

# The RTS,S malaria vaccine

First malaria vaccine recommended by the  
World Health Organization for children at risk



## Overview

Malaria kills more than 600,000 people a year worldwide and causes illness in more than 200 million more, with the majority of 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, new tools are needed.

On October 6, 2021, the World Health Organization (WHO) recommended RTS,S/AS01, the world's first malaria vaccine, for children at risk in sub-Saharan Africa and in other regions with moderate to high transmission of malaria caused by *Plasmodium falciparum*.<sup>1</sup> The WHO recommendation was informed by the findings from pilot implementation of RTS,S through routine childhood immunization in areas of Ghana, Kenya, and Malawi, as well as other available RTS,S evidence.

In December 2021, the board of Gavi, the Vaccine Alliance, approved a malaria vaccination program to support the broader rollout of the vaccine in Gavi-eligible countries. In addition, following WHO prequalification of the vaccine in July 2022, UNICEF awarded a malaria vaccine contract to GSK to supply at least 18 million doses of RTS,S over the three-year period 2023–2025. To date, more than two dozen countries have expressed interest in applying for Gavi support to rollout the vaccine.

## Pilot introduction of RTSS

In January 2016, WHO accepted the advice of its global advisory bodies on immunization and malaria to pilot implementation of the RTS,S malaria vaccine in three to five settings of moderate to high malaria transmission in sub-Saharan Africa.<sup>2</sup> This led to the RTS,S Malaria Vaccine Implementation Programme (MVIP), which launched when vaccinations began in areas of Ghana, Kenya, and Malawi in 2019.

The WHO-coordinated pilot program is designed to evaluate the feasibility, safety, and impact of the vaccine in real-life, childhood vaccination settings. The three countries have been leading the rollout of the vaccine in selected areas, with funding and technical support from global partners, including PATH. GSK, the vaccine developer and manufacturer, is donating up to 10 million doses of the vaccine for use in the pilots, which are

financed through a collaboration involving Gavi, The Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

In late 2022 and early 2023, the remaining pilot areas of Ghana, Kenya, and Malawi began receiving the vaccine as part of an initial expansion of vaccination. This expansion was made possible by a grant from US-based Open Philanthropy to PATH to support scale-up of malaria vaccine use through 2023, using vaccine doses donated by GSK, and in collaboration with WHO and other in-country partners. Across the three countries, more than 4.5 million doses of RTS,S have been administered since 2019.



Alice Musimbi received her first dose of RTS,S following the expansion of vaccine use in the remaining pilot areas of Kenya. (Photo: PATH)

## Findings generated through the pilot implementation

Key findings from the pilots in Ghana, Kenya, and Malawi informed the October 2021 recommendation for widespread use of the vaccine. High uptake of RTS,S indicated strong community demand for the vaccine and pilot data reaffirmed the vaccine's safety and showed the vaccine to be feasible to deliver. Findings from the pilots also have shown a substantial reduction in deadly severe malaria, a drop in child hospitalizations, and a reduction in child deaths within the areas providing the vaccine. All three countries had equitable coverage across socio-economic groups, regardless of gender, and more than two-thirds of children in the implementing areas who were not sleeping under a long-lasting insecticide-treated

bednet received the vaccine. This resulted in increased access to malaria prevention, with 90 percent of children benefiting from at least one preventive intervention.

Findings from health economics and qualitative survey research led by PATH also informed the WHO recommendation. Using data from the pilots, modeling shows the vaccine to be a cost-effective addition to other recommended malaria interventions, including in areas with high bednet coverage or where seasonal chemoprevention (SMC) is used, and that the vaccine's cost-effectiveness is comparable to many other new vaccines. Modeling of the pilot data was consistent with earlier modeling that showed the vaccine's potential for considerable public health impact; the 2016 analysis indicated that for every 200 fully vaccinated children, one death would be averted in areas of moderate to high malaria transmission.<sup>3</sup> A qualitative study conducted by PATH in collaboration with research consortia in Ghana, Kenya, and Malawi found that trust in the malaria vaccine has grown as caregivers see the benefits of vaccination for their children, and that the vaccine is acceptable to both health service providers and caregivers.

