



## Questions and Answers on Malaria Vaccines

October 2013

### Malaria vaccines

#### **What is the current status of malaria vaccine research?**

There are currently no licensed malaria vaccines. Over 20 vaccine projects are in clinical trials. Of these, the most advanced vaccine is being evaluated in a Phase 3 clinical trial. This vaccine is called RTS,S/AS01 and has been developed through a partnership between GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative (MVI), with funds from the Bill & Melinda Gates Foundation to MVI. The clinical testing of RTS,S is at least 5-10 years ahead of other candidate malaria vaccines. RTS,S/AS01 is a vaccine against *Plasmodium falciparum*, with no protection expected against *P. vivax* malaria.

#### **In what populations is the Phase 3 trial being conducted?**

The Phase 3 trial of RTS,S/AS01 includes 15,460 infants and young children in seven sub-Saharan African countries namely Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania. These countries represent a range of different malaria transmission settings in order to be able to determine the vaccine's usefulness in these different settings. There are two age groups in the trial. One of these age groups is infants who receive three doses of the malaria vaccine together with other routine childhood vaccines at 6, 10 and 14 weeks of age. The other age group in the Phase 3 trial is older children aged between 5 and 17 months at first dose of RTS,S/AS01.

#### **How well does the RTS,S/AS01 vaccine protect against malaria?**

As of October 2013, three sets of results are available from the Phase 3 trial. The first results were released in October 2011 and were in children aged 5-17 months at first immunization. The estimated overall efficacy was a 55% reduction in the number of all malaria episodes during the first 12 months of follow-up, with 47% efficacy against severe, life-threatening malaria estimated in this same age group. Data for children vaccinated aged 6-14 weeks of age, in co-administration with other vaccines, were released in November 2012. Estimated overall efficacy in this age group over 12 months of follow-up was 33% for all malaria episodes, and 37% for severe, life-threatening malaria.

#### **New results reported in October 2013:**

In October 2013, the third set of results reported on efficacy in both the 6-14 week and 5-17 month age groups over 18 months of follow-up, and included site-specific efficacy for the first time.

##### ***18 month follow-up results***

In the 5-17 month age group, when pooled across all sites, efficacy estimates over 18 months follow-up against clinical malaria (46%) and severe malaria (35.5%) remain highly statistically significant. Reductions in both malaria hospitalizations (41.5%) and all-cause hospitalizations (19%) were noted over 18 months. By contrast while efficacy against clinical malaria remains statistically significant in the 6-14 week age group at 27%, the efficacy estimate for severe malaria is no longer statistically significant.

##### ***Site-specific efficacy results***

In the 5-17 month age group, efficacy has been demonstrated in all 11 settings in 7 African countries. The efficacy estimates over 18 months of follow-up ranged from 40% to 77% with statistical significance at all sites. By contrast, statistically significant efficacy was confirmed at 4 of the 11 sites in the younger 6-14 week age group.



## **Why is the efficacy apparently different in the 2 age groups?**

Lower immune responses are induced by the vaccine in infants aged 6-14 weeks compared to children aged 5-17 months. The reasons for this difference are unclear but co-administration with DTP-containing vaccines and the presence of maternally acquired antibodies to malaria in the 6-14 week olds may both be factors related to this difference.

Any possible recommendation related to vaccination later than the first few months of life would require at least 2 additional immunization visits to be added to the routine immunization schedule.

## **How is WHO involved in malaria vaccine research efforts?**

WHO's role is to advise and guide the malaria vaccine development activities of the global research community. Once Phase 3 clinical trial data become available, WHO convenes its technical group to assess the safety and effectiveness of the malaria vaccine, and considers a WHO policy recommendation and prequalification, if advised that these are supported by the data. The technical group advising WHO on Phase 3 trials of malaria vaccines is the Joint Technical Expert Group (JTEG) on Malaria Vaccines, convened by the Immunization, Vaccines, and Biologicals Department and the Global Malaria Programme.

To learn more about JTEG click on the following link

[Joint Technical Expert Group on Malaria Vaccines](#)

## **Licensing, policy recommendations and prequalification**

### **When could the RTS,S/AS01 vaccine be available for African children?**

If the results from the current Phase 3 trial provide sufficient evidence of the protective effect of the vaccine against malaria, RTS,S could be a "first generation" malaria vaccine". An update to the malaria vaccine technology roadmap, which provides a framework for second generation malaria vaccine development, is to be published in November 2013. RTS,S would be partially effective, reducing the number of cases of malaria in vaccinated children, but not preventing all episodes of the disease. There are still a number of steps that usually occur before new vaccines are introduced into immunization programmes in some endemic countries. These steps include: licensure of the vaccine by regulatory authorities; a WHO recommendation for use; WHO prequalification (for countries wishing to be supplied through the United Nations, or who use WHO prequalification as the basis for procurement eligibility); then decision-making by national public health authorities in malaria-endemic countries on introduction and use of the vaccine. An affordable price is one of the many additional factors beyond efficacy that will influence country decision-making on introduction.

