SUBJECT:	**MALARIA VACCINE PROGRAMME INVESTMENT CASE**
Agenda item:	08
Category:	For Decision

Section A: Executive Summary

Context

Malaria remains one of the deadliest diseases for children under five years old, particularly those living in communities facing deprivation and exclusion. Over 90% of cases and deaths occur in Africa; six Gavi-eligible countries[1] account for 50% of global mortality. In 2015, the first vaccine for malaria, RTS,S/AS01$_{E,}$ was authorised; that year, Gavi, the Global Fund and Unitaid agreed to support pilot vaccine implementation at WHO's request to generate evidence for wider use of the vaccine. The Gavi Board also considered and approved a cost-share mechanism to enable continued production of the antigen to assure access in the event of positive policy and funding decisions. In October 2021, WHO issued a recommendation for wider use based on the evidence from the pilot implementation, and the Gavi Programme and Policy Committee (PPC) considered the case for investment in a malaria vaccine programme.

Question this paper addresses

What is the projected value, impact and strategic considerations of a Gavi investment in a malaria vaccine programme?

Conclusions

As part of a 'toolbox' of malaria control interventions, a malaria vaccine will further reduce child mortality on the African continent but is likely to incur a high cost to Gavi and countries under current assumptions. A successful malaria vaccine programme should support deliberate and intensive coordination between malaria control and immunisation programmes at global and country levels to ensure most impactful deployment of the vaccine alongside other interventions. Finally, there is a need and opportunity for market-shaping efforts to support the development of a healthy malaria vaccine market.

Section B: Background

1.1 Malaria (particularly the *Plasmodium falciparum* parasite species) is one of the leading causes of death globally. In 2019, there were 229 million cases

[1] Nigeria (23%), the Democratic Republic of the Congo (11%), United Republic of Tanzania (5%), Burkina Faso (4%), Mozambique (4%) and Niger (4%); World Malaria Report 2020

of malaria and 409,000 deaths, of which 94% were in Africa and 67% were in children under five years old (274,000 deaths).[2] Since 2000, there has been significant investment and progress in malaria control; however, this has levelled off in recent years, and global financing is plateauing around US$ 3 billion per year[3]. The need for new tools in addition to those currently recommended has been widely recognised as essential to achieve global goals related to reductions in malaria.[4] At the same time, malaria transmission dynamics are complex and heterogeneous; new tools like a malaria vaccine should be considered in the context of this 'toolbox' and deployed alongside other interventions for maximum impact.

1.2 Malaria vaccines have been in development for decades with limited success due to the technological complexity of creating a vaccine against a human parasite. The first successful candidate was the RTS,S/AS01$_E$[5] malaria vaccine ('RTS,S'), from GlaxoSmithKline (GSK), which protects against *P falciparum* malaria and was trialled in sub-Saharan Africa. In the Phase 3 trial, it demonstrated a 39% reduction of clinical malaria and a 29% reduction of severe malaria in 5-17 month old children who received 4 doses and were followed for 4 years after primary vaccination series. In longer-term follow-up (6-7 years), there was no evidence of increased susceptibility ('rebound', or age shift to older children) or of additional contribution to efficacy from vaccination in the additional follow-up period. Despite the modest efficacy, given the high burden of malaria in sub-Saharan Africa, modelling estimates indicated that the vaccine could be highly impactful, averting 1 death per 200 children vaccinated[6].

1.3 In 2015, RTS,S received a positive regulatory assessment from the European Medicines Agency (EMA). Following EMA's positive opinion, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) and Malaria Policy Advisory Group (MPAG) jointly recommended that RTS,S be further evaluated through implementation pilots. The Malaria Vaccine Implementation Programme (MVIP) was initiated to collect evidence on safety, impact, and feasibility.

1.4 In 2016, Gavi, the Global Fund and Unitaid partnered to fund the WHO-coordinated MVIP, at a combined total of US$ 72.4 million. Gavi Board members representing the African region expressed strong support for the pilots, noting the burden of malaria on their countries and the need to understand the potential value of this vaccine in practice. It was also recognised that without Gavi funding the pilots would not proceed, effectively foregoing a promising tool, and vaccine production would be terminated, with potential ramifications beyond RTS,S for similar new vaccines of greatest benefit to low income countries.

