

## RTS,S FAQs

### Contents

[The MAL 038 Trial](#)

[The RTS,S Vaccine Candidate](#)

[The RTS,S Clinical Development Team](#)

### The MAL 038 Trial

**Q: What are the key results we can take away from the MAL 038 study? How do the data compare to the previous data on RTS,S?**

A: This study is the first proof of concept of the malaria vaccine candidate RTS,S in infants, the most vulnerable age group for malaria in Africa. It demonstrates for the first time that African infants exposed to malaria transmission (*P. falciparum*) can be protected by a vaccine. RTS,S showed 65 percent efficacy against infection for the three months following the third and final dose, and 35 percent efficacy against clinical disease when measured over a six-month period following the first dose.

The endpoints and trends from this study are consistent with, and lend further support to, the findings of the larger-scale 2004 landmark trial in Mozambique (MAL 026) in children ages 1-4 that showed the vaccine provided 45 percent protection against infection, 35 percent protection against clinical disease.

The clinical malaria results from the MAL 038 study, however, should be viewed in the context that the primary endpoint was safety. The secondary endpoints are efficacy against infection and against clinical malaria. Efficacy against severe disease was not included due to the smaller size of this safety study. Importantly, aside from efficacy against infection and clinical disease, RTS,S has a promising safety and tolerability profile among the infants tested. In the study, the vaccine's safety and reactogenicity profiles were similar to those observed with standard EPI vaccines given to infants, including local pain and swelling.

These landmark results substantially advance the vision that a vaccine will be capable of protecting young African children and infants against malaria and therefore will contribute to reducing the burden and deaths caused by the disease.

**Q: What does the MAL 038 study mean for commencing Phase III RTS,S trials?**

A: The MAL 038 study moves us much closer to pivotal Phase III trials of what could become the world's first malaria vaccine.

Other Phase II studies of RTS,S are still underway evaluating schedule, dosing and an improved formulation of the vaccine. If progress continues as anticipated, Phase III will commence in the latter half of 2008.

**Q: How does this most recent study (MAL 038) compare with the earlier large-scale trial in Mozambique (MAL 026): similarities and differences?**

A: There are many similarities and differences between the two studies. A few will be highlighted here.

On similarities, both studies were conducted by CISM in the same region of Mozambique using the same vaccine; both studies affirmed the safety profile of the vaccine and its promising efficacy against malaria infection and clinical disease; and both studies served as proof of concept on important issues, i.e., for MAL 026, that a malaria vaccine can work in children, and for MAL 038, that it can work in African infants, which constitute the most vulnerable population. To sum up, the findings of MAL 038 lend additional support to those of MAL 026 and represent a significant and positive step in moving forward the world's most advanced malaria vaccine candidate.

On differences, MAL 026 was a relatively large-scale trial with more than 2,000 children (aged 1-4 years old), while MAL 038 was smaller, with just over 200 young infants. Additionally, the MAL026 findings were based on a longer follow-up period of approximately 18 months after the final dose of vaccine as compared with MAL 038 which was based on 3 months of follow-up. The trials varied because the research objectives of the trials (endpoints) required different numbers of participants and different time periods. There was also a very slight difference in the Adjuvant System formulations.

**Q: Why do the trial results state that RTS,S is 65 percent efficacious against infection but only 35 percent against clinical malaria?**

A: Efficacy against infection and efficacy against clinical malaria are two interrelated measures, with the former determined by the presence of the malaria parasites in the blood and the latter quantified by the number of cases that reach certain symptomatic and parasite thresholds. The larger and longer planned Phase III study will fully establish the value of these efficacy endpoints and determine their relationship to one another.

**Q: This trial was coordinated with the standard Expanded Program on Immunization (EPI). Do the results show that RTS,S can be administered as part of the EPI regimen?**

A: In this study of African infants, the three RTS,S doses were staggered by two weeks with the EPI vaccinations. EPI was administered at 8, 12, and 16 weeks of age and RTS,S was administered at 10, 14, and 18 weeks. A separate clinical trial is underway in order to investigate the co-administration of RTS,S with the EPI vaccines.

