Frequently Asked Questions, RTS,S/AS01 Malaria Vaccine (Mosquirix)

1. **What is Mosquirix?**

Mosquirix, also known as RTS,S/AS01, is an injectable malaria vaccine developed by GSK. GSK led the development of RTS,S/AS01 over a 30-year period. In 2001, GSK began a collaboration with the PATH Malaria Vaccine Initiative (MVI) to continue developing RTS,S. An advanced clinical trial (referred to as a Phase 3 trial) to assess the vaccine's efficacy and safety 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, including Ghana.

2. **How does Mosquirix Act?**

Mosquirix acts against *Plasmodium falciparum*, the most deadly malaria parasite globally, and the most prevalent in Ghana and the rest of sub-Saharan Africa. Mosquirix offers no protection against *Plasmodium vivax* malaria, a strain of the malaria parasite which predominates in many countries outside of Africa.

3. **Why do we need a malaria vaccine?**

Historically, vaccines have proved to be among the most effective means of preventing disease and saving lives, particularly in the case of infectious diseases. Malaria death rates in sub-Saharan Africa have dropped in recent years with the scale-up of existing tools recommended by the World Health Organization (WHO). These tools include: long-lasting insecticidal nets (LLINs), indoor residual spraying with insecticides, preventive treatment for children and during pregnancy, prompt diagnostic testing, and treatment of confirmed cases with effective antimalarial medicines. However, even with all these interventions in place, people are still getting sick and dying from malaria. Additional tools, including a vaccine, could support already existing interventions to help to reduce the burden of malaria

4. **What makes Mosquirix different from other malaria candidate vaccines currently under development?**

Mosquirix is the first and to date the only vaccine to show a protective effect against malaria among young children in phase 3 clinical trials. The vaccine would complement other measures currently used to fight malaria. Mosquirix is also the first malaria vaccine to obtain a positive scientific opinion from a stringent medicines' regulatory authority, the European Medicines Agency (in July 2015). It is also the first malaria vaccine to receive authorization from regulatory authorities in three (3) African countries: Ghana, Kenya and Malawi.

These three countries were selected by WHO to begin the introduction of Mosquirix in selected areas, as part of a large-scale pilot implementation programme, known as the Malaria Vaccine Implementation Programme (MVIP).

5. **What is the Malaria Vaccine Implementation Programme (MVIP)?**

The MVIP was established by WHO to coordinate and support the introduction of Mosquirix in selected areas of Africa through country-led routine immunization. The 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 (4) doses of the vaccine to children.
- the vaccine's role in reducing childhood deaths and
- safety of the vaccine 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 are participating in the MVIP?

Ghana, Kenya and Malawi are the three countries participating in the MVIP, with each of the 3 countries selecting the areas to be included in the pilots.

7. 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 Mosquirix (*P. falciparum*). In recent years, malaria death rates in the region have dropped significantly following a major scale-up of long-lasting insecticidal nets (LLINs), artemisinin-combination therapies (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. Mosquirix 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.

8. Why is Ghana taking part in the MVIP?

In December 2015, the WHO put out a call for interested countries in Africa to apply to participate in the MVIP. Ghana responded to this call for expressions of interest. Ghana's application was based on the country's malaria burden as well as this country's experience with Mosquirix during the clinical trials.

The existence of robust regulatory, ethical, malaria control and immunization systems and infrastructure in Ghana played a critical role in its selection as one of the three countries on the African continent to participate in this programme.

9. When will the Malaria Vaccine Implementation Programme be launched?

WHO and partners are engaged in discussions with the Ministry of Health and other stakeholders to plan for vaccine introduction and evaluations. Vaccinations are due to begin in 2019.

10. 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 Mosquirx in the context of routine use, and the vaccine's impact on child survival. Taken together, this information will inform future decisions on the wider-scale deployment of the vaccine.

11. In which countries were the Phase 3 clinical trials conducted?

The Phase 3 trial of Mosquirix enrolled over 15,000 infants and young children in seven sub-Saharan African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania). The clinical trial sites within these countries represented a range of malaria transmission settings (low, medium and high) in order to determine the vaccine's efficacy in these different settings.

12. What role did Ghanaian researchers play in the development of Mosquirix?

Researchers from the Kintampo Health Research Centre and the School of Medical Sciences, Kwame Nkrumah University of Science and Technology, participated in the Phase 2 and Phase 3 clinical trials to determine the safety, immunogenicity and efficacy of Mosquirix. The clinical trials in Ghana recruited a total of 3,439 infants and children within the ages of 6-12 weeks and 5-17 months.

