

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 Expanded Program on Immunization (EPI). A recent study published in the August 2009 issue of *The Journal of Infectious Diseases*, also demonstrated that the vaccine is capable of inducing long-term protection against malaria for up to 45 months of follow-up after initial vaccination.

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 trial builds on more than 20 years of RTS,S research and development, including 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 United States 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 grant monies from the Bill & Melinda Gates Foundation to MVI, 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, 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 Trials 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. Its safety and reactogenicity profiles were similar to those observed with standard EPI vaccines given to infants, including comparable local pain and swelling. No deaths have been attributed to the vaccine. We will continue to monitor safety closely as part of the Phase 3 trial.

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

As part of the final steps before regulatory file submission, 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 up to 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 (with a 1 month interval between doses). After a year and a half, participants 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 full Phase 3 trial will take place in 11 sites in seven African countries that represent different transmission settings: Gabon, Mozambique, Ghana, Kenya, Malawi, Tanzania and Burkina Faso. 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 world-class clinical research, strong community relations and commitment to meeting the highest international ethical, medical, clinical and regulatory standards.

7) What is the status of the Phase 3 trial?

The Phase 3 trial began in May 2009 in Bagamoyo, Tanzania. It is now underway in 10 of 11 planned sites in seven African countries: Gabon, Mozambique, Ghana, Kenya, Malawi, Tanzania, and Burkina Faso. The trial will eventually enroll up to 16,000 young children and infants.

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

More than 90 percent of malaria cases caused by the *P. falciparum* parasite 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 11 sites participating in the Phase 3 trial represent diverse transmission settings. The safety of the vaccine has been established in previous clinical trials in adult volunteers in the United States, Belgium and the Gambia. The RTS,S clinical trials are designed to adhere to the strictest international and national safety and ethical guidelines, including rigorous informed consent procedures.

9) 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 national regulatory authorities, national ethical bodies and local institutional and/or ethical review boards. In addition, an independent data monitoring committee (IDMC) oversees the trial, supported by a local safety monitor (LSM) at each of the research centers. The main objectives of the IDMC and the LSM are to oversee the safety data and data collection processes, as well as to check that the study participants' rights are respected.

10) 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 potential 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. Illiterate 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.

11) 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 (WHO). If the Phase 3 trial progresses as expected, RTS,S could be submitted for regulatory review as early as 2012.

Results from the entire development program, including the Phase 3 clinical trial, would be submitted to the European Medicines Agency (EMA) using a specific provision of the EMA legislation called Article 58. Article 58 allows the EMA to assess, in collaboration with WHO, the quality, safety and efficacy of a medicinal product intended exclusively for use outside the European Union for a disease of major public health interest. This assessment requires products to meet the same standards as medicinal products intended for use in the European Union.

In addition to the EMA, the pathway to approval and implementation will involve reviews by the WHO and national drug regulatory agencies across Africa and national public health authorities.

Under current plans, the RTS,S vaccine candidate would be submitted to regulatory authorities in 2012 based on efficacy in children 5 to 17 months of age. Additional safety and immunogenicity data from the infant population will be submitted soon thereafter, followed by efficacy data for infants once available. Depending on the final clinical profile of the vaccine and the timetable of the regulatory review process, the first vaccine introduction could take place over the next three to five years.

12) 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, the WHO, and United States Agency for International Development developed the Malaria Vaccine Decision-Making Framework to help countries prepare to make decisions related to 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 is too early to determine the exact price since the vaccine will not be submitted for initial regulatory review until 2012. 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.

13) 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 unused 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.

14) 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 the support of the Bill & Melinda Gates Foundation, which has provided more than \$200 million in grant monies to MVI for this project since 2001. GSK has invested more than \$300 million to date and expects to invest at least another \$100 million before the completion of the project.