures to fight malaria, such as bednets and indoor residual insecticide spraying. Final results of a pivotal, large-scale Phase 3 efficacy and safety trial were published in *The Lancet* in April 2015. In that article, the authors wrote that RTS,S—if used correctly—“has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures, especially in areas of high transmission.”²



Mother with her child who was among the first to receive the malaria vaccine in Kenya. Photo: WHO/Neil Thomas

What is the latest status of the RTS,S vaccine?

Vaccinations in the WHO-coordinated Malaria Vaccine Implementation Programme (MVIP) began in selected areas of Ghana and Malawi in April 2019, and in Kenya in September. The MVIP was established to support the pilot introduction of the RTS,S vaccine through routine immunization programmes in selected areas of Africa. It is an ambitious undertaking that aims

to vaccinate at least 1 million children, across three countries, with the recommended four doses of the vaccine.

In late 2015, the WHO issued a call for expressions of interest for African Ministries of Health to collaborate: 10 countries applied and three were selected, based upon standardized criteria, including those related to the strength of their immunization and malaria control programmes.

The MVIP was designed to respond to the position on RTS,S published by WHO in January 2016,³ adopting the recommendations made jointly in October 2015 by the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC). SAGE/MPAC recommended that large-scale implementation of RTS,S occur among children aged 5 to 17 months in three to five settings of moderate-to-high malaria parasite transmission in sub-Saharan Africa.

Earlier, in July 2015, the European Medicines Agency (EMA) issued a positive scientific opinion concluding that the quality of the vaccine and its risk/benefit profile is favorable from a regulatory perspective. The assessment applies the same rigorous standards as for medicines to be marketed within the European Union. According to the EMA, "...despite its limited efficacy, the benefits of Mosquirix™ outweigh the risks in both age groups studied," and "the benefits of vaccination may be particularly important among children in high-transmission areas in which mortality is very high."⁴

What are the next steps for RTS,S?

The MVIP is designed to assess the feasibility of administering the required four doses of the vaccine in children, the vaccine's role in reducing childhood deaths, and its safety in the context of routine use. Data and information derived from the MVIP will inform a WHO policy recommendation on the broader use of the vaccine. SAGE and MPAC have agreed that an updated policy recommendation is possible as soon as late 2021, if the necessary safety data are available for review. If a subsequent policy recommendation on wider use of the vaccine was positive, it would pave the way for financing decisions and thus possible wider implementation of the vaccine in Africa.

WHO is responsible for coordinating the MVIP, working in close collaboration with ministries of health in the participating countries and a range of in-country and international partners, including PATH and GSK. In each country, the ministry of health will deliver the malaria vaccine through its national immunization program in selected areas and regions. RTS,S has been approved for use in the context of the pilot introduction, associated evaluations, and Phase 4 studies by the national regulatory authority in each of the three participating countries.

WHO and PATH are working together across several areas, including on economic assessments, and in the qualitative assessment of behavior change that may occur during the introduction of the vaccine. GSK will continue to play a key role in manufacturing the vaccine and will donate up to 10 million doses for use in the MVIP and Phase 4 studies. Other

evaluation partners include a wide range of academic, medical, and other research organizations. The roles and responsibilities of WHO, PATH, and GSK in the MVIP are governed by a collaboration agreement concluded in 2017. Concurrent with the pilot implementation over the next several years, PATH, WHO, and GSK are exploring how best to assure the longer-term supply of the vaccine.

Who is funding the RTS,S Malaria Vaccine Implementation Programme?

Financing for the MVIP has been mobilized through an unprecedented collaboration between three major global health funding bodies: Gavi, the Vaccine Alliance; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and Unitaid. PATH's activities are also supported by other donors, including the ExxonMobil Foundation. However, additional resources will be needed to bring this vaccine into wide-scale use.

When might the vaccine become available for use?

The pilot introduction is making the vaccine available at a subnational level in Ghana, Kenya, and Malawi. The results of the MVIP, which will last several years, will help inform future decisions on the wider-scale deployment of the vaccine.

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What is Mosquirix™?

