

Framework for policy decision on the RTS,S/AS01 malaria vaccine

Rationale and process

1. Background

In January 2016, WHO published its first malaria vaccine position paper, officially adopting the joint recommendation by SAGE and the Malaria Policy Advisory Committee (MPAC). WHO recommends pilot implementation of the RTS,S/AS01 malaria vaccine in distinct settings in sub-Saharan Africa to generate the necessary evidence to enable consideration of a policy recommendation for broader scale use of the vaccine. The Malaria Vaccine Implementation Programme (MVIP) was designed to operationalize the recommendation for sub-national pilot implementation of the malaria vaccine in areas of moderate to high malaria transmission in Africa. Ghana, Kenya and Malawi will be piloting the malaria vaccine. Vaccine introduction will be led by the EPI Programmes in the three pilot countries and will be accompanied by an independent evaluation to address remaining questions to inform public health policy on wider use of the vaccine.

2. Rationale for developing a policy decision framework

In 2015, the Joint Technical Expert Group on Malaria Vaccines (JTEG) recommended to WHO advisory bodies the pilot implementation of the RTS,S/AS01 vaccine to:

- Assess the programmatic feasibility of delivering a four-dose schedule requiring new immunization contacts;
- Evaluate the vaccine's impact on mortality (overall and by gender); and
- Further characterize vaccine safety in the context of a routine immunization programme, with an emphasis on meningitis and cerebral malaria.

The JTEG advised WHO to monitor emerging findings from pilot implementation, and that countrywide introduction may be recommended *“if concerns about safety have been resolved, and if favorable implementation data become available, including high coverage of the fourth dose”*. However, neither JTEG nor SAGE/MPAC specified how the collected data would be used to inform a policy recommendation, e.g. what coverage levels may be considered favorable and whether demonstration of impact on mortality is required for a policy recommendation.

The WHO MVIP team has proposed to develop a framework for policy decision on RTS,S/AS01 that describes how data collected through the MVIP will be used to inform policy. Through the development of the framework:

- SAGE and MPAC members will have an opportunity to discuss and refine ideas on the relative contribution of the collected data (feasibility, safety, impact) to a future policy recommendation
- Clarity will be provided on the expected use of the data in anticipation of potential changes in SAGE/MPAC membership between the time the recommendation for pilots was made (2015) and the programme end (2022)
- Funders, potential funders, and manufacturers can refer to the framework for planning purposes, thereby reducing the risk of gaps in funding or vaccine availability should the vaccine be recommended for broader use

SAGE and MPAC welcomed the development of such a framework when the idea was presented during meetings in October 2017.

3. Outline of key questions to be included in the framework

Examples of the type of questions that will be considered through the framework include :

1. What constitutes ‘favorable implementation data’? In particular, what levels of coverage (overall and for the fourth dose) are sufficiently high to be considered good public health value?
2. Should WHO recommend wider introduction if impact on severe malaria is demonstrated despite only moderate vaccine coverage levels?
3. Is demonstration of impact on mortality through the MVIP required for a positive policy recommendation or would evidence of impact on severe disease suffice?

Supporting information to facilitate discussion of these questions, including estimated timelines for when critical data (on feasibility, safety signals, impact on severe disease, impact on mortality) become available, will be developed over the coming months.

4. Consultations

Published modelling efforts, based on data from the Phase 3 trial, estimated high vaccine impact and cost effectiveness (assuming a vaccine price of US\$5 per dose), at an assumed coverage of 90% for the first 3 doses and 72% for the 4th dose¹. To inform the framework for policy decision, WHO would like to understand whether alternative and potentially lower vaccine coverage is likely to result in impact and cost effectiveness. To assist with this question, WHO, in collaboration with PATH, has engaged two modelling groups (Swiss TPH and Imperial College) to provide estimates of impact on severe malaria and mortality at a range of vaccine coverage levels that could be achieved in the MVIP. The modelling groups will similarly estimate vaccine impact at a range of parasite prevalences that are observed across sub-Saharan Africa.

Both modelling groups participated in the WHO harmonization and comparison project evaluating RTS,S/AS01 vaccine impact and cost-effectiveness estimates using the Phase 3 trial data, mentioned above, the results of which were published in Penny *et al*¹. The process was overseen by the WHO JTEG/IVIR-AC sub-group over a period of four years from 2011-2015.

The IVIR-AC was consulted again in March 2018 to review the methods and assumptions of the modelling work proposed for the framework for policy decision, and to consider whether those methods are appropriate to address the relevant questions on the RTS,S/AS01 vaccine. The recommendations from IVIR-AC were incorporated into modelling plans, which were presented to the MVIP Programme Advisory Group in March 2018. IVIR-AC will be consulted again in September to review the results from the modelling effort. Subsequently, the framework for policy decision will be presented to the Programme Advisory Group, then to SAGE and MPAC in the October 2018 meetings.

¹ Penny MA, Verity R, Bever CA, Sauboin C, Galaktionova K, Flasche S, White MT, Wenger EA, Van de Velde N, Pemberton-Ross P, et al: **Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models.** *Lancet* 2016, **387**:367-375.

5. Modelling plans

To facilitate discussion about vaccine coverage thresholds, Swiss TPH and Imperial College will produce vaccine impact estimates for a range of vaccine coverage levels and propose a list of outcomes and outcome metrics that can be generated by their models. Modelled vaccine impact outcomes may include but are not limited to: severe malaria; hospitalized severe malaria; malaria deaths; and the incremental cost-effectiveness ratio (cost per DALY averted). The proposed list of outcomes and outcome metrics (e.g. events averted per 100,000 vaccinated children, events averted per vaccine dose, events averted per 100,000 population (all ages or 0-5 year olds) were presented to the IVIR-AC for review in March 2018.

6. Timelines for development and review of the framework

Timeline	Activity
October 2017	Proposal to develop a policy decision framework presented to SAGE and MPAC
March 2018	Feedback on the proposed modelling work received from IVIR-AC
March / April 2018	Update on framework development and feedback on proposed modelling work from MVIP Programme Advisory Group, SAGE and MPAC
April – September 2018	MVIP team to further develop key questions to be addressed in the framework, including timelines for when critical data (on feasibility, safety signals, impact on severe disease, impact on mortality) become available. Modelling groups to generate impact estimates for various coverage levels for inclusion in the framework
September 2018	Presentation of modelling estimates to IVIR-AC
October 2018	Presentation of proposed final framework for policy decision to MVIP Programme Advisory Group, SAGE and MPAC