# RTS,S (Mosquirix™) Frequently Asked Questions (FAQs)

**1. What is RTS,S?**

RTS,S is the first malaria vaccine candidate to receive a positive scientific opinion from the European Medicines Agency (EMA), whose Committee for Medicinal Products for Human Use (CHMP) agreed by consensus that the benefits of vaccination with RTS,S outweighed the risks. According to the EMA, RTS,S "could potentially save lives in the age group most at risk from malaria." This was followed in January 2016 by the publication of a position paper by the World Health Organization (WHO) that recommended large-scale pilot implementations of RTS,S in children 5 to 9 months of age, in settings of moderate-to-high parasite transmission in Africa.

Like vaccines generally, RTS,S aims to trigger the body's own immune system to defend against disease, in this case, malaria caused by *Plasmodium falciparum,* the most deadly species of the malaria parasite. 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. RTS,S also contains the AS01 adjuvant system, and in scientific papers is usually referred to as 'RTS,S/AS01'.

**3. Why, when existing interventions appear to be working 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. 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 concluded that RTS,S—if used correctly—"has the potential to prevent millions of cases of malaria."

**4. What is the latest status of the RTS,S vaccine candidate?**

The EMA announced on July 24, 2015 that its CHMP had adopted a positive opinion for the RTS,S vaccine candidate in children aged 6 weeks to 17 months. The EMA's CHMP opinion is a final stage in the Article 58 procedure initiated in July 2014, by which the CHMP gives a scientific opinion, in cooperation with the World Health Organisation, on a medicinal product for human use that is intended exclusively for markets outside of the European Union (EU). This assessment requires medicinal products to meet the same standards as those intended for use in the EU.

According to the EMA, the CHMP concluded that "…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."

Subsequent to the Article 58 process, WHO issued formal recommendations in January 2016, calling for large-scale pilot implementations of RTS,S. According to its official position paper, "WHO recommends that the pilot implementations use the 4-dose schedule of the RTS,S/AS01 vaccine in 3–5 distinct

epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings, with three doses administered to children between 5 and 9 months of age, followed by a fourth dose 15–18 months later."[1]

WHO further recommends that the pilots involve sufficiently large populations to assess, among other things, (1) the feasibility of providing all four doses of RTS,S to the target age group through existing health services; (2) the impact of RTS,S on child mortality; and (3) evidence of any causal relationship between RTS,S and either meningitis or cerebral malaria, in the context of surveillance of adverse events; as well as the compilation of evidence on the functioning of country immunization programs and the use of currently recommended malaria control measures. These implementation projects would be undertaken in addition to the Risk Management Plan agreed between the EMA and GSK in 2015.

**5. What are the next steps for RTS,S?**

WHO's publication of its position paper is an important step in the process toward making RTS,S available alongside existing tools currently recommended for malaria prevention, diagnosis, treatment, and control. Next steps include decisions about design of the pilot implementations and decisions regarding funding of the implementation programme. GSK and PATH are already working with WHO to provide the necessary information needed to facilitate the design of the pilots.

Another important step will be successful applications to national regulatory authorities by GSK, as RTS,S will need to be licensed prior to the initiation of vaccinations in the pilot implementations and Phase IV studies.

**6. What is Mosquirix™?**

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

**7. 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.

**8. 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.

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

In its evaluation of the vaccine, the European Medicines Agency 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 7 days after a dose (mostly the third dose) of Mosquirix™."

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 incidence of

such seizures within seven days of a fourth dose in children was 2.5 per 1,000 doses in those receiving four doses of RTS,S; 1.2 per 1,000 doses in those receiving three doses plus a comparator vaccine at 20 months; and 0.4 per 1,000 doses in those receiving only control or comparator vaccines. For the infant age group, febrile seizures were also noted following a fourth dose of RTS,S, at a rate of 2.2 per 1,000 doses.)

The 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. One imbalance noted in published results from the Phase III trial and the EMA's assessment concerned an imbalance in meningitis cases in older children receiving RTS,S; however no clear 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." The occurrence of meningitis as a potential risk will be followed closely in extended follow-up in 3 of the 11 study sites that conducted the Phase III trial, and in the planned pharmacovigilance study included in the Risk Management Plan approved by the EMA.

The potential for rebound—or age shifting—with respect to the incidence of severe malaria (including clinical malaria) has also been noted as a possibility. In the Phase III trial, among children 5-17 months of age at first dose, the incidence of severe malaria decreased over time in all groups. However, children protected by RTS,S are thought to develop their natural immunity against malaria more slowly than unvaccinated children. This means that in areas where malaria is present, vaccinated children may be at higher risk of disease when the protection from the vaccine decreases over time. The potential risk of rebound will be further evaluated in ongoing and long-term clinical studies.

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

Clinical study results indicate that RTS,S has the potential to help protect infants and young children living in malaria-endemic regions in sub-Saharan Africa. Over the first year after vaccination in the Phase 3 efficacy and safety trial, RTS,S reduced the number of malaria cases by half in children and by one third in infants. Vaccine efficacy was highest shortly after vaccination, but could be enhanced by a fourth dose.

The final results of the Phase 3 trial, published in April 2015 in *The Lancet,* reported that vaccine efficacy against clinical malaria for the young child category was 39% for those who received a fourth dose and 26% for those who did not receive it, over an average 48 months of follow-up.[2] Statistically significant vaccine efficacy against severe malaria to the end of the study period was observed in those who received the fourth dose, but not in those who did not.

**11. 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 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.

**12. 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.

**13. Why is RTS,S only for children and infants? Why not adults?**

RTS,S has been developed for use in preventing malaria in young children living in malaria-endemic regions in sub-Saharan Africa. Our efforts focused on this age category because most cases and deaths from malaria occur in African children under five years of age; a vaccine would represent a potential additional tool alongside existing malaria control measures.

**14. 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 438,000 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 fourth dose at 18 months after the primary schedule, 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 in areas of higher disease burden.

**15. When might the vaccine become available for use?**

The positive opinion adopted by the CHMP in July 2015 and the policy recommendation from WHO in January 2016 are key steps in the process toward making the RTS,S vaccine candidate available as an addition to existing tools currently recommended for malaria prevention and treatment. In its policy recommendation, WHO has stated that the vaccine should be implemented in 3–5 distinct epidemiological settings in sub-Saharan Africa covering moderate-to-high transmission settings. The timing or duration of the steps between the current WHO recommendation and wide-scale availability in African countries has yet to be established.

**16. How much will the vaccine cost?**

GSK has stated that RTS,S would be made available at a not-for-profit price and that the price will be the cost of manufacturing the vaccine plus a small return of around five percent, to 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.

**17. 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.

**18. 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) World Health Organization. *Weekly Epidemiological Record*. 2016; 91(4): 33–52.
2) RTS,S Clinical Trials Partnership, *The Lancet.* 2015; 386 (9988): 31–45.


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