Mosquirix™ is the name trademarked by GSK, also known as a brand name, for RTS,S/AS01. There is no molecular or chemical difference between RTS,S/AS01 and Mosquirix™.

What does the acronym RTS,S stand for?

The letters in "RTS,S" represent its composition. The 'R' stands for the central repeat region of *P. falciparum* circumsporozoite protein (CSP); the 'T' for the T-cell epitopes of the CSP; and the 'S' for hepatitis B surface antigen (HBsAg). These are combined in a single fusion protein ('RTS') and co-expressed in yeast cells with free HBsAg. The 'RTS' fusion protein and free 'S' protein spontaneously assemble in 'RTS,S' particles. RTS,S also contains the AS01 adjuvant system, and in scientific papers is usually referred to as 'RTS,S/AS01'.

What is meant by clinical malaria?

Clinical malaria refers to those cases where infection with the malaria parasite causes disease. For mild forms of malaria, symptoms include fever, shivering, vomiting, and headache. In malaria-endemic regions, children may have malaria parasites in their blood without showing any symptoms of disease.

What is meant by severe malaria?

Severe malaria refers to those malaria cases where the initial infection (with or without mild symptoms) evolves into an acute life-threatening illness, with complications such as severe anemia, or neurological disease such as convulsions and possibly coma, and may result in death if left untreated.

What do we know about the efficacy of RTS,S?

Final results of the Phase 3 trial, published in *The Lancet* in April 2015, included analysis of vaccine efficacy, immunogenicity, safety, and impact of RTS,S/AS01 over a median of 48 months of follow-up after the first dose and the effect of a fourth dose of vaccine.²

The final results demonstrated that, among children who received four doses, the vaccine prevented approximately 4 in 10 (39%) cases of clinical malaria and 3 in 10 (29%) cases of severe malaria over a four-year period. The fourth dose prolonged protection against clinical malaria, with 1,774 cases of malaria averted per 1,000 children vaccinated, on average, across all sites (site-specific cases averted ranged from 205 to 6,565 per 1,000 children vaccinated). Vaccine efficacy waned over time following the fourth dose.

A recent article in *Lancet Infectious Diseases* reports on the results of a study on the longer-term impact of the vaccine, with a focus on severe malaria.⁶ The study followed children who previously participated in the Phase 3 trial (from Nanoro, Burkina Faso; Kombewa, Kenya; and Korogwe, Tanzania) for an additional three years (for a total of seven).

As with the original Phase 3 trial, results showed that the incidence of severe malaria decreased with increasing age of the children, regardless of whether or not the children received the vaccine. Over the entire seven-year post-vaccination period, vaccine efficacy against severe malaria was 36.7 percent in children who started their four-dose vaccination schedule at the age of 5 to 17 months and there was no evidence of a rebound of severe malaria.

Based upon the results of this and other research, while there might be a short-lasting increase in susceptibility to clinical malaria at some point following a relatively long period of protection, the benefits of protection by the vaccine were still greater than any period of enhanced risk.

What do we know about the safety of RTS,S?

In its evaluation of the vaccine, the EMA concluded, "The safety profile of this vaccine is acceptable and quite similar to others apart from a higher risk for febrile convulsions in the older age group within seven days after a dose (mostly the third dose) of Mosquirix™."⁵ Side effects noted include local pain and swelling, and low-grade fever, which are similar to reactions observed with some standard vaccines given to children. The incidence of fever in the week after vaccination was higher in those who received the fourth dose of the RTS,S vaccine than those receiving the comparator vaccine, a difference that also

occurred during the primary series of vaccinations in the older children. Some of the febrile reactions were accompanied by generalized convulsive seizures, as noted above; however, all seizures resolved and no long-term effects were observed.