---

[2] World Malaria Report 2020
[3] the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) spends approximately US$ 1 billion per year; the United States President's Malaria Initiative (PMI) US$ 745 million; endemic countries US$ 0.9 billion.
[4] Malaria eradication: benefits, future scenarios and feasibility
[5] RTS,S is the antigen, while AS01E is the adjuvant
[6] *Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models* (The Lancet. Vol 387, No. 10016, p367-375, 23 January 2016)

1.5 GSK committed to donate up to ten million doses of RTS,S for the MVIP. Once these doses were produced, in the absence of confirmed future procurement, antigen manufacturing was expected to be discontinued. In December 2019, the Gavi Board agreed that it would be necessary to prevent the interruption of production and requested the Secretariat to develop a cost-share mechanism with a third-party. In March 2021, the Market-Sensitive Decisions Committee approved a mechanism between Gavi, GSK and MedAccess which was subsequently launched and will remain in force until a decision is taken by the Board on a malaria vaccine programme.

1.6 In April 2021, the MPAG agreed that sufficient data had accrued to evaluate safety concerns and effectiveness against severe malaria in an interim analysis. In October, the WHO SAGE and MPAG convened to review the evidence, noted that the vaccine had a good safety and effectiveness profile[7], and recommended that the vaccine should be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission, in the context of comprehensive malaria control. The MVIP also demonstrated high feasibility, with coverage levels similar to those of other routine vaccines. The pilots also showed that the vaccine could extend the reach of malaria control, reaching 60-70% of children not sleeping under insecticide-treated nets, and thus resulting in 90% of children reached by at least one malaria prevention tool. It should be provided in a schedule of 4 doses in children from 5 months of age. In areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks, consideration should be given to seasonal delivery through a 5-dose strategy. Further information on Gavi's historical engagement, the MVIP findings, seasonal delivery trial results, and the SAGE and MPAG evidence review can be found in Doc 08 to the October 2021 meeting of the PPC (Appendix 2).

Section C: Investment in a malaria vaccine programme

1.1 An investment case for malaria vaccines as a complementary tool was developed per the methodology used in the Vaccine Investment Strategy in 2013 and 2018. This included developing a demand forecast based on the WHO recommendation to project volumes and cost[8]. The demand forecast was also an input to external models to estimate impact. The proposed investment would include support for a programme incorporating prequalified vaccines that meet the financial and programmatic parameters of this case (e.g. consistency with WHO recommendation, comparable or

[7] Based on the analyses of 24 months of data, the MVIP Data Safety and Monitoring Board (DSMB) concluded that the safety signals seen in the Phase 3 clinical trial (2009-2014) were not seen in the pilot implementation. The evaluation results showed no evidence of an excess of meningitis, cerebral malaria, or gender-specific mortality comparing age-eligible children living in implementation areas with those in the comparison areas. The vaccine demonstrated effectiveness of RTS,S/AS01 vaccine against severe malaria, with a 30% reduction in severe malaria and a 21% reduction in hospitalisation with malaria parasitemia, both of which were statistically significant.

[8] The demand forecast includes countries with year-round transmission using the 4-dose strategy. For seasonal delivery, countries currently using seasonal malaria chemoprevention served as a proxy for introductions under a 5-dose strategy.

better impact, value for money and alignment with country preferences; products not meeting these parameters could come back to the Board for consideration).

