Update on the RTS,S/AS01 Malaria Vaccine Implementation Programme

December 2020

Background

The Malaria Vaccine Implementation Programme (MVIP) was developed to act on the 2016 World Health Organization (WHO) recommendation to pilot the RTS,S/AS01 malaria vaccine in routine immunization programmes (1). The MVIP supports the introduction of the malaria vaccine in selected areas of Ghana, Kenya and Malawi, and evaluation of the programmatic feasibility of delivering a four-dose schedule, the vaccine’s impact on mortality, and its safety in the context of routine use. The primary aim of the Programme is to address outstanding questions related to the public health use of the vaccine in order to enable WHO policy recommendations on the broader use of RTS,S/AS01 in sub-Saharan Africa.

The Programme is jointly coordinated by the Global Malaria Programme (GMP), the Immunization, Vaccines & Biologicals (IVB) Department and the WHO Regional Office for Africa, in close collaboration with other WHO departments and country offices, ministries of health in pilot countries, PATH and other partners. Introduction of the malaria vaccine is country-led. Funding for the MVIP is provided by Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Unitaid.

Information and news about the MVIP are available on the new WHO web platform (2). This includes an overview of key milestones and stakeholder engagements in the development and roll-out of the programme (3).

RTS,S/AS01 vaccine implementation

As of the end of November 2020, more than 1.2 million RTS,S/AS01 vaccine doses have been administered across the three MVIP countries and nearly 500 000 children have received the first dose. Despite the COVID-19 pandemic, the immunization programmes in all three countries have either maintained or improved their RTS,S/AS01 vaccine coverage compared to pre-pandemic levels. Based on administrative data, the coverage of dose 1 was 66% in Ghana (dose 3: 63%), 71% in Kenya (dose 3: 64%) and 85% in Malawi (dose 3: 69%) during the period from January to September 2020. This level of uptake meets or exceeds expectations for a new vaccine with a novel schedule, i.e., targeting children from 5 or 6 months of age for the first dose, and given the ongoing COVID-19 pandemic. Priority actions to maintain and further improve immunization performance have been identified and measures are being taken by the national immunization programmes, supported by partners, to address the issues noted.

Pilot evaluations

To date, COVID-19 has had minimal impact on the pilot evaluation, and surveillance for safety (with special focus on meningitis, cerebral malaria and sex-specific mortality) and impact has continued with
close monitoring of the epidemic and respecting Ethics Review Boards (ERBs) and national guidance. Evaluation partners have instituted measures to reduce the risk of COVID-19 infection among study staff and introduced mitigation measures, including means to collect data retrospectively. WHO continues to monitor the potential impact of COVID-19 on the MVIP and is in close contact with local partners to assess risks and implement mitigation measures.

The MVIP’s advisory bodies continue to meet regularly to provide oversight and guidance to the Programme. Since the last update in May, the Programme Advisory Group (PAG) has met three times: on 20 May 2020, 16 June 2020 and 24–25 September 2020. The Data Safety and Monitoring Board (DSMB) has met twice: on 7–8 July 2020 and 16 September 2020. The MVIP advisory bodies have been pleased with the overall programme progress and improvements seen in both vaccine implementation and the quality of the pilot evaluations. During its most recent meeting, the PAG was reassured that a high proportion of patients admitted to sentinel hospitals and eligible for lumbar punctures (LPs) were now receiving them, and the previous concerns about LP rates have been addressed. Therefore, if there is an excess risk of meningitis similar to that suggested in the Phase 3 trial, it should be possible to detect it in the pilot evaluations. The PAG noted that the rates of meningitis detected in sentinel hospitals are lower than originally expected. As investigations into all suspected meningitis cases are now considered to be adequate, the low rates might reflect the generally lower meningitis incidence in the region as a result of high uptake of vaccines that prevent meningitis. Based on its review of the available data during its most recent meeting in September, the DSMB recommended continuation of the MVIP.

