SUBJECT:	**UPDATE ON MALARIA VACCINE AND NEXT STEPS**
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Agenda item:	17
Category:	For Guidance
Strategic goal:	SG1 - Underused and new vaccines

Section A: Overview

1. Executive Summary

1.1. The purpose of this report is to update the Board on recent developments regarding the RTS,S malaria vaccine, most importantly the joint SAGE/MPAC recommendations issued on 23 October 23, and to present three areas for potential Gavi involvement in the coming six months. This report builds on the paper presented to the PPC during a special call on 12 November and incorporates feedback received during the discussion.

1.2. The purpose of Gavi involvement in exploratory work in the three areas described in this paper would be to generate additional information to define options for a potential Gavi role in the next steps for the RTS,S vaccine. These options would then be presented to the PPC in May 2016 for Board consideration at its meeting in June. The Board at this stage is asked for guidance on the level of Gavi engagement, if any, between now and May 2016 in each of the three work areas presented in this report.

1.3. A malaria vaccine was among five shortlisted vaccines considered in the 2013 Vaccine Investment Strategy (VIS) process for potential future inclusion in Gavi's portfolio. As final trial data and a WHO recommendation were not yet available at the time, the Board deferred a decision on a malaria vaccine and requested to review the case again once this information would be available.[1]

1.4. In anticipation of these developments, since late 2014, the Secretariat has collaborated with the Global Fund to Fight AIDS, Tuberculosis and Malaria

[1] In its decision on the 2013 VIS (Board meeting of November 2013), the Board *"noted that based on the current assessment there is a reasonable case for GAVI support for a malaria vaccine, and that the Board will consider opening a window if and when the vaccine is licensed, recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts and the Malaria Programme Advisory Committee (expected in 2015) and WHO prequalified, taking into account updated projections of impact, cost and country demand as reviewed by the Programme and Policy Committee (PPC)."*

to explore possible implications of a malaria vaccine rollout for both organisations. A joint Working Group was launched with representatives from relevant teams on each side. Initial principles were formulated to provide clarity on ingoing assumptions and positions. Three sub-teams - focusing on 1) applications and review, 2) implementation, grant management, technical assistance, M&E, and 3) resource mobilisation, advocacy and communications – developed initial thinking on what it could mean to support a health intervention that cuts across the missions of Gavi and the Global Fund, including alignment and possible integration of relevant policies and processes.

1.5. The Phase III clinical trial of the RTS,S malaria vaccine concluded in 2014 and upon review of data on the quality, safety and efficacy of the vaccine, the European Medicines Agency (EMA) provided a positive scientific opinion. According to the EMA assessment the risk-benefit balance of RTS,S is favourable, which opens the possibility for African national regulators to issue a local license. As for any new medicine, the EMA and the manufacturer agreed on a Risk Management Plan (RMP) that describes the known safety concerns and how they can be managed, as well as the additional studies that should be conducted in the post-licensure period, in parallel with first country introductions, in order to provide more information on the vaccine's safety profile. The plan includes a Phase IV safety, impact and effectiveness study to further evaluate all identified risks with RTS,S (febrile convulsions) and potential risks (including meningitis, and cerebral malaria). Meningitis and cerebral malaria were reported more frequently in the vaccinated group in the Phase III clinical trial, but the significance of these findings in relation to vaccination with RTS,S was unclear.

1.6. In a joint meeting on 21 October 2015, two advisory bodies to WHO - the Strategic Advisory Group of Expert on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) – agreed on recommendations regarding the use of RTS,S. They recommended pilot implementations of RTS,S in children of 5-17 months of age before considering wider scale-up. The primary purpose of the pilots is to provide information on the vaccine's protective effect when administered outside of a trial, as well as the feasibility of administering four doses of RTS,S in routine vaccination programmes outside of the normal EPI schedule.

1.7. Further information will also be provided in the pilots with regard to the impact of the vaccine on child mortality and with regard to the meningitis and cerebral malaria signals observed in the trial, complementing the information that will become available through the post-licensure studies identified in the manufacturer's Risk Management Plan.

1.8. SAGE and MPAC recommended pilot implementations in 3-5 distinct settings in sub-Saharan Africa with moderate-to-high transmission of malaria potentially targeting around 1 million children. Pilots may take 3-5 years to complete. However, if favourable data from safety monitoring and implementation feasibility become available earlier, SAGE/MPAC may consider a recommendation for wider use sooner.

1.9. The key next steps for the RTS,S malaria vaccine therefore consist of 1) designing, planning and costing, and executing the pilot implementations according to SAGE/MPAC recommendations; 2) implementing the post-licensure studies according to the manufacturer's Risk Management Plan, including a Phase IV safety, impact and effectiveness study; and 3) ensuring sustainability of vaccine production. The question for the Vaccine Alliance is what role, if any, Gavi should play in support of these next steps for the RTS,S vaccine.

1.10. The Independent Expert Committee (IEC) that supported the 2013 VIS process was reconvened in a teleconference on 29 October 2015. It advised that Gavi should continue to consider malaria a high priority disease area. It noted that pilot implementations of RTS,S are a critical next step to establish whether the vaccine is suitable for broader use and to provide further information about the potential value of this vaccine for Gavi's portfolio. The IEC emphasised that clear leadership is critical in the next steps to ensure that the right questions are asked to inform future decision-making on implementation and that activities go ahead in a timely manner. IEC members agreed that it would be important for Gavi to be involved in the vaccine's assessment after its licensure. Gavi could play a role in market shaping, in contributing to the questions to be addressed in the pilots, and in convening funding partners (see section 5). Several IEC members felt that Gavi should not be the sole funder of pilots. The Chair's summary of the IEC teleconference as well as the background document for this discussion are available in Annex B and C.

