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

Malaria kills approximately 438,000 people a year worldwide and causes illness in hundreds of millions more, with most deaths occurring among children living in sub-Saharan Africa. Although existing interventions have helped to reduce malaria deaths significantly over the past 15 years, 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 for use.

RTS,S/AS01, also known as Mosquirix™, is the candidate vaccine furthest along in development globally. On July 24, 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) announced that it had adopted a positive scientific opinion, under the Article 58 process, for RTS,S in children aged 6 weeks to 17 months. This was followed by the January 29, 2016 publication of a position paper on RTS,S by the World Health Organization (WHO) that recommended large-scale pilot implementations of RTS,S in children 5 months to 9 months of age in African settings of moderate-to-high parasite transmission.

The Phase III efficacy and safety trial of RTS,S showed that the vaccine candidate could provide meaningful public health benefit by reducing the burden of malaria when used alongside currently available interventions such as bed nets and insecticides.

RTS,S Development

RTS,S was created in 1987 by scientists working at GSK laboratories. Early clinical development was conducted in collaboration with the Walter Reed Army Institute for Research. In January 2001, GSK and PATH's Malaria Vaccine Initiative (PATH/MVI), with grant monies from the Bill & Melinda Gates Foundation to PATH, entered into a public-private partnership to develop RTS,S 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 *Plasmodium 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, re-enter the bloodstream, and infect red blood cells, which 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 and 2007, demonstrated that it was possible to provide partial protection against malaria to African children and infants, respectively.[1,2]

The RTS,S Phase III efficacy and safety trial—the largest malaria vaccine trial in Africa to date—began in May 2009 and ended in early 2014. The trial involved 15,459 infants and young children at 11 sites in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania).

Phase III Trial Results

Results of the study after a year of follow-up were published in the *New England Journal of Medicine* in November 2011 (for children aged 5-17 months) and December 2012 (for infants aged 6-12 weeks).[3,4] 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. In a subsequent analysis after 18 months of follow up, children vaccinated with RTS,S experienced 46% fewer cases of clinical malaria, compared to children immunized with a comparator vaccine.[6,7] Efficacy waned over time. These results were achieved on top of existing malaria interventions, such as insecticide-treated bed nets, which were used by almost 80% of the trial participants.

Final study results, published in *The Lancet* in April 2015,[7] includes analysis of vaccine efficacy, immunogenicity, safety, impact of RTS,S/AS01 over a median of 48 months of follow-up post-dose 1, and the effect of a fourth dose of vaccine.

These results demonstrated that vaccination with the 3-dose primary series reduced clinical malaria cases by 26% in young children to the end of the study.[7] A fourth dose of RTS,S, administered 18 months after the primary series, reduced the number of cases of clinical malaria by 39%.[7] Administration of the fourth dose provided longer-term protection against clinical malaria, with 1,774 cases of malaria averted per 1,000 children vaccinated, on average, across all sites (site-specific cases averted ranged from 205 to 6,565 per 1,000 children vaccinated). Vaccine efficacy waned over time following the fourth dose, and further studies are ongoing to assess longer-term efficacy and the need for additional doses.

RTS,S displayed an acceptable safety and tolerability profile throughout the entire Phase III study. 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.[2]

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, 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

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 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 RTS,S and control recipients, except for cases of meningitis, which were reported in low numbers, more often in the RTS,S group. According to the EMA, this is most likely to be a chance finding, as some of these cases occurred years after vaccination without any obvious relationship to vaccination. The occurrence of meningitis and an increased risk for severe malaria (including cerebral malaria) will be followed closely in Phase IV studies.

RTS,S and the Article 58 Process

The Article 58 procedure allows the EMA's CHMP to adopt a scientific opinion, in co-operation with the WHO, on a medicinal product for human use that is intended exclusively for markets outside of the European Union (EU). This assessment requires medicinal products to meet the same standards as those intended for use in the EU.

The positive opinion adopted by the CHMP in July 2015 was accompanied by the Risk Management Plan (Phase IV studies) that was agreed to between the EMA and GSK and followed by the October 2015 publication of the official European public assessment report (EPAR), which details the CHMP opinion. According to the EMA, "Based on the results of the trial, the CHMP concluded that despite its limited efficacy, the benefits of Mosquirix™ outweigh the risks in both age groups studied. The CHMP considered that the benefits of vaccination may be particularly important among children in high-transmission areas in which mortality is very high."[8]

The January 2016 WHO position paper that followed the CHMP opinion endorses the recommendations made by the WHO Strategic Advisory Group of Experts (SAGE) on Immunization and Malaria Policy Advisory Committee (MPAC) in October 2015. According to the position paper, "WHO recommends that the pilot implementations use the 4-dose schedule of the RTS,S/AS01 vaccine in 3–5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings," with three doses administered to children between 5 and 9 months of age, followed by a fourth dose 15–18 months later. [9]

WHO further recommends that the pilots involve sufficiently large populations to assess, among other things, (1) the feasibility of providing all four doses of RTS,S to the target age group through existing health services; (2) the impact of RTS,S on child mortality; and (3) evidence of any causal relationship between RTS,S and either meningitis or cerebral malaria, in the context of surveillance of adverse events. WHO also calls for the compilation of evidence on the functioning of country immunization programs and the use of currently recommended malaria control measures. These implementation projects would be undertaken in addition to the risk management plan previously agreed between the EMA and GSK.

The information considered by EMA and WHO included data from 11 clinical trials of RTS,S, involving over 19,000 trial participants, including the 15,459 participants enrolled in the pivotal Phase III trial.

Looking Ahead

WHO has already initiated a process of consultation regarding the design of the pilot implementations and solicited expressions of interest from African ministries of health regarding possible participation. PATH and GSK have expressed their readiness to work with WHO on the pilot implementation of the vaccine, to provide the additional information needed.

Pricing

A final price for RTS,S has not been determined; however, PATH, GSK, and other partners remain committed to helping ensure that RTS,S—if made available for widescale use—reaches the infants

and children who need it most. 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 anticipates that similar mechanisms would be implemented for a malaria vaccine. A shared goal is to have the cost of a malaria vaccine not be a barrier to access.

GSK has previously stated that the price of RTS,S 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 next-generation malaria vaccines or vaccines against other neglected tropical diseases.

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The PATH Malaria Vaccine Initiative (PATH/MVI) is a programme established at PATH in 1999. PATH/MVI's mission is to accelerate the development of malaria vaccines and catalyze timely access in endemic countries. PATH/MVI's vision is a world free from malaria. For more information, visit www.malariavaccine.org.

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References:

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3) The RTS,S Clinical Trials Partnership. *The New England Journal of Medicine.* 2011; 365: 1863–75.
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8) From the press release, available at http://bit.ly/1elUa6Z.
9) World Health Organization. *Weekly Epidemiological Record.* 2016; 91(4): 33–52.

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