13. What were the results from the Phase 3 clinical trials?

Vaccine efficacy

Among children aged 5–17 months who received three doses of Mosquirix administered at 1-month intervals, followed by a fourth dose 18 months later, the vaccine reduced malaria by 39%, equivalent to preventing nearly 4 in 10 malaria cases.

In addition, the four-dose vaccine schedule reduced severe malaria by 29% in this age group, with 37.2% reduction in malaria-related hospitalizations and 14.9% reduction in all-cause hospitalizations. A 29% reduction in blood transfusions, required to treat life-threatening malaria anemia, was also seen.

It is worthy to note that no vaccination is 100% protective; in that light Mosquirix does not prevent 100% of malaria cases. Mosquirix will therefore add to the existing malaria prevention efforts. It is meant to complement existing malaria control efforts.

Vaccine safety

In the Phase 3 trials, the vaccine was generally well tolerated and was shown to have an acceptable safety profile, with adverse events similar to those of other childhood vaccines. As with other new vaccines, and in line with national regulations, the safety profile of Mosquirix will continue to be monitored as the vaccine is made available through the MVIP.

14. What are the known side effects of Mosquirix

Known side effects include pain and fever as well as swelling in area of the limb where the vaccine is injected. These side effects are similar to reactions observed with other vaccines given to children. Occasionally, children with fevers have seizures. An increased risk of febrile seizures was seen within 7 days of the administration with any of the four doses of Mosquirix. In the phase 3 clinical trial, children who had febrile seizures after vaccination recovered completely and there were no long-lasting consequences.

Among children in the clinical trials, there was a modest increase in the number of cases of meningitis and cerebral malaria in the group receiving Mosquirix compared to the control group. However, no causal link to the vaccine was established.

As with other new vaccines, and in line with national regulations, the safety profile for Mosquirix will continue to be monitored during the MVIP. Safety signals that arose in the

clinical trials will be monitored closely as the vaccine is introduced for use during the MVIP.

15. How will unknown side effects be detected during the programme?

During the MVIP, GSK will conduct phase 4 studies in parts of the pilot areas to continue monitoring the effectiveness and safety of the vaccine in routine use. These studies are required and standard for a new vaccine and 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 evaluation of the MVIP led by WHO.

16. What role could Mosquirix potentially play in Ghana's malaria control programme?

The vaccine is being considered as a complementary malaria control tool in Ghana that could potentially be added to – and not replace – the core package of proven malaria preventive, diagnostic and treatment interventions, such as long-lasting insecticidal nets and indoor residual spraying with insecticides.

17. Where will the Pilot Implementation Programme take place in Ghana?

Assignment of areas into those that receive the vaccine and those that do not has been through a random computer-run selection that gave each district an equal opportunity of being selected for the vaccine. Introducing the vaccine into some areas, while delaying it in others is 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.

The pilot implementation programme is expected to take place in selected districts in the Brong Ahafo, Central, Volta and Upper East regions. Children in the MVIP areas will be divided into approximately two equal groups, namely, "comparison" and "implementation" districts. Children living in the areas designated as "implementation districts" within the regions will receive the vaccine whilst those in the "comparison districts" will not receive the malaria vaccine initially. The districts that are not yet receiving the vaccine are serving as comparison areas to help health officials evaluate the programme. This evaluation is meant to inform decisions on the vaccine's potential use on a wider scale in Ghana and elsewhere across Africa where malaria is a public health threat.

18. Which districts are going to participate in the MVIP?

The MVIP will take place in the three regions. Implementation and Comparison districts are listed below:

Central Region

Implementation districts:

1. Abura-Asebu-Kwamankese
2. Agona East
3. Ajumako-Enyan-Essiam
4. Asikuma-Odoben-Brakwa
5. Assin North
6. Awutu-Senya
7. Cape Coast
8. Ekumfi
9. Gomoa West

Comparison districts:

1. Agona West
2. Assin South
3. Awutu-Senya East
4. Efutu
5. Gomoa East
6. Komenda-Edina-Eguafo-Abirem
7. Mfantsiman
8. Twifu-Ati-Mokwa
9. Twifu-Hemang Lower Denkyira
10. Upper Denkyira East
11. Upper Denkyira West

Brong Ahafo Region

Implementation districts:

1. Asutifi North
2. Banda
3. Dormaa
4. Dormaa West
5. Jaman South
6. Pru
7. Sunyani
8. Tain
9. Wenchi
10. Asunafo North

Comparison districts:

1. Asunafo South
2. Asutifi South
3. Atebubu-Amanten
4. Berekum
5. Dormaa East
6. Jaman North
7. Sene East
8. Sene West
9. Sunyani West
10. Tano North
11. Tano South

Volta Region

Implementation districts:

1. Akatsi North
2. Akatsi South
3. Biakoye
4. Central Tongu
5. Kadjebi
6. Keta
7. Ketu North
8. Ketu South
9. Kpando
10. Krachi-Nchumuru
11. Krachi West
12. Nkwanta North
13. North Dayi
14. South Dayi

Comparison districts:

1. Adaklu
2. Afadjato
3. Agotime-Ziope
4. Ho
5. Ho West
6. Hohoe
7. Jasikan
8. Krachi East
9. Nkwanta
10. North Tongu
11. South Tongu

19. Which districts will participate in the phase 4 studies?

Brong Ahafo Region:

Implementation districts : -Kintampo North, Kintampo South, Techiman North and Nkoranza North

Comparison districts : Nkoranza South and Techiman South

Upper East Region:

Implementation districts : Kassena-Nankana and Kassena-Nankana West

Comparison districts : Builsa North and Builsa South

20. What went into the Selection of the Regions for the Pilot Implementation Programme?

Introduction is taking place in selected areas where the proportion of people infected with malaria is 20 percent or greater, where coverage with childhood vaccinations is high, and where there are sufficient numbers of children at the right age to receive the vaccine. Areas recommended for seasonal malaria chemoprevention are also not eligible for the pilot

implementation programme. Information garnered from the pilots will help to inform later decisions about potential wider use of the vaccine.

21. Which partners are involved in MVIP?

The MVIP is coordinated by WHO in close collaboration with the Ministry of Health and a range of in-country and international partners.

The Ministry of Health will deliver Mosquirix through the Ghana Health Service/Expanded Programme on Immunization in the selected districts (Refer 19 and 20).

The National Malaria Control Programme will ensure that existing WHO-recommended prevention tools, such as LLINs and artemisinin-based combination therapies (ACTs), continue to be deployed.

In-country research partners have been identified to lead a rigorous evaluation of the MVIP.

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 and supplying the vaccine free of charge for the MVIP.

The Food and Drugs Authority will work closely with the Ghana Health Service, GSK and in-country research partners to ensure safety of children who receive Mosquirix during the MVIP.

22. Will the Vaccine be supplied free of charge to Ghanaians?

WHO has mobilized funding for the MVIP through 2020 from Gavi, the Vaccine Alliance, The Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID. GSK will continue to play a key role in manufacturing the vaccine and supplying it free of charge to the MVIP. Over the next several years, the partners are exploring how best to assure the longer-term supply of the vaccine.

23. How will the vaccine be given?

The vaccine is recommended to be given as an injection in four doses to children, with the first dose given as soon as possible after the age of 5 months. In Ghana, it will be given at 6 months, 7 months, 9 months and 24 months of age.

24. Why is Mosquirix not for adults?

The vaccine was developed with children in mind since there are at highest risk of being ill with malaria and eventually dying Adults living in malaria-endemic areas such as Ghana usually acquire partial immunity against malaria and are less likely to die from malaria compared to children below 5 years of age.

25. What is the position of WHO on Mosquirix?

In October 2015, following a review of the Phase 3 trial results, two 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. The vaccine was recommended for

use in the pilot implementation programme, with the first dose given to children soon after the age of 5 months.

In a position paper published on 29 January 2016, WHO officially adopted the joint recommendation of SAGE and MPAC; in doing so, WHO recognized the public health potential of the 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 malaria vaccine beyond the pilot programme.

26. Malaria Control Measures-What other interventions exist for malaria control?

There are effective interventions available that can be used to reduce the burden of malaria in Africa. These include: prevention through mosquito vector control using long-lasting insecticidal bed-nets; indoor residual spraying with insecticides; seasonal malaria chemoprevention in specific settings; intermittent preventive treatment for pregnant women; prompt diagnostic testing; and treatment of confirmed cases with effective anti-malarial medicines. All the interventions are implemented nationwide with the exception of indoor residual spraying and seasonal malaria chemoprevention, which are targeted to some regions. These measures have dramatically lowered malaria disease burden in many African settings over the years. The malaria disease burden can be lowered further by continuing to scale up existing WHO-recommended control measures. Available malaria control interventions represent some of the most cost-effective measures for public health.

Mosquirix is being considered as a **complementary** intervention. This means that any use of Mosquirix would be in addition to the existing malaria preventive measures described. The use of high quality, safe and effective drugs to treat malaria will continue regardless of any deployment of a first-generation malaria vaccine.

27. Will Vaccination with the Mosquirix be optional or compulsory?

Vaccination with Mosquirix in the selected implementation areas is not compulsory, but the Ghana Health Service and partners expect that community engagement will provide sufficient information to allow parents and caretakers to make informed decisions on vaccinating their children so that they can benefit from the potential protection against malaria disease and death.

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