RTS,S Frequently Asked Questions (FAQs)

WHAT IS RTS,S?

RTS,S/AS01 (RTS,S; trade name Mosquirix™) is an injectable vaccine that provides partial protection against malaria in young children. Like vaccines generally, RTS,S aims to trigger the body's own immune system to defend against disease, in this case, malaria caused by *Plasmodium falciparum*, the most deadly species of the malaria parasite globally and the most prevalent in Africa. Specifically, RTS,S is designed to prevent the malaria parasite from infecting, maturing, and multiplying in the liver, after which the parasite would normally re-enter the bloodstream and infect red blood cells, leading to disease symptoms.

RTS,S is the first malaria vaccine candidate to receive a positive scientific opinion from the European Medicines Agency (EMA), whose Committee for Medicinal Products for Human Use (CHMP) agreed by consensus that the benefits of vaccination with RTS,S outweighed the risks. According to the EMA, RTS,S "could potentially save lives in the age group most at risk from malaria."[1] This was followed in January 2016 by the publication of a position paper by the World Health Organization (WHO) that recommended large-scale pilot implementation of RTS,S in young children, in settings of moderate-to-high parasite transmission in Africa.[2]

WHAT MAKES RTS,S DIFFERENT FROM OTHER MALARIA VACCINES?

RTS,S is the first and, to date, the only vaccine to show a protective effect against malaria among young children in Phase 3 clinical trials. Beginning in 2018, it will be the first malaria vaccine provided to young children in selected areas of three sub-Saharan African countries (Ghana, Kenya, and Malawi) through a Malaria Vaccine Implementation Programme (MVIP).

WHAT DOES THE ACRONYM RTS,S STAND FOR?

RTS,S is a scientific name given to this malaria vaccine candidate and represents its composition. The 'R' stands for the central repeat region of *Plasmodium (P.) falciparum* circumsporozoite protein (CSP); the 'T' for the T-cell epitopes of the CSP; and the 'S' for hepatitis B surface antigen (HBsAg). These are combined in a single fusion protein ('RTS') and co-expressed in yeast cells with free HBsAg. The 'RTS' fusion protein and free 'S' protein spontaneously assemble in 'RTS,S' particles. RTS,S also contains the AS01 adjuvant system, and in scientific papers is usually referred to as 'RTS,S/AS01'.

WHY, WHEN EXISTING INTERVENTIONS APPEAR TO BE WORKING, DO WE NEED A MALARIA VACCINE?

Although existing interventions have helped to reduce malaria deaths significantly over the past 15 years, a well-tolerated and effective vaccine could add an important complementary tool for malaria control efforts. The RTS,S vaccine is intended to complement existing measures to fight malaria, such as bednets and indoor residual insecticide spraying. Final results of a pivotal, large-scale Phase 3 efficacy and safety trial were published in *The Lancet* in April 2015. In that article, the authors wrote that RTS,S—if used correctly—"has the potential to make

a substantial contribution to malaria control when used in combination with other effective control measures, especially in areas of high transmission." [3]

WHAT IS THE LATEST STATUS OF THE RTS,S VACCINE?

On April 24, 2017, the WHO Regional Office for Africa (WHO/AFRO) announced that Ghana, Kenya, and Malawi will take part in the WHO-coordinated implementation program that will make RTS,S available in selected areas, beginning in 2018. This latest development builds on the outcomes of a comprehensive review process by the EMA and by WHO and its advisory bodies.

The EMA, under a process known as article 58, reviewed data on the quality, safety, and efficacy of the vaccine and issued a positive scientific opinion in July 2015. The positive opinion indicates that the quality of the vaccine and its risk/benefit profile is favorable from a regulatory perspective. According to the EMA, the CHMP concluded that "…despite its limited efficacy, the benefits of Mosquirix™ outweigh the risks in both age groups studied," and "the benefits of vaccination may be particularly important among children in high-transmission areas in which mortality is very high."[4] The EMA opinion did not consider contextual elements such as the feasibility of implementation or the likely cost-effectiveness of the intervention in different settings.

Article 58 establishes a mechanism whereby the EMA's CHMP, in cooperation with the WHO, carries out a scientific assessment on medicinal products to prevent or treat diseases of major public health impact that are intended exclusively for markets outside of the European Union. In its assessment, the CHMP applies the same rigorous standards as for medicines to be marketed within the European Union.

In October 2015, WHO jointly convened the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) to review all evidence regarding RTS,S relevant for global policy. SAGE/MPAC jointly recommended large-scale pilot implementation of RTS,S occur among children aged 5 to 17 months in 3–5 settings of moderate-to-high transmission in sub-Saharan Africa. WHO officially adopted the SAGE/MPAC recommendations in January 2016.[2]

WHAT ARE THE NEXT STEPS FOR RTS,S?

WHO's recommendations will be carried out in the context of a Malaria Vaccine Implementation Programme (MVIP) to assess, among other things, the operational feasibility of administering the required four doses of the RTS,S vaccine in children aged 5 to 17 months when delivered in real-life settings, the vaccine's potential role in reducing childhood deaths, and its safety in the context of routine use.

