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

1. **What is Mosquirix™?**

Mosquirix™, also known as RTS,S, is an injectable malaria vaccine developed by GSK. GSK led the development of RTS,S 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 trials (referred to below as Phase 3 trials) 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. While malaria death rates in sub-Saharan Africa have dropped in recent years with the scale-up of existing malaria control measures, the disease continues to take a heavy toll: there were 212 million malaria cases worldwide in 2015 with 429,000 deaths. The majority of deaths are in children under the age of five, living in sub-Saharan Africa. In Ghana, malaria caused 2,133 deaths in 2015, approximately 51% of which afflict children under the age of five.

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

Mosquirix™ is the first to date, the only vaccine to show a protective effect against malaria among young children in Phase 3 clinical trials and would complement and reinforce other measures currently used to fight malaria. Mosquirix™ is at least 5 to 10 years ahead of other vaccine candidates and 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.

5. **Why is Ghana to take part in the malaria vaccine implementation programme?**

In December 2015, the WHO put out a call for interested countries in Africa to apply to participate in the malaria vaccine implementation programme to which Ghana responded. Ghana's application was based on the country's experience with Mosquirix™ during the clinical trials, besides being a malaria-endemic country.

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

6. 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 bed nets and indoor residual spraying with insecticides.

7. What is the purpose of the World Health Organization (WHO) Malaria Vaccine Pilot Implementation Programme?

In January 2016, the WHO recommended pilot implementation of the malaria vaccine in 3–5 distinct settings in sub-Saharan Africa, at subnational level, covering moderate-tohigh transmission settings in sub-Saharan Africa, namely Ghana, Malawi and Kenya. The pilot implementation programme, coordinated by WHO, will assess the extent to which the vaccine's protective effect shown in advanced clinical trials (Phase 3 trials) can be replicated in real-life settings. Specifically, the pilot programme will evaluate the feasibility of delivering the required 4 doses of the vaccine in children; the vaccine's potential role in reducing childhood deaths and the safety of the vaccine in the context of routine use.

8. What were the criteria for the selection of countries to participate in the Malaria Vaccine Implementation Programme?

The criteria for the selection of the countries included the following:

1. Desire to engage in the Programme by national stakeholders, particularly the Ministry of Health
2. Well-functioning malaria and immunization programmes, with good coverage of recommended malaria control interventions and childhood vaccinations
3. Moderate-to-high malaria transmission despite good implementation of malaria control interventions;
4. A sufficient number of infants in the malaria control areas where the vaccine will be introduced.
5. Strong implementation research or evaluation experience in the country; and the capacity to assess safety outcomes.
6. Country participation in the Phase 3 trial of Mosquirix™ was an added benefit.

9. What is malaria?

Malaria is a parasitic infection of the blood that can cause illness, among people. Everybody in Ghana is at risk but children under five years and pregnant women are at greatest risk. Malaria can be classified into simple and severe malaria.

Simple malaria

Simple malaria refers to those malaria cases in which infection with the malaria parasite causes disease, meaning symptoms are seen or felt. 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.

Severe malaria

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

10. In which countries was the Phase 3 trial 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.

11. 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 trials to determine the safety, immunogenicity and efficacy of Mosquirix™. The trials in Ghana recruited a total of 3,439 infants and children within the ages of 6-12 weeks and 5-17 months.

12. What were the results from the Phase 3 trial?

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 fourth-dose vaccine schedule reduced severe malaria by 31.5% in this age group, with 37.2% reduction in malaria-related hospitalizations and 14.9% reduction in all-cause hospitalizations. A 28% reduction in blood transfusions, required to treat lifethreatening malaria anemia, was also seen. Among children aged 5–17 months who did not receive a fourth dose of the vaccine, the protective benefit against severe malaria was lost, highlighting the importance of the fourth dose of this vaccine to maximise its benefits.

It should be noted that the RTS,S malaria vaccine does not prevent all cases of malaria. It is meant to complement existing malaria control efforts. No vaccination is 100% protective; the RTS,S malaria vaccine will therefore add to the existing malaria prevention efforts.

Vaccine safety

In the Phase 3 trials, the vaccine was generally well tolerated, with adverse events similar to those of other childhood vaccines. The European Medicines Agency, which reviewed all the data from trials, found Mosquirix™ to have an acceptable safety profile. 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.

13. Side effects

Known side effects include pain and fever as well as swelling in 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 of any of the RTS,S vaccine doses. In the phase 3 trial, children who had febrile seizures after vaccination recovered completely and there were no long-lasting consequences

Among children in the older age group, a modest increase in the number of cases of meningitis and cerebral malaria was found in the group receiving the Mosquirix™ vaccine compared to the control group that received meningitis vaccination in place of the malaria vaccine. This observation was not seen in infants aged 6–12 weeks.

However, it is unclear whether there is a causal link between these findings and Mosquirix™; this will be further monitored in the pilot implementation programme.

