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 (P.) falciparum*, the deadliest 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 shown in Phase 3 trials to provide partial protection against malaria in young children. The vaccine has been recommended by the World Health Organization (WHO) for pilot introduction in selected areas of three African countries—Ghana, Kenya, and Malawi—expected to begin in late 2018. It will be evaluated for use as a complementary malaria control tool that could be added to (and not replace) the core package of WHO-recommended preventive, diagnostic and treatment measures.

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 through routine immunization programs. Three sub-Saharan African countries will introduce the vaccine in selected areas as part of a large-scale pilot implementation program.

WHAT DOES THE ACRONYM RTS,S STAND FOR?

RTS,S is a scientific name given to this malaria vaccine and represents its composition. The 'R' stands for the central repeat region of *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, 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."[1]

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 Malaria Vaccine Implementation Programme (MVIP) that will make RTS,S available in selected areas, and is expected to begin in late 2018.

The WHO/AFRO announcement was the latest development since the WHO published its position on RTS,S in January 2016,[2] adopting the recommendations made

jointly in October 2015 by the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC). SAGE/MPAC recommended that large-scale pilot implementation of RTS,S occur among children aged 5 to 17 months in 3 to 5 settings of moderate-to-high malaria parasite transmission in sub-Saharan Africa.

Earlier, in July 2015, the European Medicines Agency (EMA) issued a positive scientific opinion concluding that the quality of the vaccine and its risk/benefit profile is favorable from a regulatory perspective. The assessment applies the same rigorous standards as for medicines to be marketed within the European Union. According to the EMA, "…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."[3]

WHAT ARE THE NEXT STEPS FOR RTS,S?

The MVIP is designed to 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. The MVIP is expected to continue through 2022.

The pilots are being coordinated by WHO in close collaboration with ministries of health in the participating countries and a range of in-country and international partners, including PATH and GSK. In each country, the ministry of health will deliver the malaria vaccine through its national immunization program in the selected areas and regions. 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.

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 supply up to 10 million doses free of charge for the MVIP and the Phase 4 studies. As the program progresses, WHO expects other partners to become involved. The roles and responsibilities of WHO, PATH, and GSK in the MVIP are governed by a collaboration agreement concluded in 2017.

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

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.

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."[4]

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 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 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 (RMP) 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 studies.

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

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).[5] 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, included 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.[1]

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.

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 PATH's Malaria Vaccine Initiative (PATH/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 for use in infants and young children was in this region. To determine the level of protection against malaria provided by the vaccine, it is necessary to vaccinate children who may be exposed to the malaria parasite 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 provides protection. Additional studies would be needed before the vaccine could be recommended for use outside Africa.

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

While great strides have been made against malaria through the use of bednets and other measures, malaria still kills more than 400,000 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 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 to 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 COST AND WHO IS PAYING?

PATH has received more than US$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 Global Fund to Fight AIDS, Tuberculosis and Malaria; and Unitaid are partnering to support the MVIP. WHO and GSK are providing additional in-kind contributions, and PATH's activities are also supported by the Bill & Melinda Gates Foundation. The costs of the GSK-led epidemiological and studies in the RMP are additional to these costs. GSK will donate up to ten million doses of RTS,S for use in the pilots.

References:

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