1.11. As SAGE/MPAC recommendations had not yet been issued at the time of the Programme and Policy Committee meeting in October, the PPC was convened in a special call on 12th November 2015. During this call, the PPC was presented with four options for potential Gavi engagement in the immediate next phase for RTS,S and asked for guidance on whether this was the right range of options to present to the Board for consideration.[2] The options ranged from no Gavi engagement in the next steps for RTS,S (option 4) at one end of the spectrum, to a multi-pronged engagement with a role in pilot planning, market shaping and exploration of funding options with other potential donors for pilot implementations and for studies in the Risk Management Plan (option 1) at the opposite end of the spectrum.[3] None of the options required the Board to make a funding commitment in December.

1.12. Many PPC members felt that the range of options was reasonable to start a conversation at the Board, however, several members indicated that more information would be required in order for the Board to advise on options -

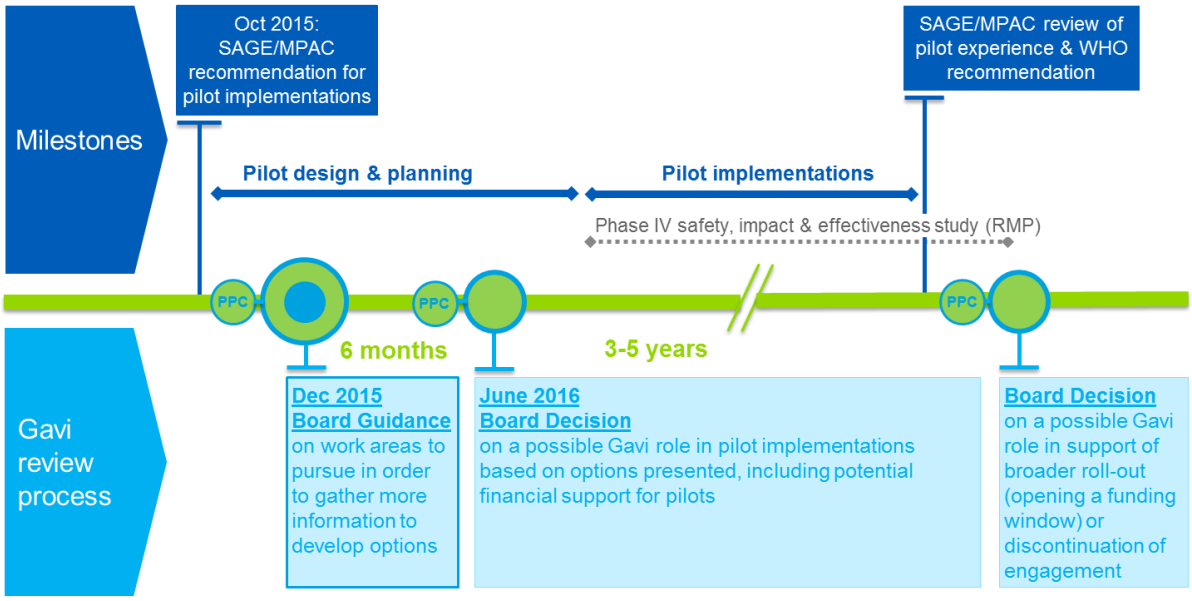
[2] The report to the PPC - Update on malaria vaccine and options for potential Gavi role in next steps, 12 November 2015 - is available on myGavi as Annex A

[3] The options presented to the PPC were: Option 1: Strategic engagement in pilot planning and market shaping, playing a role alongside other funding partners to support pilots and studies in the Risk Management Plan. Option 2: same as option 1 but without support for studies in the Risk Management Plan. Option 3: Strategic engagement in pilot planning without any role in funding or market shaping. Option 4: No engagement in the next steps for RTS,S; monitor further developments and consider Gavi support for a broad rollout if and when the vaccine is recommended for broader use by WHO in the future.

including on the cost of the pilots, the availability of funding from sources other than Gavi, the timing and complementarity of RMP studies and pilots, and risks related to vaccine production and supply that could be addressed through market shaping engagement, including potential opportunities from innovative financing mechanisms. Therefore, this paper does not present the range of options reviewed by the PPC as such, but rather the work areas of most relevance identified during the meeting discussions.

1.13. In order to develop concrete options for Gavi's potential engagement in the pilot implementation phase for decision by the PPC and Board in May/June 2016, exploratory work in three distinct areas could be pursued by Gavi in the coming six months (December 2015 – May 2016). Of note, engagement in exploratory work in any or all of these areas over the next six months would not entail any financial commitment by Gavi at this stage. Also, potential Gavi involvement in pilots would not imply a commitment for support of the vaccine beyond this phase. If, based on the findings from pilots the vaccine were to be recommended for broader use, the Board would be presented with an updated analysis of projected impact, cost and demand to inform a decision on the opening of a country support window. Such a decision is likely to be at least 3 years away. Figure 1 illustrates the anticipated milestones that would trigger a new review by the PPC and Board to decide upon the level of engagement in the subsequent phase.

Figure 1. Milestones and timing of Gavi decision-making regarding RTS,S malaria vaccine support



1.14. The three work areas identified for the coming six months are listed below. Board guidance is sought to what extent, if at all, Gavi should engage in these areas:

(a) **Work area 1: Strategic engagement with stakeholders to help design and plan for pilot implementations under the leadership of WHO**. The aim of Gavi engagement in this area would be to ensure that the pilots are set up to address key areas of uncertainty to allow future decision making by Gavi, if and when WHO recommends broader use of the vaccine.

(b) **Work area 2: Explore requirements for short and long term supply availability at sustainable cost.** The aim of Gavi engagement in this area would be to generate a better understanding of the production economics of RTS,S and related implications for availability and costs of vaccines during pilot implementations and potential broader rollout.

(c) **Work area 3: Assess funding needs and potential sources of funding for pilot implementations.** The aim of Gavi engagement in this area would be to fill the current knowledge gap with regards to the likely costs of the pilots, the availability of funding from different stakeholders and the risks associated with a potential funding deficit. Given feedback from the IEC and PPC, the Secretariat suggests to focus this work area on pilot implementations only and to consider funding for studies in the manufacturer's Risk Management Plan out of scope for Gavi.

2. Recommendations

2.1. The Board is asked **for guidance** on the level of Gavi engagement, if any, over the coming six months (December to May 2016) in each of the three work areas described in this report.

