Fact sheet: Phase III safety and efficacy trial of the RTS,S malaria vaccine candidate

RTS,S is the most clinically advanced malaria vaccine candidate in the world today; it is being developed in partnership by GlaxoSmithKline (GSK) and the PATH Malaria Vaccine Initiative (MVI), together with prominent African research centers. In Phase II clinical trials, it was the first vaccine candidate to demonstrate that it could help protect young children and infants in malaria-endemic areas against infection and clinical disease caused by *Plasmodium falciparum*, the most deadly species of the malaria parasite.[1,2]

The launch of the Phase III efficacy trial of the RTS,S malaria vaccine candidate marked an important milestone after more than 20 years of research and development. The trial started in May 2009 and is now underway at 11 sites in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania). Together, the 11 sites completed enrolment in January 2011, with 15,460 infants and young children participating, making this the largest malaria vaccine trial in Africa to date.

Design of the trial

As one of the final stages of testing before regulatory file submission, the Phase III efficacy trial is designed to continue monitoring safety and potential side-effects, while evaluating the efficacy of the vaccine in infants and young children on a large scale. To this end, researchers enrolled two groups of participants: children aged 5 to 17 months and infants aged 6 to 12 weeks. The Phase III trial is a double-blind study, in which participants initially received three doses of either RTS,S or a 'control vaccine.' After a year and a half, some participants will receive a fourth RTS,S dose to evaluate the potential benefit of a booster. The trial has been designed in consultation with appropriate regulatory authorities and the World Health Organization (WHO) and is conducted according to the highest international standards for safety, ethics, and clinical practices.

Results

The first results from the ongoing RTS,S Phase III efficacy trial were published in the *New England Journal of Medicine* in October 2011 and showed that the RTS,S malaria vaccine candidate provided young African children with significant protection against clinical and severe malaria with an acceptable safety and tolerability profile. This analysis, stipulated in the original approved protocol, was performed on data from the first 6,000 children aged 5 to 17 months, and showed that three doses of RTS,S reduced the

RTS,S Phase III sites and research partners

Burkina Faso – Nanoro
Institut de Recherche en Science de la Santé (IRSS) / Centre Muraz

Gabon – Lambaréné
Albert Schweitzer Hospital, Medical Research Unit
+ University of Tübingen

Ghana – Agogo (Kumasi)
School of Medical Sciences, Kwame Nkrumah University of Science and Technology
Kumasi Centre for Collaborative Research
Agogo Presbyterian Hospital

Ghana – Kintampo
Kintampo Health Research Centre, Ghana Health Service
+ London School of Hygiene and Tropical Medicine

Kenya – Kilifi
Kenya Medical Research Institute
+ Wellcome Trust

Kenya – Kombewa (Kisumu)
Kenya Medical Research Institute
+ Walter Reed Army Institute of Research

Kenya – Siaya (Kisumu)
Kenya Medical Research Institute
+ Centers for Disease Control and Prevention

Malawi – Lilongwe
University of North Carolina Project

Mozambique – Manhica
Centro de Investigação em Saúde de Manhiça
+ Barcelona International Health Research Centre

Tanzania – Bagamoyo
Ifakara Health Institute
+ Swiss Tropical and Public Health Institute

Tanzania – Korogwe
National Institute for Medical Research, Tanzania
Kilimanjaro Christian Medical Centre

+ Indicates an affiliated partner

risk of experiencing clinical malaria by 56 percent and severe malaria by 47 percent over the first 12 months following vaccination.[3] These results were achieved on top of existing malaria interventions, such as insecticide-treated bed nets used by 75 percent of study participants.

For every 1,000 children aged 5 to 17 months vaccinated in the control group, we recorded approximately 1,500 cases of clinical malaria over the first year of follow-up. For every 1,000 children that received RTS,S, approximately 750 cases of clinical malaria were recorded, or roughly half the number of cases found in the control group.

In addition, for every 1,000 children aged 5 to 17 months vaccinated in the control group, there were 38 children with at least one case of severe malaria over the first year of follow-up. This was reduced to 20 children with at least one case of severe malaria in the RTS,S group.

