Fact sheet: The RTS,S malaria vaccine candidate (Mosquirix™)

Malaria kills approximately 584,000 people a year worldwide and causes illness in hundreds of millions more, most of them children living in sub-Saharan Africa. Although existing interventions have helped to reduce malaria deaths significantly over the past decade, a well-tolerated and effective vaccine with an acceptable safety profile could add an important complementary tool for malaria control efforts. To date, no vaccine against malaria has been licensed.

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) announced on July 24, 2015, that it has adopted a positive scientific opinion, under Article 58, for GSK's malaria candidate vaccine Mosquirix™, also known as RTS,S, in children aged 6 weeks to 17 months.With this positive opinion, the WHO has indicated that a policy recommendation for RTS,S is possible by the end of 2015, paving the way for decisions by African nations regarding implementation of the vaccine through their national immunisation programmes. The application to the EMA included data from 11 clinical trials involving over 19,000 trial participants and multiple research partners. The pivotal multi-country phase III clinical trial enrolled 15,459 infants and young children (<2 yrs of age) and followed them up to four years post vaccination.

RTS,S Phase III sites and research partners

Burkina Faso – Nanoro
Institut de Recherche en Science de la Santé (IRSS) / Centre Muraz
+ Institute of Tropical Medicine, Antwerp, Belgium

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, 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
+ US Centers for Disease Control and Prevention

Malawi – Lilongwe
University of North Carolina Project

Mozambique – Manhiça
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

RTS,S Development

The RTS,S malaria vaccine candidate is the most advanced in development globally. It was created in 1987 by scientists working at GlaxoSmithKline's (GSK) laboratories. Early clinical development was done in collaboration with the Walter Reed Army Institute for 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 this RTS,S vaccine for infants and young children living in malaria-endemic regions in sub-Saharan Africa.

RTS,S aims to trigger the immune system to defend against the first stages when the *P. falciparum* malaria parasite enters the human host's bloodstream through a mosquito bite and infects liver cells. The vaccine is designed to prevent the parasite from infecting the liver where it can mature, multiply, and re-enter the bloodstream, where it infects red blood cells and can lead to disease symptoms.

Phase I and II clinical trials allowed an initial assessment of the candidate vaccine's safety and efficacy profile, first in adult volunteers in the United States and Belgium, followed by adults, adolescents,

children and then infants living in malaria-endemic regions in Africa. Results of Phase II proof-of-concept trials in Mozambique, published in *The Lancet* in 2004[1] and 2007[2], demonstrated that it was possible to provide partial protection against malaria to African children and infants, respectively.

The Phase III efficacy and safety trial of RTS,S started in May 2009 and was completed early 2014 at 11 sites in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania) with 15,459 infants and young children participating, making this the largest malaria vaccine trial in Africa to date.

Phase III Trial Results

Results of the co-primary endpoints of the study after a year of follow-up were published in the *New England Journal of Medicine* in November 2011[3] (children aged 5-17 months) and December 2012[4] (infants aged 6-12 weeks). These results showed that three doses of RTS,S reduced clinical malaria by approximately half in children 5-17 months of age at first vaccination[5]. In infants 6-12 weeks of age at first vaccination with RTS,S, clinical malaria was reduced by approximately one-third[5]. In a subsequent analysis after 18 months of follow up[6], children aged 5-17 months at first vaccination with RTS,S experienced 45% fewer cases of clinical malaria[7], compared to children immunised with a comparator vaccine. Infants aged 6-12 weeks at first vaccination with RTS,S had 27% fewer cases of clinical malaria[7] than infants in the control group. Efficacy waned over time in both age categories. These results were achieved on top of existing malaria interventions, such as insecticide-treated bed nets, which were used by approximately 80% of the the trial participants.

The final study results, which analyzed vaccine efficacy, immunogenicity, safety and impact of RTS,S/AS01 over a median of 38 and 48 months of follow-up (post dose 1) in infants and young children, respectively, including the effect of a booster dose of vaccine, were published in *The Lancet* in April 2015[7].

