

## Fact sheet: Phase 3 trial of RTS,S

The launch of the Phase 3 trial of GlaxoSmithKline’s (GSK) malaria vaccine candidate, RTS,S, marks a major research milestone after more than 20 years of research and development. Launched in May 2009, the Phase 3 trial will include 11 sites in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania, as required local and national reviews are obtained. Together, the 11 sites will eventually enroll up to 16,000 children and infants, making this the largest malaria vaccine trial to date.

RTS,S is the world’s most clinically advanced malaria vaccine candidate—as a result of a groundbreaking partnership between leading African research institutions, their Northern academic partners, the PATH Malaria Vaccine Initiative (MVI) and GSK Biologicals, with support from the Bill & Melinda Gates Foundation. Results of clinical studies to date have shown that RTS,S has a promising safety and tolerability profile and reduced the risk of clinical episodes of malaria in young children by 53 percent over an eight-month follow-up period, and provided 65 percent protection against risk of infection in infants over a six-month follow-up period. Recent findings, published in December 2008, indicate that RTS,S can be safely administered to infants in conjunction with traditional childhood vaccines.

One of the final stages of testing before licensure, the Phase 3 trial is designed to confirm safety and further determine the efficacy of the vaccine in infants and children. If the Phase 3 trial is successful, RTS,S will be submitted to regulatory authorities and could be introduced in 2012 for children aged 5 to 17 months with full availability in 2014 for infants aged 6 to 12 weeks.

### African researchers leading an historic effort

Behind this major scientific milestone is a landmark public-private partnership spanning three continents, with African institutions at the forefront. Top Africa-based research centers will conduct the Phase 3 trial, with support from GSK Biologicals and MVI.

This monumental research effort will help build lasting capacity for future scientific research endeavors. Sites were selected for their track record of conducting world-class research, fostering strong community relations and a commitment to meeting the most rigorous ethical and regulatory standards. Seven of the sites have hosted earlier Phase 2 trials of RTS,S. The sites coordinate their efforts and share information through a formal structure, the Clinical Trial Partnership Committee, which includes sites’ Northern academic partners, MVI and GSK, with support from the Malaria Clinical Trials Alliance.

### RTS,S Phase 3 sites and affiliated 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)**

Kumasi Centre for Collaborative Research  
Kwame Nkrumah University of Science and Technology, School of Medical Sciences  
+ Bernhard Nocht Institute  
+ Komfo Anokye Teaching 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  
+ University of Oxford  
+ London School of Hygiene and Tropical Medicine

#### **Kenya – Kombewa (Kisumu)**

Kenya Medical Research Institute  
+ Walter Reed Army Institute of Research

#### **Kenya – Siaya (Kisumu)**

Kenya Medical Research Institute  
+ Centers of 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,  
+ University of Barcelona

#### **Tanzania – Bagamoyo**

Ifakara Health Institute  
+ Swiss Tropical Institute  
+ National Institute for Medical Research, Tanzania

#### **Tanzania – Korogwe**

National Institute for Medical Research, Tanzania  
Kilimanjaro Christian Medical Centre  
+ London School of Hygiene and Tropical Medicine  
+ University of Copenhagen

+ Indicates an affiliated partner

Located in seven countries across Sub-Saharan Africa, the trial sites represent diverse malaria transmission settings, from year-round occurrence to a more limited seasonal threat.

### Structure and design of Phase 3

In order to develop a safe and effective vaccine for those most vulnerable to malaria, researchers will enroll two groups of participants: children aged 5 to 17 months, and infants aged 6 to 12 weeks. The Phase 3 trial will be a double-blind study, in which participants will initially receive three doses of either RTS,S or a “control vaccine.” After a year and a half they will receive a fourth dose in order to evaluate the impact of a “booster” dose.

All infants in the trial will also receive a standard, licensed vaccine that protects against five common childhood illnesses and is recommended by the World Health Organization (WHO). The combination vaccine will be administered alongside the study vaccinations. By delivering these vaccines together, researchers hope to confirm that RTS,S could be given as part of a standard package of childhood vaccines.