### **Additional evidence: RTS,S in seasonal use**

Results of a Phase 3 clinical trial conducted in areas of Burkina Faso and Mali with highly seasonal malaria transmission also informed WHO's recommendation of RTS,S. Led by the London School of Hygiene and Tropical Medicine, the study (2017-2022) compared the efficacy of RTS,S to that of SMC, the standard treatment for children in areas with highly seasonal malaria transmission.<sup>4</sup> Results after three years of follow-up showed that RTS,S is comparable to SMC in preventing clinical malaria—the latter having demonstrated around 75 percent efficacy—and that combining the two interventions is markedly superior to either intervention alone. Use of the two interventions together resulted in an approximately 70 percent further reduction in malaria deaths and hospitalizations, and a 60 percent reduction in uncomplicated malaria over use of SMC alone.

Drawing on this evidence, the WHO recommends that countries may consider providing RTS,S in areas with highly seasonal malaria or areas of perennial malaria transmission with seasonal peaks.

### **Development history of RTS,S**

RTS,S was created in 1987 by scientists working at GSK laboratories. 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. Early clinical development was conducted in collaboration with the Walter Reed Army Institute for

Research. In 2001, GSK and PATH's Malaria Vaccine Initiative entered into a public-private partnership to develop RTS,S for young children living in malaria-endemic regions in sub-Saharan Africa. The Bill & Melinda Gates Foundation provided catalytic funding for late-stage development of RTS,S between 2001 and 2015.

RTS,S was rigorously tested through a series of clinical trials.<sup>5,6</sup> The pivotal Phase 3 efficacy and safety trial involved 15,459 infants and young children and was conducted between 2009 and 2014 by 11 clinical research centers in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania).<sup>7</sup> The Phase 3 trial demonstrated that malaria episodes were reduced by more than half during the first year after vaccination. Over a four-year period, among children who received all four doses, the vaccine reduced malaria episodes by about 40% and severe malaria cases by about 30%.<sup>7</sup> The study also showed that at the trial site with the highest disease burden, more than 6,500 clinical malaria episodes were averted for every 1,000 children fully vaccinated with 4 vaccine doses.

A study of the longer-term impact of the vaccine, with a focus on severe malaria, was completed in December of 2016. The study followed children who participated at 3 of the 11 research centers for an additional three years, for a total of seven years of follow-up.<sup>8</sup> Results showed that the incidence of severe malaria decreased as children got older, regardless of whether children received the vaccine; there was no evidence of rebound of severe malaria following the recommended four doses of the vaccine.

### **Regulatory and policy review**

The European Medicines Agency (EMA) issued a positive scientific opinion on RTS,S (Mosquirix) in July 2015. The EMA's assessment of RTS,S is part of its cooperation with WHO to address diseases of major public health importance around the world, which require 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.<sup>9</sup> The EMA and GSK also agreed upon a post-approval plan, a standard requirement for a new vaccine. The plan includes a Phase 4 study to gather additional information on safety and impact in the context of routine use. Following the EMA opinion, RTS,S was reviewed and approved for use in the pilots by regulatory authorities in Ghana, Kenya, and Malawi. In July 2022, WHO prequalified the RTS,S vaccine, thereby making it eligible for procurement by UNICEF.

## Looking ahead

The pilot program in Ghana, Kenya, and Malawi will conclude at the end of 2023, at which time the three countries will be able to transition to doses procured by UNICEF, thanks to the Gavi-funded malaria vaccination program. A case control study that is embedded within the pilot evaluations will continue into 2024 to confirm whether the fourth dose of vaccine is necessary to achieve optimal public health impact. GSK's Phase 4 study will continue through 2025. PATH will continue its role in the pilot program, while also supporting further research on the optimal use of RTS,S.

PATH also is working with WHO and others to explore how best to ensure a healthy malaria vaccine market, recognizing that having only one vaccine or one supplier poses potential risks to vaccine access. Ensuring the availability of multiple suppliers is among the recommendations in the *Malaria Vaccine Global Market Study* published in 2021 by the Market Information for Access to Vaccines initiative at WHO.<sup>10</sup> The study included a forecast of the potential annual demand for the vaccine of approximately 110 million doses by 2036.

Efforts to assure the long-term, sustainable supply of the RTS,S vaccine include the transfer of antigen manufacturing to Bharat Biotech of India. In the medium term, however, manufacturing capacity is not expected to meet the anticipated demand. As with other new vaccines, it takes time and resources to expand manufacturing, and in the case of a vaccine like RTS,S—for which there is no market in high-income countries—external resources may be needed.

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