

The RTS,S malaria vaccine

First malaria vaccine will be piloted in areas of three African countries through routine immunization programs

Summary

Malaria kills more than 400,000 people a year worldwide and causes illness in tens of millions more, with most deaths occurring among young children living in sub-Saharan Africa. Although existing interventions have helped to reduce malaria deaths significantly over the past 15 years, a vaccine could add an important complementary tool for malaria control efforts.

RTS,S/AS01 (RTS,S) is the first malaria vaccine shown to provide partial protection against malaria in young children. It will be the first malaria vaccine provided to young children through national immunization programs in three sub-Saharan African countries—Ghana, Kenya, and Malawi. These countries will introduce the vaccine in selected areas as part of a large-scale pilot implementation program coordinated by the World Health Organization (WHO), in collaboration with the ministry of health in each country and with international partners, including PATH and GSK, manufacturer of the vaccine.

The efficacy of the RTS,S vaccine was established in a Phase 3 clinical trial that concluded in 2014. In the trial, children who received four doses of the vaccine had significantly lower risk of developing malaria, including severe malaria. A stringent regulatory authority—the European Medicines Agency (EMA)—issued a positive scientific opinion on the vaccine in July 2015, concluding that the benefits of the vaccine outweigh the risks. As with other new vaccines, and in line with national regulations, the safety profile for RTS,S will continue to be monitored as the vaccine is introduced more widely.

In January 2016, WHO endorsed the joint recommendation of two advisory bodies and recommended pilot implementation of the vaccine in three to five settings in sub-Saharan Africa. In response to that recommendation, a country-led, WHO-coordinated Malaria Vaccine Implementation Programme (MVIP) has been designed to further understand the operational issues in using the vaccine in the context of other malaria interventions. The MVIP will specifically assess the feasibility of administering the required four doses of the vaccine in children,

the vaccine's role in reducing childhood deaths and severe malaria, and its safety in the context of routine use. Data and information from the MVIP will inform a WHO policy recommendation on the broader use of the vaccine. RTS,S has been approved for use in the pilot evaluation and Phase 4 studies by the national regulatory authority in each of the three participating countries.

Financing for the MVIP has been mobilized through an unprecedented collaboration among three global health funding bodies: Gavi, the Vaccine Alliance; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and Unitaid. Additionally, WHO, PATH, and GSK are providing in-kind contributions, which include GSK's donation of the vaccine for use in the MVIP. However, additional resources will be needed to bring this vaccine into wide-scale use.



Samuel Oduor, Chief Community Relations Officer for the KEMRI-Walter Reed Project Clinical Research Center in Kombewa, Kenya, and son. Photo: 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, with grant funds from the Bill & Melinda Gates Foundation to

PATH, entered into a public-private partnership to develop RTS,S for young children living in malaria-endemic regions in sub-Saharan Africa.

RTS,S aims to trigger the immune system 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.

RTS,S has been rigorously tested through a series of clinical trials.^{1,2} The final Phase 3 efficacy and safety trial—the largest malaria vaccine trial in Africa to date—involved 15,459 infants and young children and was conducted by 11 clinical research centers in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania).³

The final results of the Phase 3 trial demonstrated that, among children who received four doses, the vaccine prevented approximately 4 in 10 (39%) cases of malaria and 3 in 10 (29%) cases of severe malaria over a four-year period. 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, and further studies have been undertaken to assess longer-term efficacy and the need for additional doses.³



The efficacy of RTS,S was evaluated in the context of existing malaria control measures, such as bednets—used by almost 80 percent of children in the Phase 3 trial. Photo: PATH/Jordan Gantz Creative.

Regulatory and policy review

The EMA carried out a scientific assessment of RTS,S and issued a positive scientific opinion on the vaccine in July 2015.⁴ This opinion was given as part of the EMA's cooperation with WHO to address diseases of major public health importance around the world. This assessment requires medicinal products to meet the same standards as those intended for use in the European Union. The EMA found that the vaccine's quality and risk-benefit profile are favorable from a regulatory perspective.

Following the EMA decision, and after a thorough review of the clinical trial results and contextual elements such as feasibility of

implementation, potential public health impact, and likely cost-effectiveness of the vaccine, WHO's independent advisory committees for immunization and malaria—the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC)—jointly called for pilot implementation of the vaccine in settings of moderate-to-high malaria parasite transmission in sub-Saharan Africa. WHO officially adopted the SAGE/MPAC recommendation in January 2016, recognizing the considerable public health potential of the vaccine, while also acknowledging the need for further evaluation before considering its wide-scale deployment.⁵

Looking ahead

The pilot implementation was designed as a six-year program, including preparation, and the evaluations are now expected to be completed by 2023. Its goal is to enable an updated WHO policy recommendation on the possible broader use of RTS,S in African children by generating additional evidence on feasibility, impact, and safety—all in the context of routine use.

As part of the implementation program, GSK is conducting Phase 4 studies in parts of the pilot areas. These studies—as required and standard for a new vaccine—will gather additional information on the vaccine's effectiveness and on any side effects associated with routine use. Data collected through the Phase 4 studies will complement data from the pilot evaluations led by WHO. PATH is working with WHO in several areas, including on economic assessments and the qualitative assessment of behavior change that may occur during vaccine introduction. GSK is donating up to 10 million doses for use in the MVIP. Other evaluation partners include a wide range of academic, medical, and other research organizations.

Additional funding is being sought to ensure completion of the pilot introduction and associated evaluations, and to assure the longer-term supply of the vaccine.

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: randomized controlled trial. *The Lancet*. 2004;364 (9443):1411-1420. 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 randomized controlled phase 1/2b trial. *The Lancet*. 2007;370 (9598): 1543-1551. doi: 10.1016/S0140-6736(07)61542-6.
3. 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 randomized, controlled trial. *The Lancet*. 2015;386 (9988): 31-45. doi: 10.1016/S0140-6736(15)60721-8.
4. First malaria vaccine receives positive scientific opinion from EMA [press release]. European Medicines Agency; July 24, 2015. <http://bit.ly/1eLUa6Z>.
5. World Health Organization. *Weekly Epidemiological Record*. 2016;91(4): 33-52. <http://www.who.int/wer>.