

RTS,S Frequently Asked Questions (FAQs)

1. What is RTS,S?

The RTS,S malaria vaccine candidate is the most clinically advanced to date globally. It became the first vaccine candidate to show in clinical trials that it can help protect young children (in 2004) and infants (in 2007) living in malaria-endemic areas against clinical disease and infection caused by *Plasmodium (P.) falciparum*, the most deadly species of the malaria parasite. Like vaccines generally, RTS,S aims to trigger the body's own immune system to defend against disease, in this case, malaria. 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.

2. What does the acronym RTS,S stand for?

RTS,S is a scientific name given to this malaria vaccine candidate and represents its composition. The 'R' stands for the central repeat region of *Plasmodium (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.

3. Why do we need a malaria vaccine?

Historically, vaccines have offered one of the most effective means of preventing infectious diseases—such as smallpox, polio, measles, and others—and saving lives. The RTS,S vaccine candidate is intended to complement existing measures to fight malaria, such as bed nets and indoor residual insecticide spraying. Even a modestly efficacious malaria vaccine could have the potential to prevent millions of malaria cases and, according to mathematical modelling, could save hundreds of thousands of lives.

4. 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.

5. 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.

6. What do the clinical studies tell us about the safety of RTS,S?

Published studies have indicated that RTS,S has an acceptable safety and tolerability profile in infants and young children. Side effects included 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 booster dose of the RTS,S vaccine than those receiving the comparator vaccine, a difference that also occurred during the primary series of vaccinations. Some of the febrile reactions were accompanied by generalized convulsive seizures (2.5 per 1000 doses for children administered the booster versus .4 for the control).

The final Phase III 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 candidate vaccine and those receiving a comparator vaccine. The meningitis signal previously reported² remained at the end of the study, with a small number of new

cases reported in older children. The occurrence of meningitis will be followed closely in an extended follow-up in three study sites and in Phase IV studies.

7. What do the clinical studies tell us about the efficacy of RTS,S?

Results of the co-primary endpoint of the study after a year of follow-up were published in the *New England Journal of Medicine* in November 2011¹ (children aged 5-17 months) and December 2012² (infants aged 6-12 weeks). These results showed that three doses of RTS,S reduced clinical malaria by approximately a half in children 5-17 months of age at first vaccination³. In infants 6-12 weeks of age at first vaccination with RTS,S, clinical malaria was reduced by approximately a third³. In a subsequent analysis after 18 months of follow up⁴, children aged 5-17 months at first vaccination with RTS,S experienced approximately 45% fewer cases of clinical malaria³, compared to children immunised with a control vaccine. Infants aged 6-12 weeks at first vaccination with RTS,S had approximately 27% fewer cases of clinical malaria³ than infants in the control group. Efficacy waned over time in both age categories

The final results, published in April 2015 in *The Lancet*, report that vaccine efficacy against clinical malaria for the young child category was 36% for those who received the booster dose and 28% for those who did not receive the booster dose, over an average 48 months of follow-up³. In the infant category, efficacy against clinical malaria was 26% for those who received the booster dose and 18% for those who did not receive the booster dose, over an average 38 months of follow-up. Statistically significant vaccine efficacy against severe malaria to the end of the study period was observed in the older age category who received the booster dose, but not in those who did not receive a booster, nor in the younger age category in either the booster or non-booster groups.

A lower immune response to the vaccine was seen in the younger age category compared to the older age category enrolled in this trial after the primary series. Efficacy of the booster dose in the younger children is thought, by some trial scientists, to be a consequence of the weaker immune response following this primary series.

8. Where was the Phase III efficacy and safety trial conducted and who participated?

The Phase III efficacy and safety trial was conducted at 11 trial sites in seven African countries with different malaria transmission intensities and patterns: the sites 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. Leading African research centers, and in some instances their Northern partners, conducted the trial together with GlaxoSmithKline (GSK) and the PATH Malaria Vaccine Initiative (MVI). 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.