Table 1. Overall impact, costs, and value for money of a malaria vaccine programme, 2021-2035

Cases averted	78 million -140 million (51 million – 180 million) *
Deaths averted	359,000-501,000 (145,000-847,000) *
Procurement and introduction costs to Gavi	US$ 2 billion
Cost to countries (procurement, introduction, recurrent delivery costs)	US$ 2.5 billion
Procurement cost per case averted	US$ 30-53 (23-81) *
Procurement cost per death averted	US$ 8,000-11,000 (5,000-28,000) *
Cost-effectiveness	US$ 97- 112 per DALY averted

* Includes range of averages derived from two impact models; estimates in parentheses include lowest minimum and highest maximum between the two models

1.2 The PPC broadly welcomed the case for investment, noting the importance of including a new tool in the malaria toolbox to advance progress and incentivising the development of a malaria vaccines market. In their deliberations, members highlighted the three following areas for further information: programme costs, collaboration, and market-shaping.

2. Costs of the programme to countries and Gavi

2.1 A malaria vaccine demonstrates impact comparable to the rest of the Gavi portfolio (e.g. pneumococcal conjugate vaccine (PCV), yellow fever, measles, rotavirus). However, with 4-5 doses per child and a higher price per child, the cost would be significantly higher. At the same time, new interventions are typically more costly at the start, and most Gavi vaccines have benefited from market-shaping efforts that improved supply and access and reduced the overall cost over time (e.g. the reduction by over 75% of the weighted average price for pentavalent vaccines[9], the establishment of the PCV Advanced Market Commitment).

2.2 A Gavi-funded malaria vaccine programme is expected to follow similar funding parameters and requirements as other vaccine programmes, per Gavi's policies. This includes funding for vaccine procurement per Gavi's Co-financing policy, introduction grants per Gavi's Health Systems and Immunisation Strengthening Support Framework, and technical assistance and learning activities under the Partners' Engagement Framework. Specific programmatic requirements would also be instituted to ensure successful roll-out and collaboration (see next section).

2.3 Under Gavi's current **Co-financing policy**, low-income countries pay US$ 0.20 per dose. For malaria this could be US$ 0.80-US$ 1.00 per child,

[9] Pentavalent vaccine: Market and Supply Update, 2017, UNICEF Supply Division

which is higher than any other Gavi-funded vaccine programme and would increase over time as GNI pc (Gross National Income per capita) increases and a country's share of the cost increases (e.g. for preparatory transition countries, country share increases 15% per year). The updated Co-financing policy will apply to both current and future new vaccine programmes. Any exceptions that would mitigate the cost to countries would need to be offset by higher cost to Gavi. Following PPC guidance, analysis is planned to assess potential exceptions (see Doc 06).

2.4 Gavi also provides a **vaccine introduction grant (VIG)** for new vaccine programmes, at US$ 0.80/US$ 0.70/US$0.60 per child in the national birth cohort, for low-income countries, preparatory transition countries and acceleration transition countries respectively[10]. Analysis from the MVIP shows that the 'start up' costs in the three pilot countries are in line with the amounts provided through the VIG, including a portion for countries to cost-share as well.

2.5 **Recurrent delivery costs**, which are borne by national immunisation programmes, were also analysed through the MVIP and were estimated at US$ 0.64 per dose on average across the three countries (range: US$ 0.40- US$ 1.10). This estimate is similar to delivery costs for other routine vaccines, such as the incremental cost to deliver one dose of PCV or rotavirus vaccines (US$ 0.84)[11]. These costs are likely to vary for other countries and in light of other ongoing priorities (e.g. other vaccine introductions, COVID-19 roll-out), with further information gleaned from programme implementation. Finally, the MVIP cost estimates assume routine delivery only; operational research could inform estimated costs of seasonal delivery through implementation.

2.6 While the MVIP has provided considerable learnings around implementation and programme feasibility (see Annex A), new programmes come with opportunities to generate further data and lessons to support wider introduction and scale-up in more countries. These learnings include **generation of data** to support countries to identify the optimal mix of interventions (e.g. cost-effectiveness analysis and modelling, timing of vaccine administration and integration with other interventions in settings with highly seasonal transmission) and development of cost-effective community-based delivery strategies to ensure reach to the most vulnerable. It is also anticipated that **strong technical assistance** will be required to support development of integrated plans for both malaria control and immunisation and effectively monitor implementation.