The MVIP is being coordinated and led by WHO in close collaboration with Ministries of Health in the participating countries and a range of in-country and international partners. The MVIP will take place in Ghana, Kenya, and Malawi, beginning in 2018, with preparations already underway. By 2020, the MVIP is expected to provide initial insights on the programmatic feasibility of delivering the vaccine in real-life settings and on the safety profile of RTS,S in the context of routine use. The MVIP will continue to monitor feasibility and safety through its expected conclusion in 2022, while also generating results on the vaccine's impact on childhood survival. The results of the MVIP will help inform future decisions on the wider-scale deployment of the vaccine.

RTS,S is expected to be approved by the National Regulatory Authorities (NRAs) in each of the three countries participating in MVIP for use in the context of the pilot evaluation and Phase 4 studies.

WHO IS FUNDING THE RTS,S MALARIA VACCINE IMPLEMENTATION PROGRAMME?

Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID are partnering to provide $49.2 million for the first phase of the pilot programme (2017-2020), which will be complemented by in-kind contributions from WHO and GSK.

WHAT IS MOSQUIRIX™?

Mosquirix™ is the name trademarked by GSK, also known as a brand name, for the RTS,S/AS01 malaria vaccine. There is no molecular or chemical difference between RTS,S/AS01 and Mosquirix™.

WHAT IS MEANT BY CLINICAL MALARIA?

Clinical malaria refers to those cases where infection with the malaria parasite causes disease. For mild forms of malaria, symptoms include fever, shivering, vomiting, and headache. In malaria-endemic regions, children may have malaria parasites in their blood without showing any symptoms of disease.

WHAT IS MEANT BY SEVERE MALARIA?

Severe malaria refers to those malaria cases where the initial infection (with or without mild symptoms) evolves into an acute life-threatening illness, with complications such as severe anemia, or neurological disease such as convulsions and possibly coma, and may result in death if left untreated.

WHAT DO WE KNOW ABOUT THE SAFETY OF RTS,S?

In its evaluation of the vaccine, the European Medicines Agency concluded, "The safety profile of this vaccine is acceptable and quite similar to others apart from a higher risk for febrile convulsions in the older age group within 7 days after a dose (mostly the third dose) of Mosquirix."[5]

Side effects noted include local pain and swelling, and low-grade fever, which are similar to reactions observed with some standard vaccines given to children. The incidence of fever in the week after vaccination was higher in those who received the fourth dose of the RTS,S vaccine than those receiving the comparator vaccine, a difference that also occurred during the primary series of vaccinations in the older children. Some of the febrile reactions were accompanied by generalized convulsive seizures, as noted above; however all seizures resolved and no long-term effects were observed. (The incidence of such seizures within seven days of a fourth dose in children was 2.5 per 1,000 doses in those receiving four doses of RTS,S; 1.2 per 1,000 doses in those receiving three doses plus a comparator vaccine at 20 months; and 0.4 per 1,000 doses in those receiving only control or comparator vaccines. For the infant age group, febrile seizures were also noted following a fourth dose of RTS,S, at a rate of 2.2 per 1,000 doses.)

The Phase 3 efficacy and safety trial has shown that the overall incidence of serious adverse events (SAEs are clinical events of such a serious nature that they are promptly reported to relevant regulatory agencies; they include death, life-threatening or incapacitating events, among others) was comparable between participants receiving the RTS,S candidate vaccine and those receiving a comparator vaccine. One imbalance noted in published results from the Phase 3 trial and the EMA's assessment concerned an imbalance in meningitis cases in older children receiving RTS,S; however no clear relationship to the vaccine has been established. The EMA concluded that "…there is no evidence in favour of immunological hypotheses," and that "Other hypotheses, like simple chance finding, should also be taken into account since it is more likely to explain the imbalance observed."[5] The occurrence of meningitis as a potential risk will be followed closely in extended follow-up in 3 of the 11 study sites that conducted the Phase 3 trial, and in the planned pharmacovigilance study included in the Risk Management Plan approved by the EMA.

The potential for rebound—or age shifting—with respect to the incidence of severe malaria (including clinical malaria) has also been noted as a possibility. In the Phase 3 trial, among children aged 5 to 17 months at first dose, the incidence of severe malaria decreased over time in all groups. However, children protected by RTS,S are thought to develop their natural immunity against malaria more slowly than unvaccinated children. This means that in areas where malaria is present, vaccinated children may be at higher risk of disease when the protection from the vaccine decreases over time. The potential risk of rebound will be further evaluated in ongoing and long-term clinical studies.

WHAT DO WE KNOW ABOUT THE EFFICACY OF RTS,S?

Clinical study results indicate that RTS,S has the potential to help protect infants and young children living in malaria-endemic regions in sub-Saharan Africa. Over the first year after vaccination in the Phase 3 efficacy and safety trial, RTS,S reduced the number of malaria cases by half in children and by one third in infants. Vaccine efficacy was highest shortly after vaccination, but could be enhanced by a fourth dose.

