

## Malaria Vaccine Development Update

### Summary

In late 2012, the World Health Organization (WHO) published an update of the “Rainbow Tables,” which identified more than two dozen active malaria vaccine candidates in clinical development (human testing) and more than a dozen in preclinical development. The vast majority of candidates in clinical development targeted *Plasmodium falciparum*, with roughly equal numbers targeting the blood and pre-erythrocytic stages of the malaria parasite. Unlike the situation two years ago, however, at least one transmission-blocking candidate was reported to be in clinical testing. The Rainbow Tables reported only one vaccine candidate in large-scale, late-stage testing, namely the RTS,S candidate under development by GlaxoSmithKline Vaccines (GSK), the PATH Malaria Vaccine Initiative (MVI), and research centers in seven African countries.

The large-scale Phase 3 efficacy trial of RTS,S began in mid-2009 and reached full enrolment of more than 15,000 participants in early 2011. Results of the first analysis of data from the Phase 3 trial, after one year of follow-up on 6,000 children aged 5 to 17 months, were published online in the *New England Journal of Medicine (NEJM)* in late 2011; first results for infants aged 6 to 12 weeks at first vaccination were published online by *NEJM* in early November 2012.

### Why a vaccine?

Real progress continues to be made in the battle against malaria in parts of Africa and Asia. Deaths due to malaria are declining, as the tools to test, treat, and prevent the disease become more available and are used by more people in malaria-endemic regions—in particular, rapid diagnostic tests, long-lasting insecticide-treated bed nets, and combination drug therapies. Yet despite these measures, malaria continues to exact a heavy toll, particularly in areas of moderate to high parasite transmission. A malaria vaccine would add an important, complementary tool to the existing interventions. At the same time, it will be essential to determine the particular role of any malaria vaccine in specific settings, as different combinations of tools to fight malaria will be appropriate in different settings in malaria-endemic countries. One size may not fit all.

### Challenges and progress to date

Many scientific and market challenges exist in malaria vaccine development. The malaria parasite has a complex life cycle, and no vaccine against a parasitic disease is approved for use in humans. The limited financial return anticipated from a market that is primarily in Africa and other developing regions holds little attraction for the private commercial sector and poses a significant barrier to progress, given the costs of developing and testing a vaccine, estimated at between US\$500 million to US\$800 million or more.

To help address these challenges, MVI was established in 1999 as a focused, portfolio-based, vaccine-development program of PATH, a global health nonprofit organization. Working in collaboration with diverse partners, MVI has advanced more than a dozen projects into first-in-human Phase 1 studies since 2003. In 2013, six MVI-supported vaccine concepts are under clinical development, including RTS,S. These projects represent about one in five of those in clinical development worldwide. A diverse group of organizations from around the world sponsors development of malaria vaccines and includes governmental, nonprofit, and for-profit entities.

### About the RTS,S vaccine development program

In January 2001, GSK and MVI—with funding from the Bill & Melinda Gates Foundation to MVI—entered into a public-private partnership to develop RTS,S for infants and children living in malaria-endemic regions in sub-Saharan Africa. In Phase 2 clinical trials, RTS,S was the first malaria vaccine candidate to demonstrate that it could help protect young children and infants in malaria-endemic areas against infection and clinical disease caused by *P. falciparum*.

In 2009, an expanded collaboration involving scientists at 11 sites in seven African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania) took RTS,S into a large-scale Phase 3 trial. Together, the 11 sites completed enrolment in January 2011, with 15,460 infants and young children participating.

### Design of the trial

As one of the final stages of testing before regulatory file submission, the Phase 3 efficacy trial is designed to continue monitoring safety and potential side-effects, while evaluating the efficacy of the vaccine in infants and young children on a large scale. To this end, researchers enrolled two groups of participants: children aged 5 to 17 months and infants aged 6 to 12 weeks. The Phase 3 trial is a double-blind, randomized, controlled study, in which participants initially received three doses of either RTS,S or a “control” (non-RTS,S) vaccine. After a year and a half, some participants will receive a fourth RTS,S dose to evaluate the potential benefit of a booster. The trial has been designed in consultation with appropriate regulatory authorities and the WHO and is conducted according to the highest international standards for safety, ethics, and clinical practices.