Vaccine efficacy against severe malaria in all 15,460 infants and children (aged 6 weeks to 17 months) enrolled in the trial was 35 percent over a follow-up period ranging between 0 and 22 months (average 11.5 months). Further results on RTS,S vaccine efficacy will become available over the next three years.

The health and safety of study participants is the highest priority of the project partners and is carefully monitored until study end. So far, side effects following vaccination included mainly local reactions (such as pain or swelling) and fever, which were observed more frequently following RTS,S immunisation as compared to the control vaccine. However, very few of these reactions were severe. The overall reporting of serious adverse events (mainly medical events requiring hospitalization, regardless of whether they are considered to be caused by the study vaccine) was comparable between the trial's RTS,S candidate vaccine recipients (18 percent) and those receiving a control vaccine (22 percent).

The trial is ongoing, and efficacy and safety results in infants 6 to 12 weeks old are expected by the end of 2012. These data will provide an understanding of the efficacy profile of the RTS,S malaria vaccine candidate in this age group, for both clinical and severe malaria. An additional data set, which will include information about the vaccine's longer-term protective ability for both groups of children, should be available by the end of 2014 and will provide evidence for national and international public health organisations to evaluate the vaccine candidate's full potential for use.

The RTS,S malaria vaccine candidate is currently under development and subject to the evaluation of its safety, quality, and efficacy, as well as its benefits and risks, by regulatory and public health authorities. If the required regulatory and public health information, including safety and efficacy data from the Phase III programme, is deemed satisfactory, the WHO has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible as early as 2015, paving the way for decisions by African nations regarding large-scale implementation of the vaccine through their national immunisation programmes.

Availability of additional data from the RTS,S Phase III efficacy trial

Group	12-month follow-up data	30-month follow-up data
5 to 17 month-olds	Results published[3]	Expected release: Fourth quarter of 2014
6 to 12 week-olds	Expected release: Fourth quarter of 2012	Expected release: Fourth quarter of 2014

Pricing

MVI, GSK, and other partners are working to ensure that RTS,S—if approved for use—reaches the infants and children who need it most, as quickly as possible. In many African countries, childhood vaccines are provided to children for free thanks to existing international and national funding mechanisms. The RTS,S partnership trusts that similar mechanisms would be implemented for a malaria vaccine to allow countries to provide the vaccine to children at nominal or no cost. In January 2010, GSK announced that the RTS,S pricing model will cover the cost of the vaccine together with a small return, which will be reinvested in research and development for second-generation malaria vaccines or vaccines against other neglected tropical diseases.

GlaxoSmithKline Biologicals (GSK Biologicals), GlaxoSmithKline's vaccines business, is one of the world's leading vaccine companies and a leader in innovation. The company is active in vaccine research, development, and production with over 30 vaccines approved for marketing and 20 more in development—both in the prophylactic and therapeutic fields. Headquartered in Belgium, GSK Biologicals has 14 manufacturing sites strategically positioned around the globe. In 2010, GSK Biologicals distributed 1.43 billion doses of vaccines to 179 countries in both the developed and the developing world. Through its accomplished and dedicated workforce, GSK Biologicals applies its expertise to the discovery of innovative vaccines that contribute to the health and well-being of people of all generations around the world. For further information, please visit www.gsk.com.

The PATH Malaria Vaccine Initiative (MVI) is a global programme established at PATH through an initial grant from the Bill & Melinda Gates Foundation. MVI's mission is to accelerate the development of malaria vaccines and ensure their availability and accessibility in the developing world. MVI's vision is a world free from malaria. For more information, visit www.malariavaccine.org.

PATH is an international nonprofit organization that creates sustainable, culturally relevant solutions, enabling communities worldwide to break longstanding cycles of poor health. By collaborating with diverse public- and private-sector partners, PATH helps provide appropriate health technologies and vital strategies that change the way people think and act. PATH's work improves global health and well-being. For more information, visit www.path.org.

***References**:*

1) Alonso P, et al. *Lancet*. 2004; 364:1411–1420.
2) Aponte JJ, et al. *Lancet*. 2007; 370:1543–1551.
3) The RTS,S Clinical Trials Partnership. *NEJM*. 2011; DOI 10.1056/NEJMoa1102287.

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