Section B: Content

3. Background on the malaria vaccine assessment in Gavi's Vaccine Investment Strategy, RTS,S clinical trial results and regulatory review

3.1. **Assessment of the malaria vaccine in the 2013 Vaccine Investment Strategy (VIS):** In 2007, the Gavi Board initiated the Vaccine Investment Strategy process as a way to determine which vaccines to include in its portfolio for the next strategic period and which to exclude in light of limited resources and relative public health priorities. A new VIS is developed every five years. It prioritises Gavi's resources and helps to pre-empt first-come-first-serve decisions by the Board on which vaccines to include in Gavi's global portfolio. It creates predictability for governments in Gavi countries and for donors. Early decisions on Gavi's vaccine priorities give an important signal to the R&D community and vaccine manufacturers.

3.2. At the conclusion of the last VIS process in November 2013, the Board deferred a decision on the RTS,S malaria vaccine, which was still in Phase

III clinical trials at the time. It concluded that "based on the current assessment there is a reasonable case for GAVI support for a malaria vaccine, and that the Board will consider opening a window if and when the vaccine is licensed, recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts and the Malaria Programme Advisory Committee (expected in 2015) and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the PPC."

3.3. **Results from clinical trials and regulatory review by the European Medicine's Agency (EMA):** The large-scale Phase III trial to assess the efficacy and safety of the RTS,S malaria vaccine candidate concluded in January 2014 and published final results in April 2015.[4] Eleven research centres in seven African countries[5] conducted the trial which involved more than 15,000 children in two age categories monitored over 3-4 years. A summary of the trial results is provided in Annex D.

3.4. Vaccine efficacy against *clinical* malaria for children vaccinated at the age of 5-17 months was 39% after receiving four doses, and 26% for those who only received three doses, over approximately 4 years of follow-up. Statistically significant vaccine efficacy against *severe* malaria to the end of the study period was 29% for children receiving four doses. There was no efficacy against *severe* malaria in those who only received three doses.

3.5. The European Medicines Agency (EMA), under a process known as article 58[6], reviewed data on the quality, safety and efficacy of the vaccine and has issued what is called "a European scientific opinion". The EMA's opinion was positive indicating a favourable assessment of the risk-benefit balance of RTS,S.

3.6. EMA concluded that the safety profile of this vaccine is acceptable and similar to others apart from a higher risk for febrile convulsions within 7 days after a vaccine dose. An increase in the number of cases of meningitis and cerebral malaria was found in the group receiving the RTS,S malaria vaccine compared to the control group. The significance of these findings in relation to vaccination is unclear. As is common for any new medicine being authorised for use, all identified potential safety issues (febrile convulsions, meningitis, cerebral malaria, auto-immune disorders, anaphylaxis, malaria rebound) will be evaluated further in post-licensure studies as part of the Risk Management Plan (RMP) agreed between EMA and the manufacturer,.

[4] Publication in the Lancet: RTS,S Clinical Trials Partnership, Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial, Lancet 2015; 386:31-45, available: http://dx.doi.org/10.1016/S0140-6736(15)60721-8

[5] Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania

[6] Article 58 of a European Community Regulation establishes a mechanism whereby the EMA may give a Scientific Opinion, in the context of cooperation with WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community

4. SAGE/MPAC recommendations

4.1. Two advisory bodies to WHO - the Strategic Advisory Group of Expert on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) – agreed on a set of recommendations regarding the use of RTS,S during a joint meeting on 21 October 2015. [7] They recommended pilot implementations of RTS,S in children of 5-17 months of age before considering a wider scale-up, in order to provide information on the vaccine's protective effect when administered outside of a trial, as well as the feasibility of administering four doses of RTS,S in routine vaccination programmes outside of the normal EPI schedule.

4.2. Further information will also be provided in the pilots with regard to the impact of the vaccine on child mortality and with regard to meningitis and cerebral malaria, which were reported more frequently in the vaccinated group in the clinical trial. This information will complement the Phase IV safety, impact and effectiveness study agreed between the manufacturer and the EMA that will further evaluate these findings post-licensure.

4.3. SAGE and MPAC recommended pilot implementations in 3-5 distinct settings in sub-Saharan Africa with moderate-to-high transmission of malaria to generate information on the issues described above. They recommend that WHO coordinate these pilot implementations. SAGE/MPAC recommended that the population vaccinated in these pilot implementations be large enough to allow for an evaluation of the impact of RTS,S vaccination on mortality, and that there be ongoing coverage of other proven malaria control prevention, diagnostic and treatment measures. The Secretariat understands that preliminary estimates are that each of the 3-5 pilots would target approximately 200,000 children, which could imply a total target population of around one million with a need for approximately four million vaccine doses in the short term.

4.4. SAGE and MPAC did not recommend the use of the malaria vaccine in the 6-12 weeks age group in view of the limited and short-term efficacy shown in this age group.

4.5. Pilot implementations may take 3-5 years. However, if favourable data from safety monitoring and implementation feasibility becomes available earlier, SAGE/MPAC may consider a recommendation for wider use sooner.

5. Review and advice by the VIS Independent Expert Committee

5.1. The VIS Independent Expert Committee was reconvened on 29 October 2015 to advise on the potential future value of a malaria vaccine for Gavi's portfolio in light of the latest evidence and SAGE/MPAC recommendations and to advise on data and information needed to inform PPC and Board deliberations on a role for Gavi in the immediate next steps for RTS,S. The

[7] All SAGE/MPAC background documents and presentations are available here: http://www.who.int/immunization/sage/meetings/2015/october/en/

background document for this call and the Chair's summary are available in Annex B and C.

5.2. Committee members noted that malaria continues to be a high-burden disease in many parts of the world, in particular in Africa, causing millions of cases and hundreds of thousands of deaths each year and increasing children's vulnerability to other infectious diseases. A malaria vaccine could play a role, alongside other interventions, in addressing this burden. Given Gavi's mission to save children's lives in the poorest countries, the IEC advised that the Vaccine Alliance should continue to consider this disease area a priority. It noted that if a vaccine were to become recommended for wider use and supported by Gavi, coordination with the Global Fund would be critical as well as technical support to NITAGs to help governments decide how best to use the vaccine given competing demands on budgets and particularities of every system.

