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

What is Mosquirix™?

RTS,S is a malaria vaccine developed by GSK. GSK led the development of RTS,S over a 30-year period. In 2001, GSK began collaborating with the PATH Malaria Vaccine Initiative (MVI) to continue developing RTS,S. A 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 manufacturer of Mosquirix™.

How does Mosquirix ™ act?

Mosquirix™ acts against *Plasmodium falciparum*, the most deadly malaria parasite globally, and the most prevalent in Africa. It offers no protection against *P. vivax* malaria, which predominates in many countries outside of Africa.

Why do we need a malaria vaccine?

Historically, vaccines have proved to be one of the most effective means of preventing disease and saving lives, particularly in the case of infectious diseases. There were 212 million malaria cases worldwide in 2015 with 429,000 deaths. The majority of deaths are in children under the age of 5 living in sub-Saharan Africa. In Ghana, malaria causes about 2,000 deaths annually, approximately 48% of which afflict children under the age of five. A vaccine would complement and reinforce the measures currently used to fight malaria.

What makes Mosquirix™ different from other malaria candidate vaccines?

Mosquirix™ is the most advanced malaria vaccine candidate the world has seen. Mosquirix™ is at least 5 to 10 years ahead of other candidate vaccines. Mosquirix™ is also the first malaria vaccine to obtain a positive scientific opinion by a stringent medicines regulatory authority, European Medicines Agency in July 2015.

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 spraying with insecticides.

What is the purpose of the World Health Organization (WHO) Malaria Vaccine 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-to-high transmission settings in sub-Saharan Africa, namely Ghana, Malawi and Kenya. The pilot programme, coordinated by WHO, will assess the extent to which the vaccine's protective effect shown in advanced clinical trials (referred to below as "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; the impact of the vaccine on lives saved; and the safety of the vaccine in the context of routine use.

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.

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. Strong implementation research or evaluation experience in the country; and the framework for a strong pharmacovigilance system.
5. Country participation in the Phase 3 trial of Mosquirix^{TM} was an added benefit.

Why did Ghana apply to take part in the malaria vaccine implementation programme?
In February 2016, 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^{TM} during the clinical trials, besides being a malaria endemic country.

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

In which countries was the Phase 3 trial conducted?
The Phase 3 trial of Mosquirix^{TM} 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.

What role did Ghanaian researchers play in the development of Mosquirix^{TM}?
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^{TM}. The trials in Ghana recruited a total of 3,439 infants and children between the ages of 6-12 weeks and 5-17 months without any safety concerns.

What were the results from the Phase 3 trial?
Vaccine efficacy
Among children aged 5–17 months who received three doses of Mosquirix^{TM} 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 4-dose vaccine schedule reduced severe malaria by 31.5% in this age group, with reductions also seen in malaria hospitalizations, all-cause hospitalizations and the need for blood transfusions. 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.

Infants received the vaccine together with other routine childhood vaccines at 6, 10 and 14 weeks of age. Among the infants, the malaria vaccine did not work sufficiently well to justify its further use in this age group.

Vaccine safety

In the Phase 3 trial, the vaccine was generally well tolerated, with adverse reactions similar to those of other childhood vaccines. Among children in the older age group, there was an increased risk of febrile seizures within 7 days after any of the vaccine doses. Among the younger infants, this risk was only apparent after the fourth dose. There were no long-lasting consequences due to any of the febrile seizures.

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 malaria vaccine compared to the control group. It is unclear whether there is a causal link between these findings and Mosquirix™; this will be further monitored in the pilot implementation programme. This observation was not seen in infants aged 6–12 weeks.

The European Medicines Agency 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.

Why did the efficacy different in the two age groups?

Lower immune responses are induced by the vaccine in infants aged 6-12 weeks compared to children aged 5-17 months. Possible factors underlying this difference include interference by co-administration with DTP-containing vaccines, the presence of maternally acquired antibodies to malaria in the 6-12 week olds, and immunological immaturity in the 6-12 week olds compared to the 5-17 month age group.

What is meant by clinical malaria?

Clinical malaria refers to those cases where 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.

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 anaemia, or convulsions and possibly coma, and may result in death if left untreated.

When will the Malaria Vaccine Implementation Programme be launched?
There is a great deal of preparatory work that will need to be done before the vaccinations begin. The WHO and partners have begun intensive discussions with national stakeholders in the selected countries since 2016. The pilot vaccinations are due to begin in 2018.

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.

What is the policy for the registration/licensure of the Mosquirix™ malaria 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 FDA, Ghana 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 risk/benefit 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.

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 prior to registering the vaccine.

What is the position of the WHO on the malaria vaccine?
In January 2016, WHO issued a position paper calling for large-scale pilot implementations of RTS,S/AS01 in children 5 to 9 months of age, alongside other malaria control interventions in settings of moderate-to-high parasite transmission in Africa. Specifically, "WHO recommends that the pilot implementations use the 4-dose schedule of the RTS,S/AS01 in 3 to 5 distinct epidemiological settings in sub-Saharan Africa, at subnational level, covering moderate-to-high transmission settings," with three doses administered to children between 5 and 9 months of age, followed by a fourth dose 15–18 months later. The pilot implementation programme will compile evidence on the feasibility, impact, and safety of the vaccine delivered in country immunization programmes alongside other currently recommended malaria control measures.

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 infants and during pregnancy; prompt diagnostic testing; and treatment of confirmed cases with effective anti-malarial medicines. 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 use of the existing non-vaccine malaria preventive measures described.

The search for high quality, safe and effective drugs to treat malaria will continue regardless of any deployment of a first-generation malaria vaccine.

References

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