Case–control study to evaluate the added benefit of the fourth dose

In light of the data that have emerged since the original WHO position paper on RTS,S/AS01, the PAG has recommended a case–control study to evaluate the added benefit of the fourth dose and to strengthen the evaluation of safety and effectiveness endpoints. An application for funding from the European & Developing Countries Clinical Trials Partnership (EDCTP) was submitted in August 2020 by a consortium of MVIP partners. While waiting for the EDCTP’s decision, the PAG recommended that data gathering for the case–control study begin, especially for meningitis and cerebral malaria. As cases are already identified through the pilot evaluations, the costs are expected to be relatively modest. WHO has been encouraged by the PAG to explore the option of using savings from existing MVIP funds to initiate this component of the case–control study as soon as possible.

Anticipated timing and process for WHO policy decision

According to the Framework for Policy Decision on RTS,S/AS01 endorsed by the Strategic Advisory Group of Experts on Immunization (SAGE) and Malaria Policy Advisory Committee (MPAC) in 2019, a WHO policy recommendation on the use of the vaccine beyond the pilot countries could be made if and when: i) concerns regarding the safety signals observed in the Phase 3 trial (i.e., related to meningitis, cerebral malaria and sex-specific mortality) have been satisfactorily resolved, and ii) severe malaria and mortality data trends have been assessed as being consistent with a beneficial impact of the vaccine (4). Based on its review of the initial data, the PAG recently confirmed that, if overall event rates for meningitis, severe malaria, cerebral malaria, and mortality persist, there will be sufficient power to conduct the planned safety and impact analyses at 24 months after first vaccination (end of April 2021). This would enable a joint policy review by SAGE and MPAC in Q4 2021. In line with the Framework for Policy Decision, adjustments or refinements to the WHO policy recommendation may subsequently be made based on the MVIP final dataset expected in 2023, including data on the fourth dose.

WHO has looked at ways to ensure the efficiency of the data review and external advisory group consultation processes leading up to the SAGE/MPAC review (see Annex 1). By streamlining the
processes, the time between data availability and policy review could be reduced to approximately six months without compromising the quality of the review. In September 2020, the PAG reviewed the proposal for a streamlined policy pathway and concluded, “The PAG supports the proposed policy pathway through 2021, and agrees with the importance of streamlining processes to avoid sequential reviews among advisory bodies”.

The PAG was established in October 2017 as the MVIP’s highest level advisory body to WHO, tasked with regularly reviewing progress and providing guidance in order to ensure sound approaches to design and implementation. The PAG’s Terms of Reference have been revised to include an expanded role as a joint SAGE and MPAC working group to review the evidence on the balance of benefits and risks of RTS,S/AS01, as it becomes available. The expanded role will call upon PAG members to review RTS,S/AS01 data from multiple sources, including MVIP data available 24 months after first vaccination (April 2021), Phase 3 trial data (MAL-055 and MAL-076 long-term follow-up), and Phase 3b trial data on RTS,S/AS01 and seasonal malaria chemoprevention (SMC) in seasonal settings. The PAG will report to SAGE/MPAC on the balance of benefits and risks, and submit recommendations on the potential wider scale use of the vaccine in sub-Saharan Africa for subsequent review by SAGE and MPAC during a joint session. Approximately two representatives from SAGE, MPAC, the Regional Immunization Technical Advisory Group (RITAG) and possibly the Global Advisory Committee on Vaccine Safety (GACVS) have been or will be appointed to serve on the PAG.