5.3. The IEC emphasised the need for a robust design of pilot implementations to ensure that all outstanding questions can be effectively addressed during this critical next phase. IEC members called for more clarity on how safety monitoring will be done in the Phase IV study conducted by the manufacturer to better understand what information this study will generate. More information on the vaccine's safety profile is critical for a future recommendation on RTS,S, especially given the availability of alternative control measures.

5.4. IEC members were in agreement that Gavi should play a role in supporting the next steps for this vaccine. Members expressed that clear leadership will be critical to ensure that the right questions are asked to inform future decision-making and to maintain momentum. Members also agreed that Gavi should not be the sole funder but given its experience in resource mobilisation, the IEC felt that Gavi might be well positioned to play a leadership role in convening funders around a shared goal. Finally, one IEC member expressed concern about the risk of the manufacturer pulling out and suggested that Gavi's expertise in market shaping could help in this area.

6. Next steps for the RTS,S malaria vaccine: Likely needs, stakeholder roles and potential gaps

6.1. Next steps for the RTS,S malaria vaccine include:

(a) **Pilot design and implementation**: as per SAGE/MPAC recommendations, to generate additional evidence to inform future considerations of wider use.

(b) **Post-licensure studies**: as per the manufacturer's Risk Management Plan agreed with the EMA to monitor the incidence of side effects following administration of the vaccine to a larger group.

(c) **Vaccine production and supply**: limited volumes of vaccine will be needed in the short term for the implementation of the RMP studies and for pilot implementation, and larger volumes in the medium term, if WHO recommends the vaccine for wider use after pilot implementations.

This section provides an overview of possible needs and known commitments by different stakeholders to contribute to these next steps.

6.2. **Pilot design and implementations**: Effective and efficient design and implementation of pilots will require:

(a) *Coordination* across relevant stakeholders (governments of malaria-endemic countries, technical and funding partners including PATH, the Global Fund, implementers, etc.). SAGE/MPAC strongly recommended that WHO coordinate the pilot implementations.

(b) *Scientific oversight* over the research component of pilots and interpretation of findings will be provided by SAGE/MPAC.

(c) *Alignment on questions* to be addressed in pilots to inform future decision making by WHO (in view of a potential recommendation for larger deployment) and decision-making by Gavi, the Global Fund and other potential funders (on whether to support this vaccine if WHO was to recommend broader use after pilot implementations).

(d) *Planning for implementation,* e.g. information, education and communication (IEC) activities, training of health care workers and EPI staff, integration and coordination with activities funded by the Global Fund and with the malaria control programme more broadly as well as integration with other relevant interventions (vaccine catch-up, nutrition, family planning, etc.), vaccination strategy planning potentially including campaigns, etc.[8] It is unclear at this stage how these elements would be taken forward and which actors may support such activities in coordination with the governments of countries identified for pilot implementations.

(e) *Funding* of the pilots. No funding source has been identified in the short time since the recommendation was announced. Key cost drivers include design choices, implementation activities and the price of the vaccine.

6.3. **Post-licensure studies according to the Risk Management Plan**: The EMA agreed with the manufacturer on a risk management plan (RMP)[9] for RTS,S, which details the measures to be taken in order to ensure that the vaccine is used safely. None of these studies are a condition of the

[8] More information on this can be found in a background paper for the SAGE/MPAC review in which WHO has provided preliminary thoughts on programmatic options for implementation of the RTS,S malaria vaccine. See: http://www.who.int/entity/immunization/sage/meetings/2015/october/3_Programmatic_options_RTSS.pdf?ua=1

[9] EMA's Summary of the risk management plan (RMP) for Mosquirix: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190200.pdf

marketing authorisation. However, as is always the case at this stage, the EMA positive opinion could be withdrawn if the plan is not implemented satisfactorily. Key components of the RMP include: 1) a baseline study to define incidence of diseases specified as potential adverse events prior to vaccine implementation, 2) a phase IV safety, impact and effectiveness study to estimate the incidence of these events in children vaccinated with RTS,S as well as to estimate the vaccine effectiveness on the incidence of any malaria, severe malaria, anaemia, hospitalisation and mortality, and 3) a malaria transmission intensity study to assess changes in parasite prevalence and malaria control measures in the areas where the two previously mentioned studies take place. The objectives, scope and timing of these studies are described in more detail in Annex D.

(a) *Funding*: these studies are currently partially funded by the Bill & Melinda Gates Foundation but gaps remain, and efforts by GSK and PATH to identify third party funders for these late stage studies are continuing but have been unsuccessful to date.

(b) Based on initial feedback from the IEC and PPC financial support from Gavi for these studies is likely to be out of scope.

6.4. **Vaccine production and supply:** RTS,S has been developed through a public-private partnership between GlaxoSmithKline and PATH's Malaria Vaccine Initiative (MVI) with investments from the manufacturer and a grant to MVI from the Bill & Melinda Gates Foundation.

(a) *Availability and affordability of short and long term supply*: as part of its commitment to the fight against malaria, GSK has reiterated its previous public commitment that the RTS,S vaccine would be a 'not-for-profit vaccine'. It would be made available, upon widespread use, at cost plus a 5% mark-up with any profits being reinvested in research and development for next generation malaria vaccines and vaccines against other neglected diseases. GSK has also committed to donating at least 12.5 million doses of RTS,S to PATH. Donation doses could be made available to support the pilot implementations, depending on the conditions under which the vaccine would be provided, including financial support for other aspects of the pilots and the RMP studies.