The final results of the Phase 3 trial, published in April 2015 in *The Lancet*, reported that vaccine efficacy against clinical malaria for the young child category was 39% for those who received a fourth dose and 26% for those who did not receive it, over an average 48 months of follow-up.[3] Statistically significant vaccine efficacy against severe malaria to the end of the study period was observed in those who received the fourth dose, but not in those who did not.

WHERE WAS THE PHASE 3 EFFICACY AND SAFETY TRIAL CONDUCTED AND WHO PARTICIPATED?

The Phase 3 efficacy and safety trial was conducted at 11 trial sites in seven African countries with different malaria transmission intensities and patterns: the sites were in Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and Tanzania. The participants were children aged 5 to 17 months and infants aged 6 to 12 weeks at the time of the first vaccination. Leading African research centers, and in some instances their Northern partners, conducted the trial together with GSK and the PATH Malaria Vaccine Initiative (MVI). The research centers were selected for their track records of clinical research, strong community relations, and commitment to meeting the highest international ethical, medical, clinical, and regulatory standards.

WHY WAS RTS,S DEVELOPED FOR AND TESTED IN AFRICA?

The great majority of malaria cases and deaths caused by the *P. falciparum* parasite occur in sub- Saharan Africa, among children under five years of age; thus, the focus of the development of the RTS,S malaria vaccine candidate for use in infants and young children was in this region. To determine the level of protection against malaria provided by the candidate vaccine, it is necessary to vaccinate children who may be exposed to the malaria arasite and track them to see whether they develop disease. If children were not at risk of contracting malaria, it would be impossible to determine whether the vaccine candidate provides protection.

WHY SHOULD A VACCINE THAT IS ONLY MODESTLY EFFICACIOUS BE CONSIDERED FOR USE IN AFRICA?

While great strides have been made lately against malaria through the use of bed nets and other measures, malaria still kills approximately 429,000 people per year, mainly children under five years of age in sub-Saharan Africa. Adding a vaccine with this efficacy profile to current interventions could enhance existing malaria control efforts.

Looking at the vaccine profile in the context of disease burden is important, for instance, in medium to high disease burden areas. For children in the 5–17 month-old age category who received a fourth dose at 18 months after the primary schedule, an average of 1,774 cases of clinical malaria were prevented for every 1,000 children vaccinated across the 11 trial sites over an average of 48 months of follow-up. The impact was greater in areas of higher disease burden.

WHEN MIGHT THE VACCINE BECOME AVAILABLE FOR USE?

Starting in 2018, the vaccine will be available at a subnational level in Ghana, Kenya, and Malawi, through the MVIP. The results of the MVIP, which is expected to conclude in 2022, will help inform future decisions on the wider-scale deployment of the vaccine.

HOW MUCH WILL THE VACCINE COST?

GSK has stated that RTS,S would be made available at a not-for-profit price and that the price will be the cost of manufacturing the vaccine plus a small return of around five percent, to be reinvested in research and development for second-generation malaria vaccines or vaccines against other neglected tropical diseases. GSK also has committed to evaluate the possibilities for reducing the cost of manufacturing.

WILL AFRICAN FAMILIES BE ABLE TO AFFORD A MALARIA VACCINE?

If African countries decide to implement a malaria vaccine, it must be accessible and affordable to those who need it most: children living in malaria-endemic areas. In many African countries, childhood vaccines are provided to

children at no cost thanks to existing international and national financing mechanisms. A long-standing shared goal of PATH and GSK is that the cost of a malaria vaccine not be a barrier to access where it would be of most use.

HOW MUCH HAS DEVELOPMENT OF THE RTS,S VACCINE CANDIDATE COST AND WHO IS PAYING?

PATH has received more than $200 million in grants from the Bill & Melinda Gates Foundation to advance the development of RTS,S. GSK has invested more than $350 million to date. WHO has estimated the cost of the WHO-led pilot evaluation to be about $100 million. Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID are partnering to provide $49.2 million for the first phase of the pilot programme (2017-2020), which will be complemented by in-kind contributions from WHO and GSK. The costs of the GSK-led epidemiological and Phase IV studies are additional to these costs. GSK and PATH will collaborate to donate doses of RTS,S for use in the WHO pilots.

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

References:

1. European Medicines Agency (EMA). Mosquirix, Summary for the public. 2015. Available at http://bit.ly/2oWfXeh.
2. World Health Organization. *Weekly Epidemiological Record*. 2016; 91(4): 33–52. Available at: http://www.who.int/wer.
3. RTS,S Clinical Trials Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: Final results of a phase 3, individually randomised, controlled trial. *The Lancet*. 2015; 386 (9988): 31–45. doi: 10.1016/S0140-6736(15)60721-8.
4. First malaria vaccine receives positive scientific opinion from EMA [press release]. EMA; July 24, 2015. Available at http://bit.ly/1elUa6Z.
5. EMA. Mosquirix, Assessment report. 2015. Available at http://bit.ly/2paE1uw.