Decision-making on malaria vaccine introduction: the role of cost–effectiveness analyses

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Status of malaria vaccine development

Policy-makers in countries where malaria is endemic are facing increasingly complex decisions about which vaccines and malaria prevention measures to include in national immunization and malaria control programmes. Several new vaccines and malaria preventive measures are already competing for limited financing in developing countries. African countries with endemic malaria should be ready to make a national policy decision on the introduction of RTS,S/AS01, a first-generation malaria vaccine, by 2015.[1] If clinical trials progress according to schedule, that same year the World Health Organization (WHO) will issue a policy recommendation on the public health use of this vaccine based on the findings of the full Phase III efficacy trial in progress, which will be available in late 2014.[2] The vaccine's manufacturers are targeting infants in malaria-endemic African countries who undergo routine vaccination through the Expanded Programme on Immunization (EPI) at 6, 10 and 14 weeks of age, with the possibility of a booster dose being needed at 9–18 months. At present WHO is assessing the evidence base for a policy position on this vaccine. The type of critical data that it will take into account during this process is shown in Box 1.

Cost–effectiveness is an important consideration in public health decision-making. This article summarizes critical parameters driving malaria vaccine cost–effectiveness predictions and discusses major uncertainties that remain in the cost–effectiveness modelling arena. It also highlights the need for ongoing work by modelling groups to further refine cost–effectiveness predictions.

Box 1. **Critical questions for formulation of policy on a new malaria vaccine**

- What is the evidence that RTS,S/AS01 vaccination is not associated with serious adverse reactions in children aged less than 17 months?
- What level of protection against clinical malaria does RTS,S/AS01 confer on infants 6 to 14 weeks of age, over 30 months of follow-up, when co-administered with routine infant vaccines in sub-Saharan African settings?
- What is the evidence that a booster dose of RTS,S/AS01 at 18 months is needed to maintain benefit following a 3-dose primary immunization series?
- Is there evidence that the efficacy of RTS,S/AS01 varies in different transmission settings?
- Do available data support a WHO policy recommendation to introduce RTS,S/AS01 into routine immunization programmes in malaria-endemic countries? What is the optimal schedule? What flexibility is there for interrupted and delayed schedules?
- What is the evidence that co-administration leads to non-inferior responses for both RTS,S/AS01 and existing EPI vaccines?
- What is the evidence that RTS,S/AS01, when administered at 6,10 and14 weeks of age, provides at least as much protection against hepatitis B as the available hepatitis B vaccines?
- How cost–effective is RTS,S/AS01 as a preventive measure in addition to LLINs?

EPI, Expanded Programme on Immunization; LLIN, long-lasting insecticide-treated nets; WHO, World Health Organization.

Malaria control

The RTS,S/AS01 vaccine is intended for use in conjunction with existing measures for malaria prevention, such as the use of long-lasting insecticide-treated nets (LLINs), which is known to be highly cost–effective. A recent systematic review[3] of cost–effectiveness studies of the use of insecticide-treated nets reported a median cost per disability-adjusted life year (DALY) averted of 27 United States dollars (US$) (range: 8–110). LLINs have been associated with reduced all-cause mortality in African children under the age of 5 years[4] and are known to greatly reduce malaria transmission.[5] So, in countries that have successfully scaled up the use of LLINs, implemented rapid malaria diagnostic testing and facilitated access to effective artemisinin-based combination therapy, how will policy-makers decide whether or not to introduce RTS,S/AS01 as an additional malaria control measure?