### Results to date

Results of the RTS,S Phase 3 trial for efficacy, safety, and immunogenicity during the first 12 months of follow-up were published online in the *NEJM* in October 2011 (children aged 5 to 17 months) and November 2012 (infants aged 6 to 12 weeks). These results showed that three doses of the RTS,S vaccine candidate reduced clinical and severe malaria over the first year of follow-up by 56 and 47 percent, respectively, in children 5 to 17 months of age at first vaccination and who received the routine DTPw-HepB/Hib vaccine prior to the RTS,S vaccine. In infants 6 to 12 weeks of age at first vaccination, who received the RTS,S vaccine together with the routine DTPw-HepB/Hib vaccine, clinical and severe malaria was reduced by 31 and 37 percent, respectively. RTS,S demonstrated an acceptable safety and tolerability profile. These results were achieved on top of existing malaria interventions, such as insecticide-treated bed nets used by 75 percent of the

older children and 86 percent of the infants.

With these efficacy results against clinical malaria, the co-primary objectives of the trial were met in both age categories. (The *NEJM* articles are available online at [www.nejm.org/doi/full/10.1056/NEJMoa1102287](http://www.nejm.org/doi/full/10.1056/NEJMoa1102287) and at [www.nejm.org/doi/full/10.1056/NEJMoa1208394](http://www.nejm.org/doi/full/10.1056/NEJMoa1208394).)

#### Looking ahead: RTS,S

Follow-up in this Phase 3 trial will continue, to provide more data for analysis to better understand the difference in findings between the age categories. These data and analyses should provide insights into the vaccine candidate's efficacy in different malaria transmission settings. More data on longer-term efficacy during 32 months of follow-up and the impact of a booster dose are expected to be publicly available by the end of 2014 and will provide evidence for national and international public health organizations to evaluate the vaccine candidate's full potential for use.

The RTS,S malaria vaccine candidate is currently under development and subject to the evaluation of its safety, efficacy, and quality, as well as its benefits and risks, by regulatory and public health authorities. If the required regulatory approvals are obtained and if the required public health information, including safety and efficacy data from the Phase 3 program, is deemed satisfactory, the WHO has indicated that a policy recommendation for the RTS,S malaria vaccine candidate is possible as early as 2015, paving the way for decisions by African nations regarding large-scale implementation of the vaccine through their national immunization programs.

#### Looking ahead: Other malaria vaccines

The field of malaria vaccine research and development (R&D) is dynamic and continually evolving, as vaccine projects move through the development pipeline. While RTS,S is the most advanced in the development process, dozens of other projects are in earlier stages of testing. Given the stringent criteria applied by US and European regulatory authorities and by WHO, however, it is unlikely that another vaccine candidate will emerge from Phase 3 testing for many years. The future development of malaria vaccines is also increasingly affected by the malaria community's growing focus on not only controlling the disease, but on its elimination and, in the long term, eradication.

Like RTS,S, many of today's malaria vaccine projects focus on the pre-erythrocytic approach, which aims to trigger the immune system to defend against the parasite as soon as an infected female mosquito injects the parasite into a person's bloodstream or the parasite infects liver cells. This prevents the parasite from infecting, maturing, and multiplying in the liver, after which time the parasite would reenter the bloodstream and infect red blood cells, leading to symptoms of disease. Numerous projects in the global malaria vaccine pipeline are using a protein that provides one of the building blocks of RTS,S, or other proteins from the sporozoite stage of the parasite's life cycle, while seeking to boost the vaccine's efficacy through the use of platforms or delivery vehicles, such as viruses, that might boost the human immune response. Another pre-erythrocytic approach involves the use of whole sporozoites that have been weakened or attenuated either genetically or through irradiation.

Other vaccine approaches under development target the malaria parasite when it is most destructive: at the blood stage, when the parasite replicates rapidly in red blood cells. Blood-stage vaccines are not expected to block infection; instead, they aim to decrease the number of parasites in the blood, reducing the severity of malaria.

A third approach focuses on developing vaccines to block the transmission of malaria between mosquitoes and humans. Transmission-blocking vaccines are being developed to interrupt the life cycle of the parasite by inducing antibodies that prevent the parasite from maturing in the mosquito after it bites a vaccinated, infected person. Transmission-blocking vaccines would not directly prevent people from getting malaria, but they could significantly limit the spread of infection.

Finally, while malaria caused by *P. falciparum*—the deadliest parasite to humans—is the principal target of malaria vaccine R&D worldwide, approaches targeting the more widespread *P. vivax* malaria parasite are needed if the goal of eradicating malaria is to be achieved.

**THE PATH MALARIA VACCINE INITIATIVE (MVI)** is a global program established at PATH through an initial grant from the Bill & Melinda Gates Foundation. MVI's mission is to accelerate the development of malaria vaccines and catalyze timely access in endemic countries. MVI's vision is a world free from malaria. For more information, visit [www.malariavaccine.org](http://www.malariavaccine.org).

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