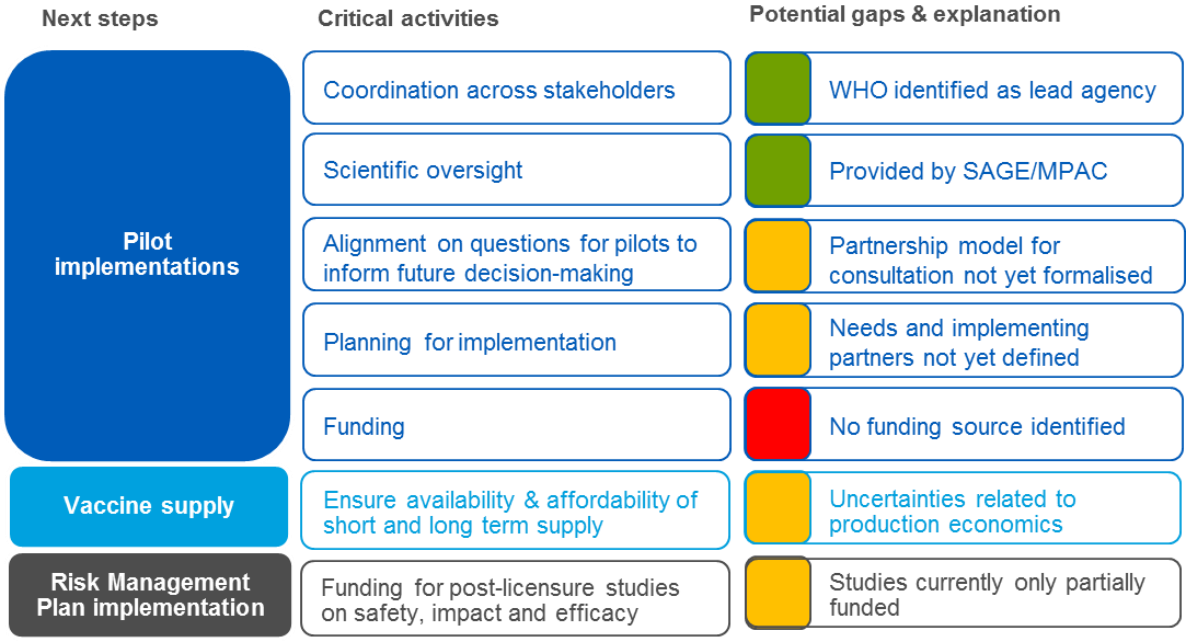
(b) For the longer term, in case WHO recommends wider deployment after pilot implementation, sufficient and reliable supply would have to be secured at a sustainable cost and may require the use of financial instruments. Consideration will be required as to whether and how to address concerns about the ability of and cost implications for the manufacturer to maintain a dedicated production facility in the absence of larger volumes of supply being required in the next 3-5 years. Since there is no dual high- and low-income country market for RTS,S, detailed understanding of demand is critical for sustaining supply in the short and long term. Further discussions on risk-sharing around supply as well as on the feasibility and need for innovative financing instruments will likely be needed.

7. Potential work areas for Gavi to pursue in the next six months (Dec 2015 - May 2016)

7.1. Figure 2 below presents an overview of the next steps for the RTS,S vaccine, the related needs and potential gaps as described in section 6. For some areas a lead agency has already been identified (green), in others there are remaining questions about who would lead or what activities will be done and how (yellow), or there is a critical gap with no lead or source identified (red).

7.2. Any role for Gavi in supporting the next steps for RTS,S should be in line with its mission, strategic interests and competencies. Considerations may also take into account past experience. Section 9 provides additional background on these elements.

Figure 2. Overview of next steps for the RTS,S vaccine and potential gaps



7.3. During a special teleconference on 12th November 2015, the PPC reviewed four options for potential Gavi engagement in the immediate next steps for RTS,S and was asked for guidance on whether this was the right range of options to present to the Board for consideration.[2] The options ranged from no Gavi engagement (option 4), to a multi-pronged engagement to help address gaps identified for pilot implementation, RMP studies and sustainable vaccine supply (option 1).[3] None of the options required a funding decision by the Board in December.

7.4. Most PPC members felt that the range of options was reasonable to start a conversation at the Board, however, several members indicated that more information would be required in order for the Board to advise on options -

including on the cost of the pilots, the availability of funding from sources other than Gavi, the timing and complementarity of RMP studies and pilots, and the risks related to vaccine production and supply that could be addressed through market shaping engagement, including potential opportunities from innovative financing mechanisms. Several PPC members advised against a role for Gavi in funding post-licensure studies mandated by the EMA.

7.5. In order to develop concrete options for Gavi's potential engagement in the pilot implementation phase for decision by PPC and Board in May/June 2016, exploratory work in three distinct areas could be pursued by Gavi in the coming six months (December 2015 – May 2016). The Board is asked for guidance on the level of engagement by the Alliance, if any, in each of these areas.

7.6. **Work area 1: Strategic engagement with stakeholders to help design and plan for pilot implementations under the leadership of WHO**. The aim of Gavi engagement in this area would be to ensure that the pilots are set up to address key areas of uncertainty to allow future decision making by Gavi, if and when WHO recommends broader use of the vaccine.

(a) What this would imply for Gavi over the next 6 months:

- Participate in planning and coordination meetings convened by WHO in order to input on pilot design questions that are relevant for Gavi future decision-making.

(b) What information would likely be available by June 2016?

- Clarity on the partnership model for RTS,S pilot implementations
- Clarity on criteria for selection of 3-5 settings/countries where pilots would be implemented
- Clarity on questions that will be evaluated through the pilots and related design choices, including improved understanding of the complementarity and timing of pilots and the studies undertaken by the manufacturer as part of the Risk Management Plan
- Greater visibility of technical support needs during pilot execution and possible providers of TA at country level
- Clarity on a roadmap and timelines for the implementation of pilots

7.7. **Work area 2: Explore requirements for short and long term supply availability at sustainable cost.** The aim of Gavi engagement in this area would be to generate a better understanding of the production economics of RTS,S and related implications for availability and costs of vaccines during pilot implementations and potential broader rollout.

(a) What this would imply for Gavi over the next six months:

- Engage in conversations with the manufacturer and other stakeholders (including PATH and BMGF) in order to better understand the long term financial view on vaccine production economics and implications for supply availability and costs in the short and long term. This would include assessment of the need for and appropriateness of different innovative financing tools, drawing on past experiences with the Advance Market Commitment (AMC), Advance Purchase Commitments (APCs) and demand guarantees, as suggested by some PPC members.

