Dated: April 2019

Questions and Answers

Malaria Vaccine Implementation Programme (MVIP)

1. What is RTS,S/AS01?

RTS,S/AS01 (RTS,S) is the world's first malaria vaccine that has been shown to provide partial protection against malaria in young children. The vaccine acts against *Plasmodium falciparum*, the most deadly malaria parasite globally and the most prevalent in Africa.[1] The vaccine has been recommended by WHO for pilot introduction in selected areas of 3 African countries. 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.

2. What makes RTS,S different from malaria vaccine candidates currently under development?

RTS,S is the first, and to date, the only vaccine to show a protective effect against malaria among young children in a Phase 3 trial. Beginning in 2019, it will be the first malaria vaccine provided to young children through routine immunization programmes. Three sub-Saharan African countries will introduce the vaccine in selected areas as part of a large-scale pilot implementation programme.

3. What is the efficacy of the RTS,S vaccine?

The Phase 3 trial, conducted over 5 years (from 2009 to 2014), enrolled approximately 15 000 young children and infants in 7 sub-Saharan African countries.[2] The trial sites within these countries represented a range of malaria transmission settings. Among children aged 5–17 months who received 4 doses of RTS,S, the vaccine prevented approximately 4 in 10 (39%) cases of malaria over 4 years of follow-up and about 3 in 10 (29%) cases of severe malaria,[3] with significant reductions also seen in overall hospital admissions as well as in admissions due to malaria or severe anaemia. The vaccine also reduced the need for blood transfusions, which are required to treat life-threatening malaria anaemia by 29%.

4. What is WHO's official position on RTS,S?

In October 2015, after a thorough review of the Phase 3 trial results, 2 independent WHO advisory groups – the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) – jointly called for pilot implementation of the vaccine in 3 to 5 settings in sub-Saharan Africa.

In a position paper published on 29 January 2016, WHO officially adopted the joint recommendation of SAGE and MPAC; in doing so, the Organization recognized the public health potential of the RTS,S vaccine while also acknowledging the need for further evaluation before considering wide-scale deployment. There is currently no WHO policy recommendation for the large-scale use of the RTS,S malaria vaccine beyond the pilot programme.

5. What is the purpose of the malaria vaccine implementation programme?

The efficacy of the RTS,S vaccine was established in the Phase 3 clinical trial (see #3, above); children who received 4 doses of the vaccine had a significantly lower risk of developing malaria, including severe malaria. The malaria vaccine implementation programme (MVIP), coordinated by WHO, 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 4 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.

6. Which countries will participate in MVIP?

Three countries – Ghana, Malawi and Kenya – are participating in the MVIP. Each of these countries has selected the areas to be included in the pilot programme.

7. What were the criteria for country selection?

In December 2015, WHO issued a call for expressions of interest from African ministries of health to collaborate in the malaria vaccine implementation programme. Of the 10 countries that responded positively, 3 were selected for the programme based on pre-specified criteria. Key among these was the expressed desire by the ministry of health to engage in the MVIP, and well-functioning malaria and immunization programmes.

Other criteria included: good coverage of recommended malaria control interventions and childhood vaccinations; moderate-to-high malaria transmission despite good implementation of WHO-recommended malaria interventions; a sufficient number of young children living in the malaria-transmission areas where the vaccine will be introduced; strong implementation research or evaluation experience in the country; and capacity to assess safety outcomes. Participation in the Phase 3 RTS,S trial was an additional criterion considered during the country selection process.

8. Within the pilot areas, which districts will receive the vaccine first?

It is important at this stage to learn how best to introduce the malaria vaccine into routine immunization systems, and to evaluate that introduction. To do this, some districts/sub-counties within the selected areas will have the opportunity to introduce the vaccine into their immunization schedules at the start of the programme, while other districts will not receive the vaccine until a later date. Assignment of areas into those that receive the vaccine and those that do not has been through a process called "randomization", based on chance using a computer programme.

Introducing the vaccine into some areas, while delaying it in others, is also important for understanding the public health usefulness of the vaccine and will provide key information on whether the vaccine should be introduced throughout the pilot countries and more broadly across Africa.

9. Who will be eligible for vaccination?

The vaccine will be made available through routine immunization programmes to young children living in selected areas in Ghana, Kenya and Malawi. Current estimates are that at least 360 000 children per year across the 3 pilot countries will receive the RTS,S vaccine from the health facilities where they

receive their routine childhood vaccinations. Some areas selected for participation in the MVIP will serve as comparator areas in which the vaccine will not be available initially.

Immunization authorities in the 3 countries will specify the vaccination schedule, based on WHO recommendations. A 4-dose schedule is required, with the first dose given as soon as possible after 5 months of age followed by doses 2 and 3 at approximately monthly intervals and the fourth dose near the child's second birthday.

10. When will the vaccinations begin?

Vaccinations began in Malawi on 23 April and in Ghana on 30 April. Kenya is expected to introduce the vaccine in the coming weeks.

11. Is the vaccine safe?

In the Phase 3 trial, the vaccine was generally well tolerated, with adverse reactions similar to those of other childhood vaccines.

A stringent regulatory authority – the European Medicines Agency – issued a positive scientific opinion of 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.

- During the Phase 3 trial of the RTS,S vaccine, there were more cases of meningitis in children who received the vaccine than in those who did not; however, no causal link to the vaccine has been established.
- Overall, there were 29% fewer cases of severe malaria in children who received the vaccine. In those children who did develop severe malaria, there were more cases of cerebral malaria, one type of severe malaria; however, no causal link to the vaccine has been established.