## **The RTS,S vaccine candidate**

**Q: When will RTS,S be brought into wide use in Africa?**

A: RTS,S is currently undergoing Phase II clinical trials. It is anticipated, if all goes well, that Phase III trials will commence in the second half of 2008. This would make it possible to submit the vaccine to regulatory authorities in 2011.

**Q: Will the national health systems in African countries be able to afford RTS,S and how much do you project it will cost per dose?**

A: PATH/MVI and GSK Biologicals are committed to making the vaccine available to those who need it -- infants and children in malaria endemic regions of Africa. It is still early to determine the exact price, which will be negotiated with the purchasers of the vaccine – likely to be multilateral groups who would cover the costs on behalf of malaria-endemic countries. The price will reflect the volume and duration of contracts as well as the cost of manufacturing and developing the vaccine.

GSK pioneered tiered pricing more than 20 years ago with multilateral purchases so that low-income countries can afford vaccines and the same principle will guide this pricing structure. All the parties involved fully expect the vaccine to be sold at prices that support the sustainable production and distribution of the vaccine to those most at risk.

**Q: How safe is RTS,S and what are its potential side effects?**

A: The safety of the vaccine is our highest priority. Published studies to date indicate that RTS,S has a promising safety profile and is well tolerated in infants. No deaths or serious adverse events have been attributed to the vaccine, and 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 ongoing Phase II trials and Phase III studies, which we expect to begin in the later half of 2008.

**Q: To date, studies show that RTS,S reduces clinical malaria by about one-third and severe malaria by about half. What level and duration of efficacy will be necessary to license the vaccine and have good uptake?**

A: Given that malaria kills approximately one million people annually, most of whom are infants and children in sub-Saharan Africa, a vaccine that reduces severe malaria by half could save hundreds of thousands of lives annually. Furthermore, reducing the burden of malaria would have a substantial positive impact for the overburdened health systems of the region.

**Q: With the significant impacts being demonstrated by bed nets and indoor spraying campaigns, is a malaria vaccine really necessary?**

A: Current anti-malaria interventions such as bed-nets and indoor spraying are critical prevention tools. However, evidence suggests that in order to control malaria and save more lives, we need more tools. Vaccines are one of the most powerful public interventions in human history. Previous experiences with smallpox and polio have shown immunizations are a highly cost effective tool against infectious disease and we foresee this to be the case with malaria as well.

We believe that a malaria vaccine is a necessary component of the multi-pronged strategy that will eventually protect the world's people against the ravages of this disease.

## **The RTS,S Clinical Development Team**

**Q: Who are the key players in the MAL 038 trial? Are there other organizations involved in the clinical development of RTS,S?**

A: A number of groups are involved in this trial. They include the Centro de Investigação em Saude de Manhiça, Mozambique (CISM); the Ministry of Health of Mozambique (MOH); the Hospital Clinic of the University of Barcelona, Spain; GlaxoSmithKline Biologicals (GSK), and the PATH Malaria Vaccine Initiative (PATH/MVI). The Bill & Melinda Gates Foundation provides funding through a grant to PATH/MVI.

Specifically, the study was conducted by the Centro de Investigação em Saude de Manhiça (CISM, Manhiça Health Research Centre) in Manhiça, Mozambique by scientists from the Hospital Clinic of the University of Barcelona and the Mozambique Ministry of Health. Core funding for CISM is provided by the Spanish Agency for International Cooperation (AECI).

GlaxoSmithKline (GSK) Biologicals invented the vaccine in 1987 and has cumulatively invested more than \$300 million in its development for over 20 years. As the developer of the vaccine, GSK has the lead role in clinical development, manufacture, interactions with the regulatory agencies, and production and commercialization of an eventual vaccine.

The PATH Malaria Vaccine Initiative provided \$107 million in funding, through a grant from the Bill & Melinda Gates Foundation to help conduct the trials. PATH/MVI plays a key role in the development and implementation of the clinical development plan, ensuring that the clinical trial sites are prepared to conduct high-quality trials, and as a catalyst in bringing all the players together.

