

Fact Sheet: RTS,S Malaria Vaccine Candidate

The RTS,S malaria vaccine candidate

Malaria kills approximately 900,000 people a year worldwide and sickens tens of millions more, most of them children living in Sub-Saharan Africa. A safe and effective vaccine is an important component of a comprehensive malaria control program and could potentially save hundreds of thousands of lives.

RTS,S (also known as RTS,S/AS) is the most clinically advanced malaria vaccine candidate in the world. In clinical trials, it was the first to demonstrate that it can 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.

The RTS,S malaria vaccine candidate was created in 1987 by scientists working at GlaxoSmithKline Biologicals' laboratories, the vaccine division of GlaxoSmithKline (GSK). Its early development was undertaken by GSK in close collaboration with the Walter Reed Army Institute of Research. In January 2001, GSK and the PATH Malaria Vaccine Initiative (MVI) – with grant monies from the Bill & Melinda Gates Foundation to MVI – entered into a public-private partnership to develop the vaccine for use in infants and young children in Sub-Saharan Africa.

The RTS,S vaccine candidate is a recombinant protein that fuses a part of the *P. falciparum* circumsporozoite protein with the hepatitis B virus surface antigen. Combined with a proprietary GSK Adjuvant System, RTS,S induces the production of antibodies and T cells that are believed to diminish the malaria parasite's ability to infect, develop, and survive in the human liver.

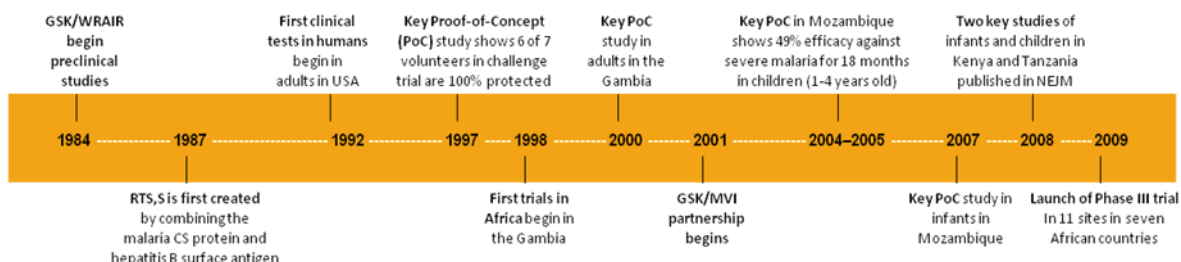
RTS,S results to date

Clinical evaluation of RTS,S began in adults in the United States in 1992, and in Africa in 1998. Results of a Phase II trial, initiated in 2003 and conducted with more than 2,000 children in southern Mozambique, demonstrated the feasibility of administering a malaria vaccine in children. Findings from this trial, published in the medical journal *The Lancet* in 2004 and 2005, showed that RTS,S was efficacious for at least 18 months in reducing clinical malaria by 35 percent, and severe malaria by 49 percent.^{1,2} A follow-up study, published in the August 2009 issue of *The Journal of Infectious Diseases*, demonstrated that the vaccine is capable of inducing long-term protection against malaria for up to 45 months of follow-up after initial vaccination.³

Data published in November 2007 showed that after a full vaccination course in infants, RTS,S reduced infection by 65 percent over a three-month follow-up period.⁴ Importantly, it displayed a promising safety and tolerability profile similar to the standard World Health Organization's Expanded Program on Immunization vaccines commonly given to infants. The trial was the first to establish proof-of-concept of efficacy in infants of any malaria vaccine candidate.

The results of two distinct studies in infants and in young children living in Africa were published in the *New England Journal of Medicine* on December 8, 2008.^{5,6} The studies demonstrated that RTS,S can provide significant protection against malaria infection and clinical disease. The study of children aged 5 to 17 months showed that RTS,S reduced the risk of clinical episodes of malaria by 53 percent over an eight-month follow-up period and was shown to have a promising safety profile. The study of infants demonstrated for the first time that, when administered together with commonly used childhood vaccines, RTS,S has both promising safety and efficacy profiles.

RTS,S key milestones



Next steps in advancing RTS,S

RTS,S is the first malaria vaccine candidate to ever reach large-scale Phase III clinical testing, the last stage of development before regulatory file submission. Based on the successful trials to date, GSK, MVI, and leading African research institutions are continuing clinical trials in infants and young children, the most vulnerable groups and those who would benefit most from an effective malaria vaccine.

A large-scale Phase III multi-center efficacy trial in both infants and in young children was launched in May 2009. This Phase III study is designed to further determine the efficacy and confirm the safety of the candidate vaccine in the target population. The RTS,S Phase III trial is underway in 11 sites in seven African countries (Gabon, Mozambique, Tanzania, Ghana, Kenya, Malawi, and Burkina Faso). This trial, which will enroll up to 16,000 infants and children, is expected to become the largest malaria vaccine trial to date. Under current plans, the RTS,S vaccine candidate would be submitted to regulatory authorities in 2012 based on efficacy in children 5-17 months of age. Additional safety and immunogenicity data from the infant population will be submitted soon thereafter, followed by efficacy data for infants once available. If all goes well, general implementation of RTS,S for infants 6 to 12 weeks of age is possible within five years or so. The vaccine could be available for targeted use among young children 5 to 17 months old as early as 2013.

Steps in malaria vaccine development

Research and preclinical development: Identify relevant antigens and create vaccine concept; preclinical evaluation; develop vaccine manufacturing process.

Phase I clinical trials: Preliminary evaluation of the safety profile and immune response in malaria-naïve and malaria-exposed populations.

Phase II clinical trials: Monitor safety and potential side effects; measure immune response; evaluate efficacy against infection and clinical disease; and determine optimum dosage and schedule.

Phase III clinical trials: Continue to monitor safety and potential side effects, and evaluate efficacy on a large scale.

Submission to regulatory authorities: Submit application to regulatory authorities for approval to market

Introduction: Make vaccine available for use.

Phase IV clinical trials: Conduct post-marketing safety monitoring; measure duration of protection and assess vaccine compliance.

Once RTS,S is licensed, GSK and MVI will work to ensure the vaccine reaches the children and infants who need it most. MVI and GSK are already working with African countries to start preparing for the day when a malaria vaccine would be available as a routine childhood immunization. The partners are committed to working with governments and international organizations to determine demand for the vaccine; to develop policies and systems for procuring a prospective malaria vaccine; and to implement vaccination programs.

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 Bio), 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.

¹ Alonso PL, Sacarlal J, Aponte JJ, et al. Efficacy of the RTS,S/AS02A vaccine against Plasmodium falciparum infection and disease in young African children: randomized controlled trial. *The Lancet*. 2004; 16-22;364(9443):1411-1420.

² 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; 10;366(9502):2012-2018.

³ Sacarlal J, Aide P, Aponte JJ, et al. Long-term safety and efficacy of the RTS,S/AS02A malaria vaccine in Mozambican children. *The Journal of Infectious Diseases*. 2009; 200:329-336.

⁴ 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.

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

⁶ Abdulla S, Oberholzer R, Juma O, et al. Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. *The New England Journal of Medicine*. 2008;359:2533-2544.