12. Are there any known side effects?

Known side effects include pain and swelling at the injection site, and fever. These side effects are similar to reactions observed with other vaccines given to children. Occasionally, children with fever have seizures. During the Phase 3 trial, an increased risk of febrile seizures was seen within 7 days of the administration of any of the RTS,S vaccine doses. Children who had febrile seizures after vaccination recovered completely and there were no long-lasting consequences.

13. Who developed and who manufactures the vaccine?

GSK led the development of RTS,S over a 30-year period. In 2001, GSK began collaborating with PATH's Malaria Vaccine Initiative (MVI) to continue developing RTS,S. A 5-year Phase 3 efficacy and safety trial was conducted between 2009 and 2014 through a partnership that involved GSK, MVI (with support from the Bill & Melinda Gates Foundation), and a network of African research centres at 11 sites in 7 countries. GSK is the vaccine manufacturer.

14. What is the purpose of the Phase 4 studies, and how do they relate to the MVIP?

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As part of the malaria vaccine implementation programme, GSK is conducting a number of 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.

15. Which partners are involved in MVIP?

The MVIP is coordinated by WHO in close collaboration with ministries of health in participating countries and a range of in-country and international partners. In each country, the ministry of health will deliver the malaria vaccine through its national immunization programme in the selected areas. National malaria control programmes will ensure that existing WHO-recommended prevention tools, such as long-lasting insecticidal nets (LLINs) and artemisinin-based combination therapies (ACTs), continue to be deployed on a wide scale. In-country research partners have been identified to lead a rigorous evaluation of the RTS,S vaccine implementation.[4]

WHO is working with PATH and GSK on the MVIP through a collaboration agreement. WHO and PATH are working together across a number of areas, including on economic assessments, and in the qualitative assessment of behaviour 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. As the programme progresses, WHO expects other partners to become involved.

16. What are the terms of the collaboration agreement between WHO, PATH and GSK?

The collaboration agreement between WHO, PATH and GSK defines the roles and responsibilities of these 3 partners for the MVIP. Specifically:

- WHO is responsible for programme oversight and coordination of all aspects of the MVIP; this includes rigorous evaluations of the feasibility of implementing the 4-dose vaccination schedule, and its impact and safety in the context of routine immunization. WHO will also provide technical assistance to the Ministries of Health in Ghana, Kenya and Malawi as the countries introduce the vaccine in selected areas through their national immunization programmes.
- As part of the MVIP, PATH will support WHO in project management and communications. PATH will also lead a qualitative study on health care utilization and assess the economics of vaccine implementation.
- GSK has committed to donating an adequate supply of the vaccine for the MVIP – up to 10 million doses. GSK will also lead Phase 4 studies to continue to monitor vaccine safety and effectiveness in routine use, as is required and standard for a new vaccine.
- Concurrent with the pilot implementation over the next several years, the partners are exploring how best to assure the longer-term supply of the vaccine.

17. Who will fund the MVIP?

In November 2016, WHO announced that funding commitments for the MVIP had been made by Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid through 2020.

18. What is the expected duration of the programme?

The MVIP is expected to continue through 2022. During this time, the MVIP will provide data on the programmatic feasibility of delivering the vaccine in real-life settings, the safety profile of RTS,S in the context of routine use, and the vaccine's impact on child survival. Taken together, these results will inform future decisions on the wider-scale deployment of the vaccine.

19. Why is the MVIP being rolled out only in Africa, and not in other regions?

The WHO African region bears the greatest burden of malaria worldwide. Most malaria illness and deaths in this region are caused by the parasite targeted by the RTS,S vaccine (*P. falciparum*). In recent years, malaria death rates in the region have dropped significantly following a major scale-up of LLINs, ACTs and other malaria control measures. However, the disease continues to take a heavy toll: in 2017, the region was home to 93% of all malaria deaths globally (or an estimated 403 000 deaths), mainly among young children.[5] The RTS,S malaria vaccine was developed for use in Africa and for African children. Additional studies will be needed before the vaccine can be recommended for use outside Africa.

19. What other interventions exist for malaria control?

Existing WHO-recommended interventions for malaria control include: LLINs, indoor residual spraying with insecticides, preventive treatment for infants and during pregnancy, and prompt diagnostic testing and treatment of confirmed cases with effective anti-malarial medicines. In the Sahel, a sub-Saharan region of Africa, seasonal malaria chemoprevention is recommended in areas with highly seasonal malaria transmission. Deployment of these tools has already dramatically lowered the malaria disease burden in many African settings. The disease burden can be further lowered through the continued scale-up of these existing control measures.

While efforts to sustain and further expand existing interventions must continue, new complementary tools and strategies are needed in some areas to accelerate the fight against malaria and further drive down the disease burden. The malaria vaccine is proposed as a potential additional tool to complement the existing package of WHO-recommended preventive, diagnostic and treatment measures for malaria.

20. Is RTS,S licensed by a regulatory authority?

Following a joint review convened by the African Vaccine Regulatory Forum (AVAREF) in May 2018, the National Regulatory Authorities of Ghana, Kenya and Malawi authorized the RTS,S vaccine for use in the pilot areas

The European Medicines Agency (EMA) carried out a scientific assessment of RTS,S and issued a "European scientific opinion" on the vaccine in July 2015. 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 but are needed to prevent or treat diseases of major public health importance around the world. 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.

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Notes:

1. The vaccine offers no protection against *P. vivax* malaria, which predominates in many countries outside of Africa.
2. These countries included: Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania.
3. Severe malaria refers to those cases where the initial infection with the malaria parasite evolves into an acute, life-threatening illness.
4. Specifically, they will evaluate the feasibility of delivering the vaccine in real-life settings, the impact of the vaccine on childhood survival and the vaccine's safety profile in the context of routine use.
5. In 2017, malaria killed an estimated 266 000 under-fives globally.