Based on what we know now, and depending on the final trial results, a WHO recommendation for use and subsequent prequalification may occur in 2015.

### **When could the RTS,S/AS01 vaccine be licensed by a regulatory authority?**

The European Medicines Agency (EMA), under a process known as article 58, will perform a scientific evaluation of this vaccine and issue what is called "a European scientific opinion". This would not be licensure or registration, but provides a scientific opinion which African regulators may use to help their own regulatory processes. It will be African national regulatory authorities which will consider licensing the vaccine in their jurisdictions. It is not clear when African regulators will consider this, but evaluation for licensure becomes relevant when sufficient efficacy data for the target population for vaccination become available.

**What is article 58 and how does the EMA work with WHO in assessing the RTS,S/AS01 vaccine?**

Article 58 is a specific legal basis in the European pharmaceutical legislation, allowing the EMA to perform an evaluation of medicinal products which are intended to be used only outside the EU to prevent or treat diseases of major public health significance. The same processes are used by the EMA as those used for marketing/registration of European Union (EU) medicinal products. This evaluation is performed with WHO and with involvement of the relevant national regulatory authorities. RTS,S/AS01 will be submitted to EMA under article 58 because it is being developed by an EU manufacturer specifically for targeted populations and against a disease which occurs primarily outside the EU. It is not expected that the manufacturer will seek to license this vaccine in European countries given its targeted intended use.

**When will WHO make a recommendation concerning use of the RTS,S/AS01 vaccine?**

Information needed to make a recommendation for use includes how long the vaccine's protection lasts, and what the protection level is in different settings in Africa. In making recommendations, the efficacy of a booster dose may also be important. According to the vaccine development partnership's timelines, the information needed for WHO to make an assessment will become available in late 2014, to allow possible recommendation for use in 2015, depending on the results. For first-in-class vaccines, a positive regulatory opinion by a stringent regulatory authority is necessary before policy recommendation by WHO, and policy timings are therefore dependent on the outcomes of regulatory processes.

Vaccines that are currently licensed against human diseases are caused by either viruses or bacteria. Should RTS,S/AS01 be licensed, it will be the first ever licensed vaccine against a parasitic disease in humans. RTS,S/AS01 would therefore be a novel health intervention. The role of WHO, as the United Nations health agency, is to fully assess its safety and effectiveness; WHO will recommend RTS,S/AS01 if and when all required conditions for such a recommendation have been met. The introduction of a new vaccine is a major public health and financial decision that needs to be thoroughly assessed.

**What is the difference between a WHO recommendation for use and WHO prequalification?**

A WHO policy recommendation is the global equivalent of a national public health authority's decision about use of vaccines. Many countries appreciate guidance from the WHO policy recommendation process on which vaccines they should seek to introduce in their national immunization programmes. Similarly, donor agencies, such as the GAVI Alliance, require a WHO recommendation for use before funding procurement of vaccines for developing countries. Before a WHO recommendation is made, the vaccine's safety, immunogenicity and efficacy are reviewed by WHO technical expert groups and the risk/benefit to vaccinees in potential target countries is assessed. The role of new vaccines in the context of existing preventive and treatment measures plays a part in this assessment, as does cost-effectiveness.

WHO prequalification ensures that a specific vaccine from a specific manufacturer meets international standards of quality, safety and efficacy and is appropriate for the target population. Only WHO prequalified vaccines can be supplied to countries through UN agencies.



## **Malaria control measures**

### **What other interventions exist for malaria control?**

There are many effective interventions now available that can be used to reduce the burden of malaria in Africa. These include: prevention through mosquito vector control and use of long-lasting insecticidal bed-nets and, in some settings, indoor residual spraying with insecticides; seasonal malaria chemoprevention in some 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. The malaria disease burden can be lowered further by continuing to scale up WHO recommended control measures. Available malaria control measures represent some of the most cost-effective measures for public health.

The potential role of RTS,S/AS01 will be in addition to fully scaled-up access to and use of non-vaccine malaria preventive measures, prompt diagnostic testing and effective anti-malarial medicines.

The need for high quality, safe and effective drugs to treat malaria will continue regardless of any deployment of a first-generation malaria vaccine such as RTS,S/AS01.