These final results demonstrated that vaccination with the 3-dose primary series reduced clinical malaria cases by 28% in young children and 18% in infants to the end of the study[7]. A booster dose of RTS,S, administered 18 months after the primary series, reduced the number of cases of clinical malaria in young children (aged 5-17 months at first vaccination) by 36% and in infants (aged 6-12 weeks at first vaccination) by 26% to the end of the study[7]. Administration of the booster dose provided longer term protection against clinical malaria in both groups, with 1774 and 983 cases of malaria averted per 1000 children vaccinated in the older (age 5-17 months) and infant (6-12 weeks) age groups, respectively. The vaccine efficacy waned over time following the booster dose and further studies are ongoing to assess longer term efficacy and the need for additional doses.

RTS,S continued to display an acceptable safety and tolerability profile during the entire phase III study period. In both age categories, adverse events after vaccination included local reactions (such as pain or swelling), which were observed more frequently after RTS,S administration compared to the comparator vaccine. In the younger age category (i.e., infants 6-12 weeks of age at first injection), injection site reactions were reported less frequently after RTS,S administration compared to the standard vaccines routinely used in the African EPI[2].

The incidence of fever in the week after vaccination was higher in children who received the RTS,S vaccine than in those receiving the comparator vaccine. In some children this resulted in febrile reactions that were accompanied by generalized convulsive seizures, but all those affected fully recovered within seven days.

The rates of other serious adverse events seen in the trial (mainly medical events requiring hospitalization, regardless of whether they were considered to be caused by the study vaccine) were comparable between the trial's RTS,S candidate vaccine recipients and those receiving a control vaccine, except for cases of meningitis, which were reported in low numbers, but more often in the RTS,S group compared to the control. The meningitis signal previously reported remained in the older age category, including a small number of new cases reported after the booster dose. This could be a

chance finding as comparisons were made across groups for many different diseases, and because some of these cases happened years after vaccination without any obvious relationship to vaccination. If RTS,S is licensed, the occurrence of meningitis will be followed closely in post-registration studies.