Vaccine supply and access

As highlighted during the Malaria Vaccine Stakeholder Meeting convened by WHO in October 2019, timely access to affordable vaccine supply upon policy recommendation is of crucial importance. An unresolved near-term challenge is the need for financial support to ensure continuous production of RTS,S antigen prior to a policy decision. Without external financial support, manufacturing will stop in early 2021 and only resume following a policy recommendation and funding decision for procurement. According to GSK, restarting production could take up to three years, implying a delay in vaccine availability until possibly 2025. Besides the considerable loss of lives from delaying the expansion of vaccine use in MVIP countries and deployment in non-MVIP countries, not securing continued production could also jeopardize longer term supply by putting the product transfer process at risk and delaying decisions on production capacity scale-up. Acknowledging these negative implications, in December 2019, the Gavi Board approved a Gavi intervention to enable continued production of RTS,S bulk antigen, whereby Gavi identifies a third party(ies) as guarantor and devises a de-risk mechanism to minimize Gavi’s exposure to financial risk. Despite active engagement with the lead third party expressing interest in supporting continued production, a solution has not yet been found. This matter has become critically urgent and is a determining factor for future access to the vaccine.
References


Contact

For more information, please contact:

Mary Hamel, MVIP lead, WHO HQ, Immunization, Vaccines & Biologicals, hamelm@who.int
David Schellenberg, Scientific Adviser, WHO HQ, Global Malaria Programme, schellenbergd@who.int
Annex 1: Oversight, analysis and development of draft policy recommendations for joint review by SAGE and MPAC

**Proposed timelines and processes (see schema next page)**

- Regular updates on MVIP progress to the PAG (quarterly), DSMB (quarterly), SAGE (biannually), MPAC (biannually), RITAG (biannually), IVIR-AC (as needed), AACVS (at inaugural and biannual meetings) and GACVS (biannually).

1. **IVIR-AC** recommendations on methods feed into modelling for impact and cost-effectiveness. The outputs from the recommended models are provided to PAG.

2. **DSMB** considers formal analysis of MVPE safety data (based on 24 months of evaluation).

3. **DSMB** provides a formal presentation of the analysis results to PAG, in the presence of GACVS, AACVS and RITAG members. Documentation should be shared in advance of the PAG meeting so that questions and comments can be formulated among the advisory committees. Note that the DSMB report will focus on safety, potentially without considering the results on impact. During the PAG meeting, sufficient time will be allotted to considering the questions and comments from the advisory committees.

4. **PAG** reviews and summarizes the body of evidence, taking into account the DSMB analysis and inputs received from GACVS, AACVS and RITAG.

5. **PAG** sends its recommendations to SAGE/MPAC for policy review.

6. Joint review meeting is held by **SAGE/MPAC** (special session or VC may be required). The RITAG Chair, GACVS Chair, AACVS Chair and regional office are represented.
   - If recommended for use by SAGE/MPAC, the vaccine will go through the WHO Prequalification expedited process.

**Acronyms:**

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<th>Acronym</th>
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<td>AACVS</td>
<td>African Advisory Committee on Vaccine Safety</td>
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<td>GACVS</td>
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- Safety-related committee

*Of note: Timings of future meetings are tentative / based on usual frequency*

### MVIP specific:
- **Q3 2020**: DSMB
- **Q4 2020**: DSMB, PAG
- **Q1 2021**: DSMB, PAG
- **Q2 2021**: DSMB, PAG
- **Q3 2021**: DSMB
- **Q4 2021**: DSMB

### Global advisory bodies:
- **Q3 2020**: IVIR-AC Update + consultation
- **Q4 2020**: SAGE Update
- **Q1 2021**: IVIR-AC Update
- **Q2 2021**: MPAC Update, GACVS Update
- **Q3 2021**: Formal analysis
- **Q4 2021**: SAGE & MPAC Joint policy review

### Regional advisory bodies:
- **Q3 2020**: AACVS Update
- **Q4 2020**: AACVS Update
- **Q1 2021**: AACVS Update
- **Q2 2021**: AACVS Update
- **Q3 2021**: AACVS Update
- **Q4 2021**: AACVS Update

**IVIR-AC presents safety data analysis to PAG, in presence of GACVS, AACVS & RITAG members**

**Analysis & policy recommendation development**