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 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 (RTS,S), also known as Mosquirix™, is the first malaria vaccine shown to provide partial protection against malaria in young children. Beginning in 2018, it will be the first malaria vaccine provided to young children through routine 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 health ministry in each country and international partners, including PATH and GSK, manufacturer of the vaccine. RTS,S is the outcome of a long-standing collaboration between PATH and GSK that began in 2001.

The efficacy of the RTS,S vaccine was established in a Phase 3 clinical trial that concluded in 2014. Children who received four doses of the vaccine had a 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. Any safety signals that arose in the clinical testing phase will be monitored closely 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 3 to 5 settings in sub-Saharan Africa. In response to that recommendation, a country-led, WHO-coordinated Malaria Vaccine Implementation Programme (MVIP) has been designed to address several outstanding questions related to the public health use of the vaccine. Specifically, the MVIP will assess the feasibility of administering the required four doses of the vaccine in children; the vaccine's role in reducing childhood deaths; and its safety in the context of routine use. Data and information derived from the MVIP will inform a WHO policy recommendation on the broader use of the vaccine.

Financing for the MVIP has been mobilized through an unprecedented collaboration between three major global health funding bodies: Gavi, the Vaccine Alliance; the Global Fund to Fight AIDS, Tuberculosis and Malaria; and Unitaid. WHO and GSK are providing additional in-kind contributions, and PATH's activities are also supported by the Bill & Melinda Gates Foundation.

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).[3] 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. 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.

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.[4]

The final results 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 life-threatening 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 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.

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.[5] This opinion was given as part of the EMA's cooperation with WHO, whereby EMA provides opinions on medicines that are not intended for use in the European Union (EU) but are needed to prevent or treat 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 EU. The EMA found that the quality of the vaccine and its risk-benefit profile are favorable from a regulatory perspective.

EMA's opinion did not consider contextual elements such as the feasibility of implementation, the value of the vaccine in the context of other malaria control measures, and the likely cost-effectiveness of the intervention in different settings. RTS,S will only be introduced in the context of the pilots after it has been reviewed and approved by the national regulatory authorities in each of the three countries participating in the MVIP.

Following the EMA decision, and after a thorough review of the clinical trial results, WHO's top advisory committees for immunization and malaria—the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC)—jointly called in October 2015 for pilot implementation of the vaccine in 3 to 5 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.[6] WHO further endorsed the recommendation for pilot introduction of the vaccine.

LOOKING AHEAD

The goal of the MVIP is to enable an updated WHO policy recommendation on the possible broader use of RTS,S for children in sub-Saharan Africa by generating additional evidence on feasibility, impact, and safety. In each country, national regulatory authorities will review the vaccine and consider authorization for its use in their own countries. Vaccine implementation will only begin after such authorization is provided. The pilots are expected to begin in late 2018 and to continue through 2022.

As part of the MVIP, 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.

WHO and PATH are working together across several areas, including on economic assessments, and in the qualitative assessment of behavior change that may occur during the introduction of the vaccine. GSK will continue to play a key role in manufacturing the vaccine and will donate up to 10 million doses for the MVIP, including the Phase 4 studies. As the implementation program progresses, WHO expects other partners to become involved.

References:

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