Overview

Malaria kills more than 600,000 people a year worldwide and causes illness in more than 200 million more. The vast majority of illnesses and deaths occur among young children living in sub-Saharan Africa. Although existing interventions reduced malaria deaths significantly between 2000 and 2015, progress has stalled since then, highlighting the urgent need for new tools.

On October 6, 2021, the World Health Organization (WHO) recommended RTS,S/AS01, the world’s first malaria vaccine, for use in children at risk of malaria caused by Plasmodium falciparum. The WHO recommendation was informed by available evidence on RTS,S, including findings from pilot implementation of the vaccine through routine childhood immunization in areas of Ghana, Kenya, and Malawi.

In December 2021, the board of Gavi, the Vaccine Alliance approved a malaria vaccine program to support the broader rollout of malaria vaccines in Gavi-eligible countries. RTS,S was granted WHO prequalification in July 2022, allowing UNICEF to procure the vaccine.

Pilot program showed real-world impact

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. This led to the Malaria Vaccine Implementation Programme, which began vaccinations in areas of Ghana, Kenya, and Malawi in 2019 and continued until the end of 2023. Across the three countries, more than 6 million doses of RTS,S were administered between April 2019 and December 2023.

Data from the pilot evaluations reaffirmed the vaccine’s safety, showed the vaccine to be feasible to deliver, and documented a 13% drop in deaths among children eligible to receive the vaccine and a 22% reduction in hospital admissions with deadly severe malaria. All three countries had equitable coverage across socioeconomic 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. Thus, more than 90% of children benefited from at least one malaria preventive intervention.

Findings from health economics and qualitative survey research led by PATH also informed the WHO recommendation. Using data from the pilots, modeling showed the vaccine to be a cost-effective addition to other recommended malaria interventions, including in areas with high bednet coverage or where seasonal malaria chemoprevention (SMC) is used. Modeling also showed the vaccine’s cost-effectiveness as comparable to many other new vaccines.

Modeling of the pilot data was consistent with earlier modeling, published in 2016, that showed the vaccine’s potential for considerable public health impact, such that, in areas of moderate to high malaria transmission, one death would be averted for every 200 children fully vaccinated. A qualitative study conducted in collaboration with research consortia in Ghana, Kenya, and Malawi found that trust in the malaria vaccine increased as caregivers saw the benefits of vaccination for their children, and that the vaccine was acceptable to both health care providers and caregivers.

Alice Musimbi received her first dose of RTS,S following the expansion of vaccine use in pilot areas of Kenya. Photo: PATH.
Additional evidence: RTS,S in seasonal use

Results of a Phase 3 clinical trial in Burkina Faso and Mali (2017–2022), led by the London School of Hygiene and Tropical Medicine, also informed WHO’s recommendation. The study compared efficacy of RTS,S to that of SMC, the standard treatment for children in areas of highly seasonal malaria transmission. Results after three years of follow-up showed that RTS,S was comparable to SMC in preventing clinical malaria, with around 75% efficacy—and that combining the two interventions was markedly superior to either one alone. Results from five years of follow-up published in 2023 showed the vaccine-drug combination reduced cases of severe malaria and deaths from malaria in young children by nearly two-thirds and clinical malaria episodes by 60%, compared with either RTS,S vaccination or SMC alone.

Development history of RTS,S

RTS,S was created in 1987 by scientists at GSK. Early clinical development was conducted in collaboration with the Walter Reed Army Institute of Research. A first-in-human study was conducted in US adults in 1992, and the first trial in a malaria-endemic country began in 1998. In 2001, GSK and PATH entered into a public-private partnership to develop RTS,S for young children living in malaria-endemic regions in sub-Saharan Africa. Proof of concept in children under 5 years of age was established in a Phase 2b study conducted in Maputo, Mozambique.

The pivotal Phase 3 efficacy and safety trial of RTS,S, conducted by 11 clinical research centers in seven African countries (2009–2014), involved 15,459 infants and young children. Final results were published in 2015.

Looking ahead

PATH continues to support the ministries of health in Ghana, Kenya, and Malawi in their implementation of the vaccine and is assisting other countries as they prepare to introduce and roll out approved malaria vaccines. PATH looks forward to engaging in further research regarding optimal use of malaria vaccines.

A case control study embedded within the pilot evaluations is expected to yield data in 2024 regarding the need for a fourth dose of RTS,S to achieve optimal public health impact. GSK’s Phase 4 study, part of the post-approval plan agreed upon with the European Medicines Agency, is expected to conclude in 2025.

PATH continues to work with WHO and other partners to explore how best to ensure a healthy malaria vaccine market, recognizing the benefit of having more than one vaccine and supplier, given the scale of projected demand. Efforts to ensure the long-term, sustainable supply of the RTS,S vaccine include the transfer of antigen manufacturing to Bharat Biotech of India. The availability of R21 to complement RTS,S should accelerate the pace of vaccine introduction and more rapidly reduce the burden of malaria in young children.

References