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

A great deal of preparatory work is required before the vaccinations with Mosquirix™ begin. The WHO and partners are engaged in intensive discussions with national stakeholders in the selected countries since 2016. Vaccinations are due to begin in mid2018.

15. Who will fund the Malaria Vaccine Implementation Programme?

The WHO has mobilized funding for the first phase of the pilot programme (2017-2020) from the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID and Gavi, the Vaccine Alliance.

16. What is the policy for the registration/licensure of Mosquirix™?

Mosquirix™ has not yet been registered for use as a malaria vaccine in Africa. Regulators in Ghana, Malawi and Kenya will jointly review the documentation submitted by the manufacturer (GSK) prior to registering the vaccine.

The European Medicines Agency (EMA), under a regulatory procedure known as Article 58, assessed the quality, safety and efficacy of Mosquirix™ and its benefit-risk balance.

Following this, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive Scientific Opinion for Mosquirix™. This procedure is used for medicines that will not be marketed in the EU. African regulators including the Ghana Food and Drugs Authority may use this assessment to facilitate their own regulatory review to reach a decision on licensure. EMA's opinion was positive indicating that, in their assessment, the quality of the vaccine and its benefit-risk profile is favourable from a regulatory perspective. This opinion, however, does not take into account 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.

The earliest time vaccines will be used in Ghana for the pilot implementation is the mid 2018 only after they have been registered for use. The time between now and mid 2018 will be used for planning, training, logistics mobilization and public education in order to prepare for a successful pilot implementation.

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

The pilot implementation programme is expected to take place in selected districts in the Brong Ahafo, Central, Upper East and Volta Regions. Children in the vaccination areas will be divided into approximately two equal groups, namely, the "comparator" and the "implementation" groups. Children living in the areas designated as "implementation group" within the regions will receive the vaccine whilst those in the "comparator group" will not receive the malaria vaccine initially. The purpose of this division is to compare the two groups during and after the pilot implementation to answer questions regarding the safety and efficacy of the vaccine.

18. What goes into the Selection of the Regions for the Pilot Implementation Programme?

High malaria burden areas (parasite prevalence of >20%), is a priority, as this is where the benefit of the vaccine is predicted to be highest. Information garnered from the pilots will help to inform later decisions about potential wider use of the vaccine.

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

WHO has mobilized funding for the first phase of the MVIP (2017-2020) 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.

20. 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, 7, 9 and 24 months of age.

21. What is the position of the WHO on the malaria vaccine?

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.

22. 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 antimalarial 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, i.e., 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.

23. Will Vaccination with the RTS,S malaria vaccine be optional or compulsory?

Vaccination with Mosquirix™ is not compulsory but the Ghana Health Service and partners urge all parents in the pilot implementation areas to endeavor to vaccinate their children in order to benefit from any potential protection them malaria disease and death.

24. Why is the RTS,S malaria vaccine not for adults?

Adults living in malaria endemic areas such as Ghana have partial immunity against malaria and do not die from malaria compared to children below 5 years of age.

References

1. World Health Organization (WHO). Q&A on the malaria vaccine implementation programme (MVIP). http://www.who.int/malaria/media/malaria-vaccineimplementation-qa/en/ Accessed 29 Jul 2017
2. World Health Organization (WHO). Questions and answers on the Phase 3 trial results for malaria vaccine RTS,S/AS01 http://www.who.int/malaria/media/rtss-phase-3-trial-qa/en/ Accessed 20 April 2017
3. World Health Organization (WHO). 10 facts on malaria. http://www.who.int/features/factfiles/malaria/en/. Accessed 10 Apr 2017
4. Malaria Vaccine Initiative (MVI) . RTS,S (Mosquirix™). Frequently Asked Questions (FAQs). http://www.malariavaccine.org/sites/www.malariavaccine.org/files/content/page/files/RTSS%20FAQs_FINAL.pdf. Accessed 9 Apr 2017
5. World Health Organization (WHO). (2016). Malaria vaccine: WHO position paper. *WeeklyEpidemiological Record;* 91(4): 33–52. http://www.who.int/wer/2016/wer9104.pdf. Accessed 9 Apr 2017
6. Ghana District Health Information Management System (DHIMS)2, 2015.
7. RTS,S Clinical Trials Partnership. (2015). 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*. DOI: http://dx.doi.org/10.1016/S0140-6736(h15)60721-8
8. World Health Organization (WHO). World Malaria Report, 2016. http://apps.who.int/iris/bitstream/10665/252038/1/9789241511711-eng.pdf. Accessed 19 July, 2017.
9. Ghana Statistical Service (GSS), Ghana Health Service (GHS), and ICF International. 2015. Ghana Demographic and Health Survey 2014. http://dhsprogram.com/pubs/pdf/FR307/FR307.pdf. Accessed 20 Jul 2017.