(b) What information would likely be available by June 2016?

- Clarity on the availability of donated vaccine doses for pilot implementations
- Greater visibility of the manufacturer's plans and conditions for maintaining a RTS,S vaccine production facility that would allow sufficient doses to be available at sustainable costs if and when WHO recommends broader use of the vaccine
- Projected financials for production and studies in the Risk Management Plan to gain an understanding of funding risks
- Insights as to whether specific market shaping tools, drawing on features such as those of an AMC, APC or others would be suitable to address current uncertainties or achieve better outcomes

7.8. **Work area 3: Assess funding needs and potential sources of funding for pilot implementations.** The aim of Gavi engagement in this area would be to fill the current knowledge gap with regards to the likely costs of the pilots, the availability of funding from different stakeholders and the risks associated with a potential funding deficit.

(a) What this would imply for Gavi over the next six months:

- Work with WHO and other partners to estimate the cost of pilot implementations based on emerging information on pilot design, planned implementation activities and availability of donated vaccines.
- Engage in conversations with interested funders (bilateral, multilateral, foundations, private sector) to explore the availability and willingness of these institutions to contribute funding towards the pilot implementations. Given feedback from the IEC and PPC, the Secretariat suggests to focus this work area on pilot implementations only and consider funding for studies in the manufacturer's Risk Management Plan out of scope for Gavi.

(b) What information would likely be available by June 2016?

- Detailed estimates of likely costs related to pilot implementations
- Greater visibility on potential availability of funding from different sources for pilot implementations

- Better understanding of the remaining funding gap and the implications for pilot implementations
- Options for potential Gavi funding contribution to pilots, if any

8. Process for Gavi decision-making

8.1. Given the SAGE/MPAC recommendation for pilot implementations before considering a wider scale up, a Gavi decision on inclusion of the malaria vaccine in its portfolio is several years away (see Figure 1). The critical milestone that would trigger a PPC/Board review and decision regarding the 'opening of a funding window' is the future WHO recommendation on the use of RTS,S. This recommendation will be informed by the evidence generated by the use of RTS,S in the pilots and by data from the post-licensure studies. If the vaccine were to be recommended for broader use, the PPC and Board would be presented with an updated analysis of projected impact, cost and demand to inform a decision about Gavi support. Such a decision is likely to be at least 3 years away.

8.2. The question about Gavi's role in the pilot implementation phase will be addressed in two steps:

(a) First, the Board is asked for guidance in December (this paper) on the level of engagement, if any, over the coming six months in the three described work areas. This engagement will generate the information required to propose concrete options for a Gavi role and their financial implications. Exploratory work over the next six months will not imply a commitment by Gavi for future engagement or support. However, Board guidance not to engage in one or more of these areas would signal lower appetite to consider a future role in these areas.

(b) Second, the PPC will review options for Gavi's role in the pilot implementation phase at its meeting in May 2016 and make a recommendation to the Board for decision in June. Again, any role Gavi may play during the pilot implementations does not constitute a commitment for support of the vaccine beyond this phase.

9. Additional background for consideration

9.1. Any role for Gavi in supporting the next steps for RTS,S should be in line with its mission, strategic interests and competencies, which include vaccine introduction support, market shaping, convening stakeholders and resource mobilisation. Considerations may also take into account Gavi's past experience in funding evidence generation activities:

9.2. Although Gavi has never had a stand-alone research funding program, over the years it has invested in different studies to strengthen the evidence base on vaccine-preventable disease burden, vaccine safety and effectiveness, cost-effectiveness and programmatic feasibility of new vaccines. This includes investments in a 'learning agenda' and post-licensure studies for selected vaccines ahead of inclusion in Gavi's portfolio as well as

investments in studies and demonstration projects related to current Gavi vaccines.

9.3. **Accelerated Development and Introduction Plans (ADIPs):** In 2003, Gavi launched the Accelerated Development and Introduction Plans (ADIPs) to put two new life-saving vaccines that had not yet been recommended by WHO for global use on the agendas in both donor and developing countries: PneumoADIP, led by Johns Hopkins University Bloomberg School of Public Health, which focused on pneumococcal vaccines; and RotaADIP, led by PATH, WHO and US CDC, which concentrated on rotavirus vaccines. The Gavi Board approved an initial envelope of US $30 million for each ADIP for the period 2003 – 2007, which was later extended to 2008. Amongst other things, the ADIPs supported clinical trials of rotavirus vaccines and effectiveness studies to assess the immunogenicity, safety, efficacy and effectiveness of pneumococcal and rotavirus vaccines in developing countries. In 2006, the Gavi Board approved US $15 million for the completion of clinical trials of rotavirus vaccines in Africa and Asia, which had previously only been tested in and recommended for use in North America, Latin-America and Europe. Data from these trials informed the 2009 WHO recommendation for universal introduction of rotavirus vaccines. Pneumococcal conjugate vaccines were recommended for global use by WHO in 2007 and Gavi started to support national introductions in 2010.

9.4. **Learning agenda for rabies and oral cholera vaccines:** Following the 2013 VIS assessment of rabies and cholera vaccines, the Board decided not to add these vaccines to Gavi's portfolio at this time, but to invest in a 'learning agenda'. For cholera vaccines, the aim is to identify, through the design, implementation and evaluation of field-based assessments, cost efficient settings and strategies where vaccination can contribute to control of endemic transmission while optimizing health impact. For rabies vaccines, the aim is to evaluate the feasibility and logistics requirements of increasing access to post-exposure prophylaxis rabies vaccination and to estimate rabies burden and vaccination impact in endemic Gavi countries. The objective of the learning agenda investments of around US $6 million is to address evidence gaps to better inform consideration of potential Gavi support for these vaccines in the 2018 Vaccine Investment Strategy.