Cost–effectiveness models

Policy-makers are encouraged to use economic evidence from cost–effectiveness models, in addition to burden of disease and attainable coverage, to guide their decision-making. During 2010 and 2011, WHO undertook an analysis of model structure, assumptions and key parameters to identify the factors driving uncertainty in malaria vaccine cost–effectiveness models. It received independent expert advice from two groups: the Joint Technical Expert Group (JTEG) and the Quantitative Immunization and Vaccines Related Research (QUIVER) Advisory Committee. JTEG is composed of malaria vaccine experts and QUIVER provides technical advice in areas such as vaccine modelling and cost–effectiveness tools. In March 2011, a subgroup of JTEG and QUIVER members met with representatives of five modelling groups – the Swiss Tropical and Public Health Institute, Imperial College, Intellectual Ventures,

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GlaxoSmithKline Biologicals and the PATH Malaria Vaccine Initiative.[6] So far only one of these groups has published cost–effectiveness predictions for the introduction of RTS,S/AS01 into national immunization programmes[7] and at least one more is planning to publish a malaria vaccine cost–effectiveness model.[8] Other malaria vaccine cost–effectiveness models and tools are expected to become available over the next few years as Phase III trial results fuel further work.

Transmission models

The meeting between JTEG/QUIVER members and modelling groups resulted in an assessment of the uncertainty underlying model parameters. In the field of malaria epidemiology, major uncertainty still surrounds certain parameters, most notably the incidence of clinical and severe malaria and malaria-related mortality in older children and adults. In addition, major uncertainties remain in connection with the relative effects of age and exposure to malaria parasites on naturally-acquired immunity,[9] the interaction between vaccine-induced immunity and naturally-acquired immunity,[10] and the potential impact of different types of malaria vaccines on malaria transmission (i.e. herd effects). All of these are important parameters to consider when making cost–effectiveness predictions.[7] We therefore encourage multiple groups using different modelling designs, structures, tools and plausible assumptions to provide cost–effectiveness predictions, as we have done in the course of other vaccine modelling efforts.[11] We also support ongoing efforts to fully explore and discuss the uncertainties underlying malaria transmission models; to iteratively improve model parameterization through data fitting, and to carry out further sensitivity analyses to better characterize the parameters driving uncertainty.

Impact and cost–effectiveness models

Two published transmission models have so far predicted that RTS,S/AS01 is unlikely to substantially affect transmission if administered at 6–14 weeks of age through routine EPI programmes.[8,12] This needs to be confirmed or proven false through clinical studies, but it highlights the importance of considering RTS,S/AS01 within a framework in which mosquito vector control measures, such as the use of LLINs or indoor residual spraying, have already reduced malaria transmission. Another prediction is that vaccine cost–effectiveness will be highest in settings where transmission is low to moderate (i.e. annual entomological inoculation rate (EIR) above 1–2 but less than 100). The EIR, a measure of transmission intensity, is the number of infectious mosquito bites received per person per unit of time.

A recent probabilistic sensitivity and uncertainty analysis of one model provided useful insights into some of the uncertainties involved in parameterizing malaria transmission models.[7] According to this report, the use of RTS,S/AS01 could be highly cost–effective in many settings with low to moderate transmission, depending on the price of the vaccine and the duration of the vaccine's protection. In this model cost–effectiveness decreases as transmission intensity increases above an annual EIR of 100. If final Phase III trial data shows that the efficacy of RTS,S/AS01 is lower in high-transmission settings, it will be critical to maximize *Anopheles* vector control to reduce transmission intensity wherever the introduction of RTS,S/AS01 is being considered.

Parameters driving cost–effectiveness predictions

What are the key drivers of cost–effectiveness predictions? Most groups use similar parameters for initial efficacy, as there are now multiple clinical trial estimates of the initial efficacy of RTS,S/AS01. Initial efficacy estimates from the Phase III trial for infants 6–14 weeks of age who receive RTS,S/AS01 together with other infant vaccines will be available before the end of 2012. Efficacy estimates for this age group are already available from Phase II trials.

