

The RTS,S malaria vaccine candidate

Long-standing collaboration between PATH and GSK yields first malaria vaccine recommended for pilot implementation in Africa

SUMMARY

Malaria kills approximately 429,000 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, the outcome of a long-standing collaboration between PATH and GSK that began in 2001. The large-scale Phase 3 efficacy and safety trial of RTS,S (which concluded in January 2014) 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 bednets and insecticides.

In July 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 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 young children in African settings of moderate-to-high parasite transmission.

Over the course of 2016, WHO undertook to finalize the pilot design, mobilize the necessary resources, and to complete the process of selecting countries to partner in this first Malaria Vaccine Implementation Programme (MVIP). Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID are partnering to support the first phase of the pilot

programme (2017-2020), complemented by in-kind contributions from WHO and GSK.

The pilot implementation will take place at a sub-national level in Ghana, Kenya, and Malawi and is expected to start in 2018. The MVIP encompasses all aspects of the pilot implementation of the malaria vaccine, including: (1) administration of the vaccine by the three countries' national immunization programs; (2) the WHO-led evaluation of feasibility, impact, and safety; and (3) the GSK-led baseline epidemiological research and Phase 4 pharmacovigilance studies that comprise the risk management plan agreed upon by GSK and the EMA. PATH will provide technical assistance to WHO across a number of areas, including on economic assessments, pharmacovigilance, and in the qualitative assessment of behavior change that may occur during the introduction of the vaccine (for example, with respect to use of other malaria prevention measures or immunizations, treatment-seeking behavior).



Samuel Oduor, Chief Community Relations Officer for the Kombewa Clinical Research Center, Kenya, and son. Photo credit: PATH/ Jordan Gantz Creative

DEVELOPMENT HISTORY OF RTS,S

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, reenter the bloodstream, and infect red blood cells, which can lead to disease symptoms.

Phase 1 and 2 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 2 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 3 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 3 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 to 17 months) and December 2012 (for infants aged 6 to 12 weeks).^{3,4} These results showed that three doses of RTS,S reduced clinical malaria by approximately half in children 5 to 17 months of age at first vaccination. In a subsequent analysis after 18 months of follow up, children vaccinated with RTS,S experienced 46 percent 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 bednets, which were used by almost 80 percent of the trial participants.

RTS,S Phase 3 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 – Manhica

*Centro de Investigação em Saúde de Manhica
+ 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

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

The final results demonstrated that efficacy against clinical malaria was 39 percent over four years of follow-up in children receiving four doses.⁷ Vaccination with the 3-dose primary series reduced clinical malaria cases by 26 percent in young children to the end of the study.⁷ The addition of a fourth dose of RTS,S, administered 18 months after the primary series, resulted in a reduction of clinical cases by 39 percent over an average of four years of follow-up.⁷ Administration of the fourth dose prolonged 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.



The efficacy of RTS,S was evaluated in the context of existing malaria control measures, such as insecticide-treated bednets, which were used by almost 80 percent of the children and infants in the Phase 3 trial. Photo credit: PATH/ Jordan Gantz Creative

RTS,S displayed an acceptable safety and tolerability profile throughout the entire Phase 3 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

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 4 studies.

RTS,S AND THE ARTICLE 58 PROCESS

The Article 58 procedure allows the EMA's CHMP to adopt a scientific opinion, in cooperation 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 information considered by EMA and WHO included data from 11 clinical trials of RTS,S, involving more than 19,000 trial participants, including the 15,459 participants enrolled in the pivotal Phase 3 trial.

The positive opinion adopted by the CHMP in July 2015 was accompanied by the Risk Management Plan (Phase 4 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 four-dose schedule of the RTS,S/AS01 vaccine in three to five distinct epidemiological settings in sub-Saharan Africa, at sub-national 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 to 18 months later.⁹

LOOKING AHEAD

The goal of the MVIP is to enable an updated WHO policy recommendation on the use of RTS,S for children in sub-Saharan Africa by generating necessary evidence on feasibility, impact, and safety. The pilots, which are expected to conclude in 2022, will assess the extent to which the vaccine's protective effect, demonstrated in children 5 to 17 months of age in Phase 3 testing, can be replicated in real-life settings. They will also evaluate the feasibility of: (1) the feasibility of providing all four doses of RTS,S through existing health services; (2) the vaccine's potential role in reducing childhood deaths; and (3) its safety in the context of routine use. RTS,S will be delivered through the routine national immunization programs in the areas and regions selected, and rigorous evaluation will be undertaken.



Samuel Oduor and son, Kombewa, Kenya.
Photo credit: PATH/ Jordan Gantz Creative

References:

1. Alonso P, Aponte J, Aide P, et al. Efficacy of the RTS,S/AS02A vaccine against *Plasmodium falciparum* infection and disease in young African children: randomised controlled trial. *The Lancet*. 2004; 364 (9443):1411–20. doi: 10.1016/S0140-6736(04)17223-1.
2. Alonso P, Aponte J, Aide P, 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. doi: 10.1016/S0140-6736(07)61542-6.
3. The RTS,S Clinical Trials Partnership. First results of Phase 3 trial of RTS,S/AS01 malaria vaccine in African children. *The New England Journal of Medicine*. 2011; 365: 1863–75. doi: 10.1056/NEJMoa1102287.
4. The RTS,S Clinical Trials Partnership. A Phase 3 Trial of RTS,S/AS01 malaria vaccine in African infants. *The New England Journal of Medicine*. 2012; 367: 2284–95. doi: 10.1056/NEJMoa1208394.
5. According to Protocol analysis (ATP).
6. The RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine during 18 months after vaccination: A Phase 3 randomized, controlled trial in children and young infants at 11 African sites. *PLoS Medicine*. 2014;11(7): e1001685. doi: 10.1371/journal.pmed.1001685.
7. RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: Final results of a phase 3, individually randomised, controlled trial. *The Lancet*. 2015; 386 (9988): 31–45. doi: 10.1016/S0140-6736(15)60721-8.
8. First malaria vaccine receives positive scientific opinion from EMA [press release]. European Medicines Agency; July 24, 2015. Available at <http://bit.ly/1eUa6Z>.
9. World Health Organization. *Weekly Epidemiological Record*. 2016; 91(4): 33–52. Available at: <http://www.who.int/wer>.

PATH is the leader in global health innovation. An international nonprofit organization, we save lives and improve health, especially among women and children. We accelerate 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, we take innovation to scale, working alongside countries primarily in Africa and Asia to tackle their greatest health needs. Together, we deliver measurable results that disrupt the cycle of poor health. Learn more at www.path.org.

PATH's MALARIA VACCINE INITIATIVE (MVI) accelerates malaria vaccine development and catalyzes timely access in endemic countries, toward a world free from malaria. Standing at the intersection of malaria and immunization, MVI is part of PATH's Center for Malaria Control and Elimination and PATH's Center for Vaccine Innovation and Access, which brings together PATH's expertise across every stage of vaccine research, development, and introduction to make lifesaving vaccines widely available to women, children, and communities across the world. Learn more at www.malariavaccine.org and <http://sites.path.org/cvia>.