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 (RTS,S), 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*.[1] 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. On December 2, 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.

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.[2] Based upon that advice, the RTS,S Malaria Vaccine Implementation Programme (MVIP) was launched in 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. Through the MVIP, the three countries have been leading the rollout of the vaccine in selected areas.

Global partners are providing funding and other support for the pilots. GSK, the vaccine developer, is donating up to 10 million doses of the vaccine for use in the pilots; financing is provided through a collaboration among Gavi, The Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

Lusitana, the child who received the first dose of the malaria vaccine in the pilot program, and her mother, at Mitundu Community Health Center, Malawi. (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. Data and insights generated from two years of routine vaccination showed that delivery of the vaccine is feasible and increased equity in access to malaria prevention in vaccinating areas. High uptake of RTS,S indicated strong community demand for 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 bednet received the vaccine. This resulted in 90 percent of children benefiting from at least one preventive intervention. Pilot findings also reaffirm the vaccine's favorable safety profile, and in the areas where it is being deployed, vaccination has substantially reduced the incidence of life-threatening severe malaria.

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.[3] Results of a qualitative study conducted by PATH in collaboration with research consortia in Ghana, Kenya, and Malawi indicate that trust in the malaria vaccine has grown as caregivers have seen the benefits of vaccination for their children, and that the vaccine was found to be acceptable to both health service providers and caregivers.

Additional evidence: RTS,S in seasonal use

Results of a recent 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 (with partial funding from PATH), the study compared the efficacy of RTS,S to that of SMC, which is the standard treatment for children in areas with highly seasonal malaria transmission.[4] The results showed that not only is RTS,S comparable to SMC in preventing malaria, but 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. The Phase 3 trial has been extended to a total of five years.

Drawing on this evidence, the WHO recommendation also notes 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 January 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.[5,6] 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).[7] The Phase 3 trial demonstrated that, among children who received four doses, the vaccine reduced malaria episodes by about 40% and severe malaria cases by about 30% over a four-year period.[7] 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.[8] 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. 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.[9] 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.

Looking ahead

The WHO recommendation and Gavi financing decision pave the way for countries to consider whether to adopt

the vaccine and, if eligible for Gavi support, to apply for funding. Such expressions of interest from malaria-endemic countries would help confirm demand for the vaccine and inform investment decisions in manufacturing capacity. The Gavi decision may also inform vaccine financing decisions from other organizations.

The pilot implementation in Ghana, Kenya, and Malawi will continue through 2023 to generate additional evidence on the value of the fourth dose and on the vaccine's impact against severe disease and death. 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* recently published by the Market Information for Access to Vaccines initiative at WHO.[10] 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. Broad access to the vaccine could also be accelerated by mobilization of resources to further scale up production, as current manufacturing capacity is not expected to meet the anticipated demand in the medium term. 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 will be needed. Together with partners and other stakeholders, PATH is working to help ensure that sufficient malaria vaccine supply will be available to meet potential demand in the future.

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