2.7 The PPC requested a more detailed understanding of the projected costs of a malaria vaccine programme. **Table 2** provides more detail on the costs by strategic period. As with other new vaccine programmes, the initial years represent a ramp-up period in which countries begin to introduce the vaccine and scale up over a few years. Thus, a malaria vaccine programme

[10] HPV (Human papillomavirus) vaccine introductions are eligible for US$ 2.40 per targeted girl in the routine cohort or a lump sum of US$ 100,000, whichever is higher, and regardless of the country's transition phase
[11] Immunization Delivery Cost Catalogue

will incur lower costs in the Gavi 5.0 period, and the costs (and volumes) could increase significantly in subsequent periods. In the 6.0 period, a supply constraint is expected and will reduce volumes and costs. In the outer years of Gavi 6.0 and Gavi 7.0, there is high uncertainty; if and when new vaccines enter the market[12], the balance of cost and supply could shift significantly.

Table 2. Estimated costs of a malaria vaccine programme, by strategic period

	Gavi 5.0 (2021-2025)	**Gavi 6.0 (2026-2030)[13]**	**Gavi 7.0 (2031-2035)**
Gavi procurement costs and vaccine introduction grants	US$ 132 million (additional to antigen cost-share mechanism)	US$ 650 million-US$ 900 million	US$ 1.1 billion
Partner's Engagement Framework (technical assistance and learning)	US$ 20 million	-	-
Country procurement costs	US$ 40 million	US$ 600 million-US$ 700 million	US$ 1.2 billion
Country delivery costs (including country share of introduction costs)	US$ 30 million	US$ 200 million	US$ 300 million

3. Collaboration with the malaria community

3.1 The PPC strongly noted that a malaria vaccine be placed in the appropriate context to ensure it is used most impactfully. Roll-out of a vaccine would be a complement to, and not a substitute for, existing malaria control interventions, and will require deliberate global and national level coordination.

3.2 At **global and regional level**, WHO's Global Malaria Programme provides technical and operational guidance for countries to develop the appropriate package of interventions that suits their contexts. For example, the 'High Burden to High Impact' approach recognises that given the heterogeneity of malaria epidemiology, there is no 'one size fits all' for malaria control. Countries are supported to utilise strategic information to design a tailored mix of interventions at subnational level. Funders such as the Global Fund and the President's Malaria Initiative also work with technical and advocacy partners to coordinate their own activities in support of National Malaria Control Programmes (NMCPs).

3.3 A Gavi-funded malaria vaccine programme would be integrated into the **global malaria funding ecosystem**, closely coordinating with existing funders and actors and leveraging Alliance partners' existing activities (e.g. financing, technical support and research funding at WHO, UNICEF, the World Bank, the Bill & Melinda Gates Foundation (BMGF), etc). In

[12] A second malaria vaccine, R21/Matrix-M, is currently in phase 3 clinical trials and several other candidates are in pre-clinical and phase 1 studies, including mRNA candidates
[13] Range includes estimated costs for constrained and unconstrained supply

anticipation of a future malaria vaccine programme, Gavi and other stakeholders have initiated discussion to facilitate alignment of future programmes. This includes funding analysis to generate data around key parameters of country decision-making (e.g., cost-effectiveness, equity and sustainability of the mix of interventions); and exploring joint approaches to programmatic requirements (e.g. inclusion of the vaccine in national malaria control plans, aligned co-financing requirements to support domestic resource mobilisation, metrics to monitor both programmes) and to the application process (e.g. joint review by Gavi's Independent Review Committee and the Global Fund's Technical Review Panel of the respective components of both applications).

3.4 At **national level**, the MVIP has demonstrated the feasibility of integration between NMCPs and national immunisation programmes. In the pilot countries, Ministries of Health established technical working groups to facilitate joint decision-making and implementation. This also included joint communication and community-engagement strategies and integration of key monitoring metrics into both immunisation administrative data reports and malaria control routine reporting (See Annex A).