Overall, for the RTS,S Phase II trials, PATH/MVI and GSK are collaborating with many research institutions in Africa and the rest of the world in order to facilitate activities at seven clinical trial sites in Mozambique, Tanzania, Gabon, Ghana, and Kenya. For Phase III, three additional sites are anticipated in Malawi, Burkina Faso, and Kenya.

The Bill & Melinda Gates Foundation provide invaluable financial support to PATH/MVI to fund this work.

**Q: Why is a public-private partnership necessary to develop a malaria vaccine like RTS,S?**

A: Market forces alone will not lead to the aggressive development of a vaccine needed primarily by developing countries. Public-private partnerships such as this one are important for several reasons: (1) they help share the risks and speed learning of R&D; (2) they leverage additional R&D funding for vaccines and medicines that would not normally meet a company's return on investment; and (3) they ensure that these vaccines and medicines get to those most in need as rapidly as possible.

The ongoing work on RTS,S serves as an excellent model of how the public and private sectors can work together in a productive way in order to deliver an effective malaria vaccine as quickly as possible to those who need it most. Long-term success will require wider partnership with national governments, donor governments, malaria control and EPI programs, multilateral agencies, GAVI, the Vaccine Fund, the pharmaceutical industry, and others.

**Q: If the vaccine is licensed and deployed, who will profit the most from it?**

A: We can start saving millions of lives with an effective vaccine and every day counts. The greatest beneficiaries will be the nations and people of sub-Saharan Africa who will see a reduction in the tremendous burden of malaria.

The Africa clinical trial sites will be recognized in-country and internationally for their key role in bringing the vaccine to fruition.

PATH/MVI, whose focus is on identifying the most promising vaccines and technologies and implementing targeted partnerships with private industry, academia, governmental and other institutions, will move forward in its mission to accelerate the development of promising vaccine candidates and ensure their availability and accessibility in the developing world.

GSK has been making vaccines that address global health needs for more than 30 years, especially major threats to infants and children. It is also developing other second generation malaria vaccines and will continue to invest in the field.

**Q: Aside from the development of a malaria vaccine, does this vaccine development program offer any benefits to African health systems or institutions?**

A: There are diverse ancillary benefits for the African partners through participation in the RTS,S trials, the value of which can extend far beyond the individual vaccine being tested.

At many of the trial sites, equipment has been purchased by PATH/MVI to upgrade facilities to enable them to conduct analyses at world-class levels and to better safeguard the health and wellbeing of trial participants. Capacity building and training of local staff by GSK and PATH/MVI helps strengthen and upgrade the research capabilities and overall health services at the sites.

Also, data gained through the trials helps provide greater understanding about the persistence of disease in certain areas of high transmission that could inform other anti-malaria initiatives, such as bed nets, spraying, and allocation of resources for medicines.

Finally, given the likelihood that a malaria vaccine could be submitted to regulatory authorities relatively soon, the experience gained through the RTS,S clinical development allows the host country to learn more about what implementing a vaccine entails. This knowledge can be applied to other vaccine initiatives in the future. Such preparatory work is now being carried out by the RTS,S development team with stakeholders including international health organizations and the governments of interested countries to gain better insights on efficacy, the population's reaction to immunization, and local concerns and questions about malaria vaccines. Complementary experience is being gained at the national level on regulatory issues.

**Q: Do African countries need to participate in the trials in order to receive and use the vaccine if and when it becomes available?**

A: No, this is not a requirement for use of the vaccine when it becomes available.

**Q: Do public-private partnerships like the one between GSK and PATH/MVI exist for other diseases and interventions?**

A: The PATH/MVI-GSK collaboration agreement formalized a landmark alliance that, if all the project milestones are achieved, will take the world's most advanced malaria vaccine through licensure and introduction to the benefit of African children towards the combat of malaria. We believe this innovative public-private partnership on RTS,S demonstrates a new paradigm in meeting the critical health challenges of Africa and the developing world, and may serve as a model for other public-private partnerships that are seeking solutions for seemingly intractable public health problems in developing countries.

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