

Questions and Answers on Malaria Vaccines

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Malaria vaccines

What is the current status of malaria vaccine research?

There are currently no licensed malaria vaccines. Over 20 research projects are in clinical trials. Of these 20, the most advanced is in Phase 3 clinical trials. 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. RTS,S is at least 5-10 years ahead of other candidate malaria vaccines. RTS,S is a *Plasmodium falciparum* vaccine, with no protection expected against *P. vivax* malaria.

Who is involved in the Phase 3 trial?

The Phase 3 trial of RTS,S includes 15,460 infants in seven different sub-Saharan African countries namely Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania. 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. This is the expected target population. The other age group in the Phase 3 trial is older children aged between 5 and 17 months at first dose of RTS,S.

How well does RTS,S work?

The results of the Phase 3 trial will become available to WHO in three stages: late 2011, late 2012 and late 2014. A WHO recommendation for use will most likely be based on data from all three stages, and can be expected in 2015.

The first of these interim reports became available in October 2011. The efficacy figure was 55% reduction in frequency of malaria episodes during the 12 months of follow-up in children 5-17 months of age at first immunization. This is not the vaccine development partnership's stated target population, which is children aged 6-14 weeks of age, in co-administration with other vaccines. The efficacy in this target population is not yet known.

Efficacy here means reducing how often vaccinated children get clinical malaria. It does not mean half of the children are completely protected. We do not know how long the vaccine's protection lasts, we do not know if a booster dose will be needed and we do not know whether this level of protection is the same in countries with different intensities of malaria transmission. We should have more information on all of these issues by the end of the Phase 3 trial in 2014.

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 on Malaria Vaccines, convened by the Immunization, Vaccines, and Biologicals Department and the Global Malaria Programme.

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

Licensing, policy recommendations and prequalification

When could RTS,S be available for African children?

If the current Phase 3 trial goes well, RTS,S could be a "first generation" malaria vaccine. This means that RTS,S would be partially effective, reducing but not necessarily preventing all cases of malaria in vaccinated children. 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. Cold-chain capacity and an affordable price are two of the many additional factors beyond efficacy that will influence country decision-making on introduction.

Based on what we know now, if all goes well in the Phase 3 trial and depending on the final trial results, a WHO recommendation for use and subsequent prequalification may occur in 2015.

When could RTS,S 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 data from the target population becomes available.

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

Article 58 is a specific legal basis in the European pharmaceutical legislation, allowing the EMA to perform an evaluation of medicinal products, using the same processes as those used for marketing/registration of European Union (EU) medicinal products, but for medicines to be used outside the EU and intended to prevent or treat diseases of major public health significance in those countries. 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 primarily outside the EU. The manufacturer is not expected to license this vaccine in European countries given its targeted intended use.

Why wait until 2015 for a recommendation for use for RTS,S/AS01?

The WHO Joint Technical Expert Group on Malaria Vaccines has consistently stated that at least 24 months follow-up data from the target population will be needed from a pivotal Phase 3 trial before policy recommendation can be considered, unless vaccine efficacy is much higher than had been expected from the earlier stage clinical trials, particularly for severe malaria. According to the vaccine development partnership's timelines, the needed information will become available in late 2014, to allow possible recommendation for use in 2015, depending on the results.

Should RTS,S/AS01 be licensed, it will be the first ever licensed vaccine against a parasite for humans. Existing vaccines protect against viruses or bacteria; and parasites are very different. RTS,S would therefore be a novel health intervention. Our role as the United Nations health agency is to fully assess its safety and effectiveness; we will recommend RTS,S 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 for malaria control. These include: prevention through mosquito vector control with long-lasting insecticidal nets and in some settings indoor residual spraying with insecticides; intermittent preventive treatment 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 settings. The malaria disease burden can be lowered further by continuing to scale up WHO recommended control measures.