9.5. **Impact assessments and other post-licensure research:** The Gavi-funded Hib Initiative (US $37 million) supported WHO estimation of the burden of Hib disease as well as development of a surveillance protocol; it funded surveillance and impact studies in Africa and a vaccine probe study in India (US $9 million) to assess impact of Hib vaccine in a country with unclear disease burden. The work of the Hib Initiative contributed to the revision of the WHO Position Paper on Hib vaccine. In 2009, Gavi launched the Accelerated Vaccine Introduction (AVI) initiative. Part of AVI's funding has been dedicated to "special studies" to support decision making and assess vaccine impact. A research budget of around US $60 million was committed for 2009-2015 to cover assessments of the health and economic impact of pneumococcal conjugate and rotavirus vaccines in early adopter

countries; assessments of the risk of pneumococcal serotype replacement; and assessments of safety related to rotavirus (intussusception)[10] and rubella vaccines. In the past three years, Gavi has spent around US $11 million per year on these special studies.

9.6. **Demonstration programmes for vaccine delivery outside the infant EPI schedule:** Countries without experience in delivering vaccines to school-age girls can apply for Gavi support to conduct small-scale demonstration programmes. The objective of these 2-year programmes is to support countries in developing and gaining experience with effective delivery strategies in order to prepare for a national rollout. Of note, in contrast to the RTS,S malaria vaccine, the HPV vaccine had already been recommended by WHO for inclusion in national immunisation programmes when Gavi support for national roll-out and demonstration programmes started. The HPV demonstration programmes primarily serve the applying Gavi eligible country to assess implementation feasibility and to help prepare for a subsequent national rollout. In contrast, the RTS,S pilot implementations will be primarily aimed at gathering further information to assess general feasibility and public health value of the vaccine in order to guide future recommendations by WHO on broader use of the vaccine.

9.7. **Projected impact under a broad future roll-out scenario (post pilot implementations)**

(a) The Secretariat collaborated with PATH and four modelling groups[11] to update the 2013 VIS estimates of the potential future impact of the malaria vaccine if wider scale-up was recommended by WHO. The updated estimates now take into account final Phase III clinical trial data to inform assumptions of vaccine efficacy after the 4th dose[12], which were not available in 2013. The outputs of this preliminary update can be found in Annex C.

(b) Updated assumptions with regard to vaccine introduction timing, vaccine uptake in-country, wastage, etc. were developed by the Secretariat in consultation with experts. A key change compared with 2013 is the use of sub-national data on malaria parasite prevalence and the assumption that RTS,S would only be introduced in areas where the percentage of 2-10 year olds infected by the parasite ($PfPR_{2-10}$) is above 10%, corresponding to medium to high transmission settings. This reduced the country scope from 34 Gavi-eligible countries in the 2013 VIS to 23, some of which would only introduce at sub-national level

[10] Rotavirus vaccines are associated with an increased (up to 6-fold) risk of intussusception after the first dose of vaccine in some populations. Initially, WHO recommended an age restriction for administration of rotavirus vaccines, given a potentially higher risk of intussusception beyond the recommended age. Ultimately, in 2012, WHO removed the age restriction since the benefits of providing rotavirus vaccine to more children (including those that present beyond the recommended age range) far outweighed the risks of intussusception. WHO recommends active surveillance of intussusception in countries that plan to introduce rotavirus vaccines.

[11] Imperial College London; Swiss Tropical and Public Health Institute; Institute for Disease Modelling and GlaxoSmithKline Vaccines

[12] The models assume 20% drop-out from dose 3 to dose 4

rather than nationwide. Of note, these scenarios assume (country-driven) vaccine use starting from 2018. Given the SAGE/MPAC recommendation for limited initial use in pilot implementations, the projected demand and impact would shift out by 3 to 5 years (everything else held constant) compared to what is presented here.

(c) While the RTS,S trial was not able to show an effect of vaccination on mortality (probably due to the high standard of care and close follow up of all trial participants[13]), mathematical modelling suggests a 10% to 28% reduction of malaria deaths in fully vaccinated children under 5 years living in moderate to high transmission settings. .[14] The updated impact estimates produced by the modelling groups suggest that the RTS,S vaccine could avert up to 100 million malaria cases and approximately 500,000 deaths in Gavi supported countries over the period 2018-2030. This translates into approximately 410 to 570 deaths averted per 100,000 children vaccinated, as compared to a point estimate of 540 deaths averted per 100,000 vaccinated children estimated in 2013. The models predict that an additional 250,000 deaths could be averted in 5 countries not projected to qualify for Gavi support under current policy (over 90% of which is projected impact in Nigeria).

(d) The IEC background paper (Annex C) includes additional details on the projected impact of RTS,S compared to other vaccines in Gavi's portfolio .

10. Next steps

10.1. Gavi will engage in the different work areas over the next six months as per the guidance received from the Board in December. The additional information thereby generated will inform the options for a possible Gavi role in the pilot implementation phase beyond June 2016. These options will be presented to the PPC in May 2016 for recommendation to the Board in June.

Section C: Risk implication and mitigation and Financial implications

11. Financial implications

11.1. This paper is for guidance, hence there are no programmatic financial implications at this point. Engagement over the next six months in the work

[13] A case-control analysis at the KEMRI/CDC RTS,S trial site in Kisumu Kenya identified a 70% reduction in mortality among children who participated in the trial compared to those who live in the demographic surveillance system (DSS) catchment area but did not participate in the trial. These data suggest that considerable reduction in child mortality could be achieved by reducing barriers to health care and providing quality care according to national guidelines. Source: Hamel MJ, Oneko M, Williamson J. A marked reduction in mortality among participants in a clinical trial that removed barriers to care and implemented national case management guidelines. 63rd Annual meeting of the American Society of Tropical Medicine and Hygiene; New Orleans, LA; Nov 2–6, 2014. 631 (abstr).

[14] Background paper on the RTS,S malaria vaccine, prepared by JTEG and WHO Secretariat (September 2015). Available: http://www.who.int/immunization/sage/meetings/2015/october/1_Final_malaria_vaccine_background_paper_v2015_09_30.pdf?ua=1

areas presented in this paper will enable development of concrete, costed options for a possible Gavi role in the subsequent phase, for Board decision in June. Preliminary estimates suggest that the total cost of pilots could range from $50 to $150 million, depending on design choices, implementation activities and vaccine costs. However, more work is needed to understand the detailed cost implications of pilots.

