

RTS,S frequently asked questions

1) Why do we need a malaria vaccine?

Vaccines have historically offered one of the most effective means of preventing disease and saving lives, particularly for infectious diseases. Malaria kills close to 900,000 people each year with the majority of deaths occurring in children under the age of five in sub-Saharan Africa. Even a partially effective malaria vaccine would have the potential to save hundreds of thousands of lives. A vaccine would complement and enhance existing measures to fight malaria, such as bed nets and indoor residual spraying.

2) What is RTS,S? How effective is the vaccine?

RTS,S (also called RTS,S/AS) is the most clinically advanced malaria vaccine candidate in the world. It became the first vaccine to demonstrate that it can protect young children (in 2004) and infants (in 2007) living in malaria-endemic areas against clinical disease and infection, caused by *Plasmodium falciparum*, the most deadly species of the malaria parasite.

Results from two separate Phase 2 trials, reported in December 2008 in *The New England Journal of Medicine*, found that RTS,S had a promising safety and tolerability profile and reduced the risk of clinical episodes of malaria by 53 percent in children aged 5 to 17 months over an eight-month follow-up period. Data also showed for the first time that the vaccine candidate can be safely administered alongside standard infant vaccines that are part of existing African national immunization programs, called the World Health Organization (WHO) Expanded Program on Immunization (EPI).

3) Who is responsible for the development of RTS,S? What are the roles of the various partners? How long has it been in development?

The Phase 3 clinical trials build on more than 20 years of RTS,S research and development, including nearly ten years of clinical trials in Africa. The vaccine was invented and developed in laboratories at GlaxoSmithKline (GSK) Biologicals' headquarters in Belgium in the late 1980s. Early development and clinical testing of the vaccine was part of an ongoing collaboration between GSK and the Walter Reed Army Institute of Research.

RTS,S was initially tested in healthy adults in the United States and Belgium before the first study in Africa was conducted in adults living in the Gambia in 1998. In January 2001, GSK and the PATH Malaria Vaccine Initiative (MVI), with support from the Bill & Melinda Gates Foundation, signed a collaboration agreement to pursue pediatric clinical development of RTS,S in Africa. To advance the development program, African research centers and collaborating institutions have since joined the partnership.

MVI ensures the clinical trial sites are prepared to conduct high-quality trials, including assisting with the technical design of the trials as well as conducting and participating in training and oversight of the trials.

GSK takes the lead role in the clinical development, manufacturing, interactions with the regulatory agencies, and in the commercialization and distribution of an eventual approved vaccine. GSK is also responsible for manufacturing, including scale-up of production.

The clinical development of RTS,S is being implemented by the Clinical Trials Partnership Committee, a collaboration of leading African research institutes, Northern academic partners, MVI and GSK, with support from the Malaria Clinical Trial Alliance.

4) How safe is RTS,S and what are its potential side effects?

Our highest priority is ensuring the safety of the children receiving the vaccine. Published studies to date indicate that RTS,S has a promising safety and tolerability profile in infants and young children. No deaths or serious adverse events have been attributed to the vaccine. Its safety and reactogenicity profiles were similar to those observed with standard EPI vaccines given to infants, including comparable local pain and swelling. We will continue to monitor safety closely as part of the Phase 3 studies.

5) What is a Phase 3 trial? How will this Phase 3 trial work?

As part of the final steps before licensure, the Phase 3 trial is designed to confirm safety and further determine the efficacy of the vaccine in infants and children. This landmark Phase 3 study is expected to enroll more than 16,000 infants and children at 11 sites in seven African countries, making it the largest malaria vaccine trial to date.

It is a double-blind, controlled trial. Participants will initially receive three doses of either RTS,S or a control vaccine (on a 0, 1, 2 month schedule). After a year and a half they will receive a fourth dose of either RTS,S or another control vaccine to assess whether a “booster” dose may enhance the protective effect of RTS,S.

6) Where will Phase 3 take place and who will participate?

The trial will begin in the coming months in 11 sites in Gabon, Mozambique, Ghana, Kenya, Malawi, Tanzania, and Burkina Faso, pending required local and national approvals. The participants are children aged 5 to 17 months, and infants 6 to 12 weeks old. Leading African research institutions and their Northern academic partners will conduct the trials. The sites were selected for their track record of conducting world-class research, strong community relations and a commitment to meet the most rigorous ethical and regulatory standards.

7) Why is RTS,S being developed and tested in Africa?