9. 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 candidate for use in infants and young children was in this region. To determine the level of protection against malaria provided by the candidate 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 candidate provides protection.

10. Why is the vaccine only for children and infants? Why not adults?

The vaccine candidate RTS,S is initially being developed for use in preventing malaria in young children living in malaria-endemic regions in sub-Saharan Africa. Our efforts focus on this age category because

most cases and deaths from malaria occur in African children under five years of age and thus there is a critical need to bolster the existing malaria control measures with additional tools.

11. Why should a vaccine that is only modestly efficacious be considered for use in Africa?

While great strides have been made lately against malaria through the use of bed nets and other measures, malaria still kills approximately 584,000 people per year, mainly children under five years of age in sub-Saharan Africa. Adding a vaccine with this efficacy profile to current interventions could enhance existing malaria control efforts.

Looking at the vaccine profile in the context of disease burden is important, for instance, in medium to high disease burden areas. For children in the 5-17 month age category who received a booster dose at 18 months after the primary schedule, an average of 1774 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. For infants aged 6-12 weeks at first vaccination with RTS,S, who received a booster dose, an average of 983 cases of clinical malaria were prevented for every 1,000 infants vaccinated across the 11 trial sites over an average of 36 months of follow-up. The impact for both age categories was greater in areas of higher malaria transmission.

12. When might the vaccine become available for use?

The submission to the European Medicines Agency (EMA) in June 2014 is the first step in the regulatory process toward making the RTS,S vaccine candidate available as an addition to existing tools currently recommended for malaria prevention and treatment. If a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) is granted, the World Health Organization (WHO) has indicated a policy recommendation may be possible by end of 2015. A policy recommendation is a formal review process by WHO designed to assist in the development of optimal immunisation schedules for diseases that have a global public health impact, such as malaria.

A positive opinion from the EMA's CHMP would also be the basis for marketing authorisation applications to National Regulatory Authorities (NRAs) in sub-Saharan Africa, as review by the EMA is required by the majority of African countries prior to registration of a medicinal product manufactured in Europe. If positive, these regulatory decisions would help pave the way toward the introduction of the vaccine through African national immunisation programmes. The timing or duration of the steps between WHO policy making and vaccine introduction in African countries is yet to be established, and based on experience with other vaccines, this is likely to take a few years.

13. What is Article 58?

Article 58 allows the EMA's CHMP to give scientific opinions, in co-operation with the WHO, on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU). Medicines eligible for this procedure are used to prevent or treat diseases of major public health interest. This includes vaccines used in the [WHO Expanded Programme on Immunization](#) or for protection against a public health priority disease.

14. How much will the vaccine cost?

GSK has stated that the price of RTS,S will be the cost of manufacturing the vaccine plus a small return of around five percent, which will be reinvested in research and development for second-generation malaria vaccines or vaccines against other neglected tropical diseases. GSK also has committed to evaluate the possibilities for reducing the cost of manufacturing.

15. 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. The RTS,S partnership hopes that similar mechanisms would be implemented for a malaria vaccine to allow countries to provide it to children at nominal or no cost. A shared goal is to have the cost of a malaria vaccine not be a barrier to access where a vaccine would be of most use.

16. How much has development of the RTS,S vaccine candidate cost and who is paying?

MVI has received more than \$200 million in grants from the Bill & Melinda Gates Foundation to advance the clinical development of RTS,S. GSK has invested more than \$350 million to date and expects to invest another \$260 million before the completion of the project.

- 1) The RTS,S Clinical Trials Partnership. *NEJM* 2011; 365: 1863-75.
- 2) The RTS,S Clinical Trials Partnership. *NEJM* 2012; 367: 2284-95.
- 3) Intention to Treat analysis (ITT)
- 4) The RTS,S Clinical Trial Partnership, *PloS Medicine*, 2014; 11(7): e1001685

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