

Fact sheet: Results of two RTS,S/AS clinical trials reported in the *New England Journal of Medicine*, December 2008

Recent results from Phase II studies of GlaxoSmithKline (GSK) Biologicals' malaria vaccine candidate RTS,S/ASⁱ demonstrate that the vaccine candidate can provide significant protection against malaria infection and the progression of infection to clinical disease. For the first time, RTS,S/AS administered together with commonly used childhood vaccines has been shown to have both promising safety and efficacy profiles.

The results of two distinct studies conducted in Africa were published online in the prestigious *New England Journal of Medicine* on December, 8 2008.^{ii,iii} Together, these studies substantiate the ongoing efforts for the launch of large-scale Phase III trials of RTS,S/AS in target populations of infants and children. These results build on previous findings, including a 2007 Phase II trial published in *The Lancet* that demonstrated proof of concept that RTS,S/AS could prevent infection in infants.^{iv}

The final step before registration, Phase III trials are designed to confirm safety and further determine the efficacy of the vaccine in infants and children. The Phase III efficacy study is expected to commence in early 2009, pending regulatory approval. The Phase III trial will eventually be conducted at 11 sites across seven African countries. If the Phase III trials are successful, RTS,S/AS could be submitted to regulatory authorities for approval as early as 2011.

Child study: 53 percent efficacy in children

A Phase II trial provided the first demonstration of efficacy of a different formulation of RTS,S/AS against episodes of clinical malaria disease in children.¹ The primary objective of this trial, which was conducted in 894 children in Kenya and Tanzania, was to assess the safety and efficacy of RTS,S, in combination with AS01, a proprietary GSK Adjuvant System.

The trial showed that RTS,S/AS01 reduces episodes of clinical malaria by 53 percent for an eight-month period among children aged 5 to 17 months. Previous studies with another GSK Adjuvant System (AS02) have shown 35 percent efficacy against episodes of clinical malaria for 18 months among children 1 to 4 years old.^v

Researchers concluded that these study results support the use of RTS,S/AS01 for an upcoming Phase III trial. The study in Kenya and Tanzania was led by researchers from KEMRI (Kenya), the National Institute for Medical Research (Tanzania), the Joint Malaria Programme (Tanzania), the Centre for Tropical Medicine at the University of Oxford (UK) and the London School of Hygiene and Tropical Medicine, in collaboration with GSK and the PATH Malaria Vaccine Initiative (MVI).

DESIGN OF THE CHILD STUDY

A Phase IIb, randomized, controlled, double blind trial was conducted at two sites in Tanzania and Kenya with 894 children between the ages of five and 17 months at time of first dose. Participants received either 3 doses of RTS,S/AS01 or a rabies vaccine on a 0-, 1-, 2-month schedule. Children were followed for an average of 8 months to determine safety and efficacy of RTS,S/AS01 against clinical malaria disease.

SAFETY

All children were observed for an hour after each vaccination, and visited in their homes at least once a day for seven days following each dose. After the full course of vaccination, children were visited in their homes weekly for the duration of the study.

EFFICACY OF RTS,S/AS01

Researchers evaluated the immune response induced by RTS,S/AS01 by measuring antibodies against malaria in the blood. The vaccine's efficacy against episodes of clinical malaria was evaluated. Clinical cases of malaria were detected on weekly home visits to children and at clinics in the study area.

Infant Study: Effective co-administration with EPI vaccines

The Phase II study in Tanzania of RTS,S/AS02 in infants demonstrated that the vaccine candidate has a promising safety profile. It also reported 65 percent efficacy against malaria infection in protecting infants from 8 weeks of age over a six-month period.²

The study of 340 infants was also the first to show that RTS,S/AS is efficacious when co-administered alongside the World Health Organization's schedule for the Expanded Programme on Immunization (EPI) and does not compromise the immune response to other vaccines in the current schedule. The EPI is the primary delivery platform for childhood vaccines in developing countries.

The infant trial was conducted in Tanzania by the Ifakara Health Institute (Tanzania), the Tanzanian Ministry of Health, the Swiss Tropical Institute, and the London School of Hygiene and Tropical Medicine, in collaboration with GSK and MVI.

More than 20 years of progress

RTS,S/AS is the most clinically advanced malaria vaccine candidate in the world. RTS,S/AS 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 and from reentering the bloodstream, where the host would begin to show symptoms of infection.

To stimulate an immune response to the malaria parasite, the RTS,S antigen fuses a critical circumsporozoite (CS) protein, the surface protein that helps the parasite invade human liver cells, with a protein found in GSK Biologicals's hepatitis B vaccine. The addition of the proprietary GSK Adjuvant System (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. In January 2001, GSK and the 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. The clinical development of RTS,S/AS is conducted by the Clinical Trial Partnership Committee, a collaboration of leading African research institutes, Northern academic partners, MVI and GSK with support from the Malaria Clinical Trial Alliance.

DESIGN OF THE INFANT STUDY

This Phase IIb single center, double-blind, controlled trial enrolled 340 infants in Tanzania who received either 3 doses of RTS,S/AS02 or a licensed hepatitis B vaccine (*Engerix-B™*) at 8, 12 and 16 weeks of age in co-administration with a licensed DTPw/Hib vaccine. Infants were then followed for six months to determine safety and efficacy of RTS,S/AS02 against malaria infection and immunogenicity of co-administered vaccines.

SAFETY

All participants were observed for one hour after each vaccination and visited in their homes at least daily for the six days following each dose. After the full course of vaccination, children were visited in their homes at least monthly for the duration of the study.

EFFICACY OF RTS,S/AS02

Researchers evaluated the immune response induced by RTS,S/AS02 by measuring antibodies to malaria in the blood. The vaccine's efficacy against malaria infection was evaluated by detecting infection at two weekly home visits and at health facilities in the study area.

IMPACT ON EPI ANTIGENS

All participants received oral polio vaccine and BCG at birth. Infants were also given a tetravalent DTPw/Hib combination vaccine co-administered with either the study vaccine or a control vaccine. The immune responses to DTPw/Hib components—as indicated by antibody levels—were measured.

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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. Founded in 1977, 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.

GlaxoSmithKline Biologicals (GSK), 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. GSK Bio employs more than 1,600 scientists, who are devoted to discovering new vaccines and developing more cost-effective and convenient combination products to prevent infections that cause serious medical problems worldwide. In 2007, GSK Bio distributed more than 1.1 billion doses of vaccines to 169 countries in both the developed and the developing world, an average of more than 3 million doses per day. 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.

ⁱ Formulated with GSK's proprietary Adjuvant System (AS).

ⁱⁱ Bejon P, Lusingu J, Olotu A, et al. Efficacy of RTS,S/AS01E: clinical malaria in 5 to 17 month old children. *New England Journal of Medicine*. 2008; 359; 24: 2521-2532.

ⁱⁱⁱ Abdulla S, Oberholzer R, Juma O, et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *New England Journal of Medicine*. 2008;359; 24:2533–2544.

^{iv} Aponte JJ, Aide P, Renom M, et al. Safety of the RTS,S/AS02D candidate malaria vaccine in infants living in a highly endemic area of Mozambique: a double blind randomised controlled phase I/IIb trial. *The Lancet* 2007;370(9598):1543–1551.

^v Alonso PL, Sacarlal J, Aponte JJ, et al. Duration of protection with RTS,S/AS02A malaria vaccine in prevention of Plasmodium falciparum disease in Mozambican children: single-blind extended follow-up of a randomised controlled trial. *The Lancet*. 2005 :366(9502):2012–2018.