More than 90 percent of malaria cases and the great majority of malaria deaths occur in sub-Saharan Africa. To determine whether the candidate vaccine confers immunity and protection against the *P. falciparum* parasite, it is necessary to test it in an environment where participants are exposed to infection. The safety of the vaccine has been established in previous clinical trial in adult volunteers in the United States, Belgium and The Gambia. The 11 sites participating in the Phase 3 trial represent diverse transmission areas. The RTS,S clinical trials are designed to adhere to the strictest international and national safety and ethical guidelines, including rigorous informed consent procedures.

8) How will the partners ensure that trials are conducted safely and ethically?

The Phase 3 trial, as those that preceded it in Phase 1 and Phase 2, is conducted according to the International Conference on Harmonization Good Clinical Practice guidelines, and on-site clinical trial monitoring is conducted by GSK Biologicals. The trial is reviewed by international and national regulatory authorities, national ethical bodies, and by local institutional and/or ethical review boards. In addition, an independent Data Monitoring Committee will also oversee the trials to ensure the

ongoing safety of the study participant. Local safety monitors at each of our sites liaise with the Data Monitoring Committee that reviews adverse events in real-time.

Safety is always our most important concern, and if at any point it is determined that children's safety is at risk, the trial will be stopped immediately.

9) How will you ensure informed consent? What does informed consent mean in a trial like this?

Informed consent is a critical process in any clinical trial to ensure that participants and/or their parents understand the objectives of a research endeavor, and the risks and benefits of participation. This is also an important educational and community outreach aspect of RTS,S clinical development.

Even before a trial starts, the teams at each of the centers hold public meetings and informational sessions. This is done with the participation of local leaders including the chiefs of the local villages. Those parents who are interested in the studies are invited to come to the health clinic.

Prior to confirming individual consent, individual or group sessions are held with parents where they are informed in detail about previous results and the forthcoming study. Parents are encouraged to ask the clinical trial investigators anything they would like. It is stressed that participation is voluntary.

Written informed consent using approved forms in the appropriate local language is obtained before study procedures begin. Non-literate parents are educated about the consent form's content and indicate approval by using a thumbprint with a signature from a literate witness to the consent procedure.

10) What happens after Phase 3? When will the vaccine be approved for use in Africa?

The Phase 3 efficacy trial has been designed in consultation with appropriate regulatory agencies and the World Health Organization. If the Phase 3 trial progresses as expected, RTS,S could be submitted for regulatory review as early as 2011.

Results from the entire development program, including Phase 3 clinical trials would be submitted to the European Medicines Agency (EMA) under a new mechanism called Article 58 of EU Medicines Legislation. In addition to the EMA, the pathway to licensure will involve discussions with the WHO and national drug regulatory agencies across Africa and national public health authorities.

Should regulatory clearance be granted, the vaccine could be introduced in 2012 for children aged 5 to 12 months with full availability by 2014 following approval for infants, potentially saving hundreds of thousands of lives.

11) How will you ensure that every child in Africa will get the vaccine if it is approved?

MVI and GSK are committed to making the vaccine available and affordable to those who need it most—young children in malaria endemic regions in sub-Saharan Africa. GSK and MVI are already working with malaria-affected countries and international institutions to achieve this goal.

MVI and the WHO developed the Malaria Vaccine Decision-Making Framework to help countries prepare for future adoption of a malaria vaccine and avoid unnecessary delay between recommendations for use of a vaccine and its availability in low-income countries.

The partners agree that price will not stand in the way of access, but it's too early to determine the exact price since the vaccine will not be submitted for regulatory review until 2011. GSK expects to

collaborate closely with multilateral groups such as the GAVI Alliance, UNICEF, and others to allow these organizations to purchase the vaccine in large volumes at affordable prices. They in turn will distribute the vaccine to African governments and mothers—a child will not be turned away because of the price of the vaccine.

12) Why should Africa start preparing now if the vaccine will not be approved for several years and there is no guaranteed funding for its purchase?

The world has never been closer to having a malaria vaccine. We have learned from other interventions that if planning for a decision is not started years in advance, the intervention may ultimately, and unfortunately, remain un-used years after availability. The planning and decision-making process takes time and careful evaluation; the goal for RTS,S is that there is minimal, if any, delay between time of regulatory clearance and uptake.

By beginning the process now of gathering data and establishing systems to aid in decision-making, countries can determine the appropriate role of a malaria vaccine in their health systems years sooner than seen with other interventions, thus saving many additional lives.

13) How much will development of the vaccine cost and who is paying?

Funding for the development of this vaccine candidate has been made possible through a US\$107.6 million grant from the Bill & Melinda Gates Foundation to MVI. GSK has invested more than \$300 million to date and expects to invest at least another \$100 million before the completion of the project.