The price per dose of vaccine is a key driver of cost–effectiveness. At a cost of US$ 1 or 2 per dose, high cost–effectiveness is predicted for most African settings even with the expected four-dose schedule, according to the most extensively published model.[7] Since countries are unlikely to introduce RTS,S/AS01 unless they find funding beyond what is needed to support universal access to LLINs or indoor residual spraying, rapid diagnostic tests, and artemisinin-based combination treatment, it becomes apparent that price will be a key factor in public health decision-making surrounding any first-generation malaria vaccine.

The duration of protection is another critical parameter, and this is currently unknown. Although it is difficult to infer efficacy half-life from the clinical trial data currently available, almost all experts concur that this is less than 5 years in the case of RTS,S/AS01. Some predictive models used a less credible half-life of 10 years, although sensitivity analyses were conducted to illustrate the effect of shortening vaccine half-life on predicted cost–effectiveness. These analyses suggest that a vaccine half-life of less than 2 to 3 years reduces predicted cost–effectiveness substantially.[7] We need ongoing research to better characterize the function describing the decay of vaccine efficacy and thus accurately parameterize the cost–effectiveness models for this key variable.

The true number of incident malaria infections in a given setting is also an important parameter. Because RTS,S/AS01 acts by reducing incident infections,[13] and since all other outcomes follow from this primary biological effect and its interaction with naturally-acquired immunity, it would be helpful to have access to better data on the true incidence of new infections in different settings.

Finally, the mechanism by which the vaccine achieves a given level of efficacy at the group or population level is potentially important for cost–effectiveness predictions but remains poorly understood. We know that RTS,S/AS01 reduces the frequency of new malaria infections, but we do not know how much protection varies from person to person. For example, if on average the vaccine reduces the frequency of new infections by 50%, in a vaccinated population does protection vary from 10% among some to 90% among others or does the population uniformly experience a 50% reduction in the rate of infection? This variability is referred to as the "heterogeneity of vaccine mode of action". The sensitivity analyses show that such variability is a substantial driver of model cost–effectiveness predictions.[7] To date there are few data regarding this potential heterogeneity.

If the malaria vaccine cost–effectiveness field progresses with the publication of new model-based cost–

effectiveness analyses by multiple groups, WHO may facilitate formal comparative assessments of cost–effectiveness tools, as it did for vaccines against human papillomavirus, rotavirus and pneumococcus.[11]

In conclusion, we have conducted an analysis of model structures, assumptions and key parameters driving uncertainty in the field of malaria vaccine cost–effectiveness models. The key drivers of predicted cost–effectiveness will be price per dose, efficacy, duration of protection and malaria transmission intensity (incidence of new infections per unit of time). Phase III trial data, expected to become available in late 2014, may help address some of the current limitations of model-based cost–effectiveness predictions, as outlined above. Additionally, further advances in modelling are expected as multiple groups continue to refine their models. RTS,S/AS01 will be considered for use in conjunction with key preventive measures that exist already, particularly the use of LLINs.

Modelling in Phase IV trials

Current leading malaria transmission models may have a place in the design of Phase IV trials of malaria vaccines. They may be especially useful in determining the immunization strategies that would best reduce malaria transmission in settings with different transmission characteristics. Until such data from Phase IV trials become available, recommendations for malaria vaccine use, expected in 2015, are likely to be restricted to the age groups for which Phase III trial data are available, i.e. children from 6 weeks to 17 months of age. Whether or not a formal cost–effectiveness tool assessment is performed, we will continue to critically appraise the results of model-based cost–effectiveness evaluations.[11]

Vaccine introduction decision-making

As highlighted earlier, cost–effectiveness is only one criterion among many that influence decision-making in public health. When deciding to implement an intervention, efficiency must always be balanced with other criteria, including implementation capacity, feasibility and impact on poverty and equity.[14] In the case of RTS,S/AS01, WHO will provide an updated cost–effectiveness assessment in 2015, at the time when decision-making by countries will be necessary. The status of the field of malaria vaccine cost–effectiveness does not yet support the use of simple, national-level vaccine impact or cost–effectiveness tools by country programmes. ■

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