

RTS,S Malaria Vaccine: Frequently Asked Questions

What is the RTS,S vaccine?

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

Why do we need a malaria vaccine?

Historically, vaccines have proved to be one of the most effective means of preventing disease and saving lives, particularly in the case of infectious diseases. Malaria kills around 800,000 people each year and the majority of deaths are in children under the age of 5 living in sub-Saharan Africa. Even a partially effective vaccine could potentially save hundreds of thousands of lives. A vaccine would complement and reinforce the measures currently used to fight malaria, such as bed nets and indoor spraying with insecticides that have residual effects.

What age groups participated in the RTS,S malaria vaccine trial for which the results have just been published?

The data on the RTS,S malaria vaccine released in October 2011 come from an interim analysis of the results of a Phase III clinical development trial in 2 age groups: infants between 6 and 12 weeks old and children aged 5 to 17 months. The results published report prevention of severe malaria in both groups and of clinical malaria in the children aged 5 to 17 months.

What is a Phase III trial?

A Phase III trial is one of the last steps that must be carried out prior to the submission of an application to the regulatory authorities for approval to market the vaccine. The aim of this particular trial is to confirm the safety and to determine more accurately the efficacy of the candidate vaccine in infants and children. This landmark Phase III study, which started in 2009, has enrolled 15,460 infants and children in 11 trial sites spread across 7 African countries (Mozambique, Tanzania, Kenya, Malawi, Ghana, Gabon and Burkina Faso), making it the largest trial of a malaria vaccine ever conducted.

Is the level of efficacy obtained in the Phase III trial the maximum possible for a malaria vaccine?

The results of this trial confirm the efficacy levels previously observed in Phase II. Levels of efficacy remained high in this study, although work continues on the evaluation of other products that may offer even greater efficacy. Consequently, it is essential to persevere with the many lines of malaria research and different ways of preventing the disease.

Does the data being presented today represent the definitive results?

The data being presented today are interim results, although the information is the definitive initial evaluation of efficacy and safety data called for by the analysis plan.

Can this new RTS,S malaria vaccine be administered now to the people who need it most? What happens next?

The next step is to complete the Phase III clinical trial in both age groups and to obtain sufficient data to support definitive conclusions. This will probably take until 2014-2015. Once final results have been obtained, it is expected that the World Health Organization will recommend the use of the RTS,S vaccine.

How long has it taken to develop this vaccine?

This Phase III clinical trial is the culmination of more than 20 years of research and development of the RTS,S vaccine, including 10 years of clinical trials in Africa. The vaccine was invented and developed in laboratories at the headquarters of GlaxoSmithKline (GSK) Biologicals in Belgium in the late 1980s.

Early development and clinical testing of the vaccine was undertaken by GSK in collaboration with the Walter Reed Army Institute of Research in the USA.

The results of a Phase II trial started in 2003 in southern Mozambique demonstrated the feasibility of administering a malaria vaccine to children. Findings from that trial, which was led by Dr. Pedro Alonso at the Manhica Health Research Centre (CISM) in collaboration with Barcelona Centre for International Health Research (CRESIB, Hospital Clínic-Universitat de Barcelona), showed that RTS,S was efficacious for at least 18 months in reducing clinical malaria by 35% and severe malaria by 49%.

In 2007, the results of a second study showed that after a full vaccination course in infants, RTS,S reduced infection by 65% over a 3-month follow-up period. Importantly, the vaccine also displayed a promising safety and tolerability profile, similar to the standard required for the vaccines commonly given to infants in the World Health Organization's Expanded Program on Immunization.

Who developed the RTS,S vaccine?

The later stages of clinical development of RTS,S in children have been carried out jointly by GlaxoSmithKline and the PATH Malaria Vaccine Initiative, a non-profit organization based in Seattle (USA) with financial support from the Bill & Melinda Gates Foundation and the collaboration of academic institutions throughout the world, including 11 research centres in 7 sub-Saharan African countries.

Why is this vaccine being developed in Africa?

P. falciparum, the most lethal malaria parasite, is predominant in sub-Saharan Africa, the area where most deaths from malaria occur. To determine whether

the candidate vaccine confers immunity and protection against the *P. falciparum* parasite, it must be tested in an environment where participants are naturally exposed to infection. The 11 trial sites participating in the Phase III trial represent diverse transmission settings. The safety of the vaccine was established in earlier trials in adult volunteers in the USA, Belgium and The Gambia. The RTS,S clinical trial is designed to comply with the strictest national and international safety and ethical protocols, including rigorous informed consent procedures.

Why can the vaccine not be used now, at least in places where it has shown partial efficacy?

While the availability of a vaccine will be a great step forward, malaria can also be prevented using traditional methods, such as mosquito nets impregnated with insecticide. Moreover, there are treatments that can quickly and effectively cure infection in most cases. The final results of the Phase III trial are needed before the vaccine can be used generally.

What will be the price of the RTS,S vaccine and who will pay?

Access to a preventive measure for those most in need is a very important issue. However, the cost of the RTS,S vaccine and who will pay for it has not yet been determined and will depend on agreements reached between the developers of the vaccine and the institutions interested in its distribution to populations at risk of malaria, the governments of the countries most affected, and the international organizations that promote vaccination against communicable diseases.

How will you ensure access to those who most need the vaccine?

The Malaria Vaccine Initiative, the World Health Organization and the United States Agency for International Development have developed the *Vaccine Decision-Making Framework* to help decision makers in each country to prepare themselves for the decisions that will have to be taken to ensure the future adoption of a malaria vaccine. The aim of this framework document is to avoid unnecessary delay between recommendations for use and eventual availability in low-income countries.

All of the partners have agreed that price will not be a barrier to access to the vaccine, but it is too early to determine the exact price since the vaccine will not be submitted for regulatory review until 2014-2015.

Does administration of the RTS,S obviate the need for all other malaria prevention measures ?

Although these early results are very promising, the role the RTS,S vaccine may play in the control of malaria will still depend on the results achieved in the coming years. RTS,S is a key new tool which, as long as these promising initial results are confirmed, will be a welcome addition to the current arsenal of malaria-control measures, which includes the use of insecticide-impregnated mosquito nets, and timely and appropriate treatment of diagnosed cases of malaria. Since the efficacy of the vaccine is partial, it will complement rather than replace other measures, providing, in conjunction with these, a more complete approach to the prevention of malaria.

Is this vaccine a preventive measure against malaria for use by travellers?

No, this vaccine has been designed to prevent childhood disease in populations where malaria is endemic.

What role did Spanish researchers play in the development of this vaccine?

The Barcelona Centre for International Health Research (CRESIB, Hospital Clínic de Barcelona) in collaboration with the Manhica Health Research Centre (CISM) in Mozambique conducted key proof-of-concept trials to confirm the safety, immunogenicity and efficacy of the vaccine in children aged 1 to 4 years and infants. These trials were essential to the later implementation of the Phase III program.