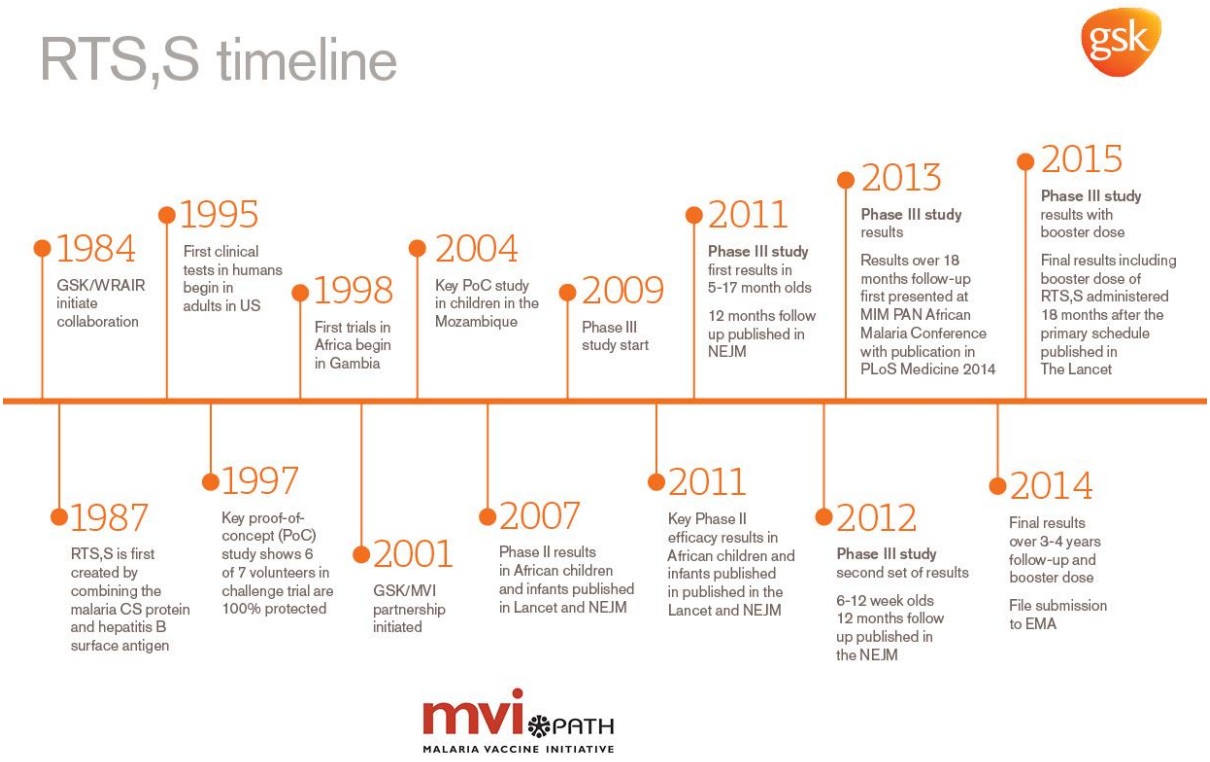
Looking Ahead

The next milestone through which RTS,S has to pass in the decision-making process is review by the WHO for a policy recommendation. This formal WHO review process is designed to assist in the development of optimal prevention and treatment guidelines for diseases that have a global public health impact. If a WHO policy recommendation is positive, then additional steps in the pathway prior to implementation include: 1) WHO prequalification, which signals to endemic countries and agencies that finance or procure vaccines that the manufacturing process meets international standards, 2) decisions by the countries themselves regarding licensure and implementation, and 3) necessary financing and procurement pathways. Positive outcomes throughout the policy and regulatory process and the availability of the necessary financing, are prerequisites for the introduction of RTS,S through African national immunisation programmes.

Pricing

PATH, 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 at no cost to children or their families thanks to existing international and national financing mechanisms. The RTS,S partnership hopes that similar mechanisms would be implemented for a malaria vaccine to allow countries to provide it to children at nominal or no cost. A shared goal is to have the cost of a malaria vaccine not be a barrier to access.

In January 2010, GSK announced that the RTS,S pricing model will cover the cost of manufacturing the vaccine together with a small return of around five percent, which will be reinvested in research and development for second-generation malaria vaccines or vaccines against other neglected tropical diseases.



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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 catalyze timely access in endemic countries. MVI's vision is a world free from malaria. For more information, visit www.malariavaccine.org.

PATH is the leader in global health innovation. An international nonprofit organization, PATH saves lives and improves health, especially among women and children. PATH accelerates innovation across five platforms—vaccines, drugs, diagnostics, devices, and system and service innovations—that harness our entrepreneurial insight, scientific and public health expertise, and passion for health equity. By mobilizing partners around the world, PATH takes innovation to scale, working alongside countries primarily in Africa and Asia to tackle their greatest health needs. With these key partners, PATH delivers measurable results that disrupt the cycle of poor health. Learn more at www.path.org.

References:

1) Alonso P, J Aponte, P Aide et al. *The Lancet.* 2004; 364 (9443):1411–20.
2) Alonso P, J Aponte, P Aide et al. *The Lancet*. 2007; 370 (9598): 1543–1551.
3) The RTS,S Clinical Trials Partnership. *NEJM* 2011; 365: 1863–75.
4) The RTS,S Clinical Trials Partnership. *NEJM* 2012; 367: 2284–95.
5) Intention to Treat analysis (ITT)
6) The RTS,S Clinical Trial Partnership, *PloS Medicine*, 2014;11(7): e1001685
7) RT,S Clinical Trials Partnership, *The Lancet.* 2015; 386 (9988): 31–45.

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