3.5 Should the Board approve the programme, Gavi and country and global stakeholders would launch **programme design** immediately. Critical next steps would include the development of technical guidance from WHO (expected in early 2022), aligned programme funding guidance and communication from the Alliance and the Global Fund (expected mid-2022), an updated Gavi Co-financing policy in June 2022 and development and launch of applications materials from both Gavi and the Global Fund in the latter half of 2022. Per the PPC's request, the Secretariat and partners would bring an update to the PPC in May 2022 on these activities.

4. Market shaping and supply

4.1 The RTS,S vaccine is the first of its kind, and would establish a starting point for the malaria vaccine market going forward. Given the lack of a "dual market" for childhood malaria vaccines in higher income countries, a funded malaria vaccine programme for endemic countries will be necessary to underpin a sustainable vaccine market. Without this signal of demand to industry, available supply would remain limited (and likely terminate), and the progress of pipeline malaria vaccines would be at significant risk.

4.2 Some key market challenges are already evident, particularly around supply and price, and others might emerge over time. As with any new Gavi-funded vaccine programme, the Secretariat and core market shaping partners will convene to develop a **Market Shaping Roadmap**, with additional partners (including new stakeholders) to be engaged as appropriate. The Roadmap will articulate the long-term vision for a healthy malaria vaccine market, and will launch a strategy, including targets and interventions to achieve this vision across a specific time horizon. Gavi will commence the process immediately following Board approval, beginning with a market shaping stakeholder convening in early December. UNICEF SD (Supply Division),

with close Gavi Secretariat collaboration, has finalised a malaria vaccine procurement strategy in anticipation of the Gavi funding decision and intends to launch the tender for malaria vaccines before year-end, with the goal of ensuring timely supply availability should a Gavi programme be approved. The tender is expected to conclude in Q2 2022. The Roadmap will be finalised by mid to late-2022, with a public summary version shared directly with the PPC.

4.3 The ongoing agreements between Gavi, GSK and MedAccess have enabled GSK to continue to produce the bulk antigen in anticipation of a Gavi funding decision, which will prevent the anticipated long production ramp-up phase that would occur if GSK would have had to restart the dedicated antigen production facility. Further, the accelerated UNICEF SD tender process will help enable timely availability of doses. However, these actions – while avoiding delays to programme launches – will not fully mitigate the mismatch expected between supply and demand in the initial years of the programme. While the Market Shaping Roadmap will primarily identify potential medium- to long-term solutions and aim to maximise supply available in the short term (primarily through the tender process), **a clear and equitable framework for allocating supply** will be needed during the period of supply constraint. WHO is coordinating the development of such a framework in collaboration with key African stakeholders and expects to have it in place in early 2022. Further details can be found in Annex A.

Section C: Actions requested of the Board

The Gavi Alliance Programme and Policy Committee **recommends** to the Gavi Alliance Board that it:

a) **Approve** support for a malaria vaccine programme, beginning in January 2022, noting that the additional financial implications for 2022-2025 are expected to be approximately US$ 155.7 million, which includes approximately US$ 23.2 million for Secretariat and Partners' Engagement Framework costs to adequately support technical assistance and learning activities;

b) **Request** the Secretariat and Alliance partners to closely coordinate with countries, the Global Fund and other malaria stakeholders on (i) programme design, (ii) implementation and (iii) monitoring, including key considerations (such as eligibility, the optimal mix of malaria interventions, allocation of scarce supply and country financing), and provide an update to the PPC in May 2022; and

c) **Note** the need for additional work on market shaping in relation to malaria vaccines to support the development of a secure supply with innovative and cost-effective products.

Annexes

Annex A: WHO background note on operationalisation: supply allocation framework, technical guidance and integration between malaria control and immunisation

Additional information available on BoardEffect

Appendix 1: *Malaria Vaccine Programme Investment Case, November 2021*

Appendix 2: **(in October 2021 PPC meeting book):** Doc 08 *Malaria Vaccine Programme Investment Case*

Appendix 3: **(in October 2021 PPC meeting book):** Annex B to Doc 08 Malaria Vaccine *Supply and Pipeline*

Additional reference materials online:

SAGE Yellow Book; October 2021