The Phase 3 efficacy and safety trial has shown that the overall incidence of serious adverse events (SAEs are clinical events of such a serious nature that they are promptly reported to relevant regulatory agencies; they include death, life-threatening or incapacitating events, among others) was comparable between participants receiving the RTS,S vaccine and those receiving a comparator vaccine. One imbalance noted in published results from the Phase 3 trial and the EMA's assessment concerned the imbalance in meningitis cases in older children receiving RTS,S; however, no relationship to the vaccine has been established. The EMA concluded that "...there is no evidence in favour of immunological hypotheses," and that "Other hypotheses, like simple chance finding, should also be taken into account since it is more likely to explain the imbalance observed."⁵ The occurrence of meningitis as a potential risk was followed closely in extended follow-up in 3 of the 11 study sites that conducted the Phase 3 trial, and will also be followed in the planned pharmacovigilance study included in the Risk Management Plan (RMP) approved by the EMA.

The potential for rebound—or age shifting—with respect to the incidence of severe malaria (as well as clinical malaria) was also noted as a possibility. In the Phase 3 trial, among children aged 5 to 17 months at first dose, the incidence of severe malaria decreased over time in all groups. However, because children protected by RTS,S are thought to develop their natural immunity against malaria more slowly than unvaccinated children, it was unclear if vaccinated children might be at higher risk of disease when the protection from the vaccine decreases over time. The potential risk of rebound has been further evaluated and concerns about the longer-term risk of severe malaria resolved (see previous question and answer).

Where was the Phase 3 efficacy and safety trial conducted, and who participated?

The Phase 3 efficacy and safety trial was conducted by 11 research centers in seven African countries, in areas with different malaria transmission intensities and patterns: the centers were in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania. The participants were children aged 5 to 17 months and infants aged 6 to 12 weeks at the time of the first vaccination. The research centers were selected for their track records of clinical research, strong community relations, and commitment to meeting the highest international ethical, medical, clinical, and regulatory standards. The trial was overseen by a joint committee involving the African research centers, and in some instances their northern partners, together with GSK and PATH's Malaria Vaccine Initiative.

The Phase 3 efficacy and safety trial was part of a comprehensive clinical development program supported through grant funding from the Bill & Melinda Gates Foundation to PATH, starting in 2001.

Why was RTS,S developed for and tested in Africa?

The great majority of malaria cases and deaths caused by the *P. falciparum* parasite occur in sub-Saharan Africa, among children under five years of age; thus, the focus of the development of the RTS,S malaria vaccine for use in infants and young children was in this region. To determine the level of protection against malaria provided by the vaccine, it is necessary to vaccinate children who may be exposed to the malaria parasite and track them to see whether they develop disease. If children were not at risk of contracting malaria, it would be impossible to determine whether the vaccine provides protection. Additional studies would be needed before the vaccine could be recommended for use outside Africa.

Why should a vaccine that is only partially efficacious be considered for use in Africa?

While great strides have been made against malaria through the use of bednets and other measures, malaria still kills more than 400,000 people per year, mainly children under five years of age in sub-Saharan Africa. Adding a vaccine such as RTS,S to current interventions could enhance malaria control efforts.

Results from the Phase 3 trial illustrated how disease burden interacted with vaccine efficacy to determine the impact of the vaccine. Among children receiving four doses of the vaccine, an average of 1,774 cases of clinical malaria were prevented for every 1,000 children vaccinated across the 11 trial sites over an average of 48 months of follow-up. The impact was greater, however, in areas of higher disease burden: one site in Kenya recorded 6,565 cases averted for every 1,000 vaccinees.

Modeling conducted by four groups, with guidance from WHO, found that 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. The four groups modelled the impact of RTS,S against death and provided an estimated impact of one death averted for every 233 children vaccinated.⁷

How much will the vaccine cost?

If African countries decide to implement RTS,S/AS01, it must be accessible and affordable to those who need it most—children living in malaria-endemic areas. GSK has stated that RTS,S would be made available at a not-for-profit price. The company also has committed to evaluate the possibilities for reducing the cost of manufacturing. The final price of the vaccine is dependent on future decisions regarding deployment of and demand for the vaccine.

Will African families be able to afford a malaria vaccine?

If African countries decide to implement a malaria vaccine, it must be accessible and affordable to those who need it most—children living in malaria-endemic areas. In many African countries, childhood vaccines are provided to children at no cost thanks to existing international and national financing mechanisms.

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