The RTS,S development partners have placed the utmost emphasis on the health and safety of the study participants. The Phase 3 trial will be conducted according to the highest international standards for safety, ethics and clinical practices. The trial has been designed in consultation with appropriate regulatory authorities and the WHO. An independent data monitoring committee will also oversee the trial to ensure the ongoing safety of the study participants.

### More than 20 years of progress

Today, RTS,S is the most clinically advanced malaria vaccine candidate in the world. RTS,S aims to trigger the immune system to defend against the *Plasmodium falciparum* malaria parasite as soon as it enters the human host’s bloodstream and/or when the parasite infects liver cells. This prevents the parasite from maturing and multiplying in the liver, reentering the bloodstream and infecting red blood cells, where the host would begin to show symptoms of disease.

To stimulate an immune response to the malaria parasite, the RTS,S antigen fuses a critical circumsporozoite protein—the surface protein that helps the parasite invade human liver cells—with a protein found in GSK Biologicals’ hepatitis B vaccine. The addition of GSK’s proprietary Adjuvant Systems (AS) strengthens the immune response even further. The RTS,S vaccine candidate was invented in 1987 by scientists working in GSK Biologicals’ laboratories.

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 MVI, with support from the Bill & Melinda Gates Foundation, entered into a public-private partnership to develop an RTS,S-based vaccine for infants and children living in malaria endemic regions in Sub-Saharan Africa.

#### Protocol of the Phase 3 study

The multi-center, double-blind, controlled trial will enroll up to 16,000 participants; at least 6,000 in each of two age groups: children, aged 5 to 17 months and infants, 6 to 12 weeks old.

Participants will initially receive three doses of either RTS,S formulated with GSK’s AS01E Adjuvant System 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 (at month 20) to assess whether a “booster” dose may enhance the protective effect of RTS,S. Neither the volunteers nor the investigators will know which vaccine is being administered in order to ensure there is no bias when interpreting the results.

*Two age groups:* Study participants will be divided into two age groups, each of which has three “arms.” The first group, children aged 5 to 17 months, will be randomly selected to receive: (a) four doses of RTS,S, (b) three doses of RTS,S and one of meningitis C vaccine, or (c) three doses of rabies vaccine and one of meningitis C.

The second group, infants aged 6 to 12 weeks, will also be randomly assigned to one of three “arms” which will receive: (a) four doses of RTS,S, (b) three doses of RTS,S and one of meningitis C, or (c) four doses of meningitis C. All infants—regardless of which arm they are assigned to—will receive the first three doses at the same time as a licensed DTPw/HepB/Hib vaccine as recommended by the WHO’s Expanded Program on Immunization schedule.

*Endpoints:* To measure the vaccine’s efficacy, researchers will follow participants for at least two and a half years, and monitor cases of clinical malaria disease. Clinical malaria is a highly relevant public health outcome for a vaccine and is characterized by a fever and other symptoms as well as the presence of parasites in the blood. Researchers will also monitor the incidence of severe malaria and other endpoints.

**About the PATH Malaria Vaccine Initiative (MVI)**

The PATH Malaria Vaccine Initiative (MVI) is a global program 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, please visit [www.malariavaccine.org](http://www.malariavaccine.org).

**About PATH**

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, please visit [www.path.org](http://www.path.org).

**About GlaxoSmithKline (GSK) Biologicals**

GlaxoSmithKline—one of the world's leading research-based pharmaceutical and healthcare companies—is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For company information, please visit [www.gsk.com/media](http://www.gsk.com/media).

GSK Biologicals, one of the world's leading vaccine manufacturers, is headquartered in Rixensart, Belgium, where the majority of GlaxoSmithKline's activities in the field of vaccine research, development, and production are conducted. In 2006, GSK Biologicals distributed more than 1.1 billion doses of vaccines to 169 countries. Of these doses, seventy-five percent of these went to the developing world. Approximately 136 million were doses of combination pediatric protect the world's children from up to six diseases in one vaccine.