11.2. Financial implications for the Secretariat relating to engagement in the work areas over the coming six months (e.g. a consultant to support this work) would be covered under the current budget submission for 2016.

12. Risk implication and mitigation

Short-term risks:

12.1. The PPC and Board are not asked for a decision on funding RTS,S pilots at this stage. There is a risk that the absence of commitments in the short term by Gavi and/or other funders create uncertainties that may delay planning and implementation of pilots and RMP studies, and ultimately the potential wider availability of a malaria vaccine.

12.2. There is a risk that Gavi engagement in some or all of the three work areas in the coming six months creates expectations about future financial contributions by Gavi. This risk could be mitigated by clearly communicating the timelines and milestones to be achieved in order to trigger a Gavi decision on support for the next phase.

12.3. There is a risk that Gavi engagement in any of the three work areas raises expectations about Gavi's engagement in 'upstream' work on other (non-Gavi) vaccines. This is mitigated by clearly communicating the rationale for Gavi's involvement in this vaccine at this time.

12.4. If Gavi does not engage in the planning of RTS,S pilots, there is a risk that questions to inform Gavi's future decision-making are not taken into consideration for pilot design and remain unanswered. This could be mitigated by pursuing informal discussions with WHO through existing engagement to convey Gavi concerns and interests as relevant to a future investment decision.

Medium-long term risks:

12.5. The medium-long term risks depend on Gavi's role in the pilot implementations, which will be decided upon in June 2016. The exploratory work in the coming six months will provide a better understanding of the likelihood and severity of the risks outlined below.

12.6. There is a risk that absence of financial support by Gavi (to be decided in June) causes delays in the execution of pilots. If no funders for pilot implementations are found, pilots may not be pursued which would prevent future WHO consideration of the vaccine for wider use. This risk may be mitigated by advocating for commitments by other stakeholders to support the next steps for this vaccine.

12.7. In the absence of a cost-sharing strategy among stakeholders and funding partners, there is a risk that the manufacturer is unable to sustain RTS,S production. Such a scenario may have implications for the prospects of future Product Development Partnerships (PDP) for products without a dual market in developing and high/middle income countries.

12.8. There is a risk that funding commitments by donors for the next steps for RTS,S reduce the overall available funding for other malaria interventions. Resources needed for RTS,S must be additional to existing malaria financing and not detract from other key interventions for malaria control or immunisation. To mitigate this risk, if Gavi were to support pilots and if the resource needs could not be covered with existing Gavi resources, resource mobilisation for RTS,S would be undertaken in coordination with the Global Fund so as not to interfere with their 2016 replenishment, likely occurring in summer/early fall 2016.

12.9. Some stakeholders have indicated the risk that Gavi could lose credibility if there was no engagement in pilots of a vaccine solely created for children in the poorest countries, after WHO has called for such pilots to occur.

Section D: Implications

13. Impact on countries

13.1. There are no implications for countries in relation to the work areas presented in this paper. Countries where pilots will be conducted will be identified as part of the WHO-led design process.

14. Impact on Gavi stakeholders

14.1. There are no implications for Gavi stakeholders at this stage.

15. Impact on Secretariat

15.1. Engagement in exploratory work over the coming six months in the areas outlined in this paper may require limited additional human resource capacity. It is expected that this could be covered under the current Budget submission for 2016.

16. Legal, governance and gender implications

16.1. There are no legal, governance and gender implications in relation to the work areas presented in this paper.

17. Consultations

17.1. The VIS Independent Expert Committee will be consulted prior to the May PPC meeting on the options developed for PPC and Board decision.

17.2. Gavi stakeholders would be consulted in the course of Gavi's engagement in pilot planning to help inform Gavi's input into strategic questions.

17.3. Prior to the SAGE/MPAC recommendations, for over a year, Gavi has cooperated closely with the Global Fund to jointly prepare for the possible rollout of RTS,S. Under the current recommendation for pilot implementations, Gavi would continue to coordinate closely with the Global Fund to ensure that: 1) RTS,S implementation in pilot settings is integrated with other malaria activities supported by the Global Fund, and 2) pilots are used to test joint approaches and document lessons for a potential wider roll-out in the future.

Annexes

Annex A: Report to the PPC, Update on malaria vaccine and options for potential Gavi role in next steps, 12 November 2015

Annex B: Chair's summary of the VIS Independent Expert Committee call

Annex C: Background document for the VIS Independent Expert Committee call

Annex D: Summary of Phase III clinical trial results, EMA regulatory review and Risk Management Plan

Report to the Programme and Policy Committee
12 November 2015

SUBJECT:	**UPDATE ON MALARIA VACCINE AND OPTIONS FOR POTENTIAL GAVI ROLE IN NEXT STEPS**
Report of:	Aurélia Nguyen, Director, Policy & Market Shaping
Authored by:	Judith Kallenberg, Eliane Furrer
Agenda item:	02
Category:	For Guidance
Strategic goal:	SG1 - Underused and new vaccines

Section A: Overview

1. Executive Summary

1.1. The purpose of this report is to inform the PPC about the joint SAGE/MPAC recommendations regarding the RTS,S malaria vaccine and to present options for potential Gavi engagement in the next steps. The PPC is asked for guidance on whether this is the right range of options to present to the Board for consideration at its December meeting.

1.2. The malaria vaccine was among five shortlisted vaccines considered in the 2013 Vaccine Investment Strategy (VIS) process for potential future inclusion in Gavi's portfolio. As final trial data and a WHO recommendation were not yet available at the time, the Board deferred a decision on the malaria vaccine and requested to review the case again once this information would be available.[1]

1.3. In anticipation of these developments, since late 2014, the Secretariat has collaborated with the Global Fund to explore possible implications of a malaria vaccine rollout for both organisations. A joint Working Group was launched with representatives from a range of relevant teams on each side. Initial principles were formulated to provide clarity on ingoing assumptions and positions. Three sub-teams - focusing on 1) applications and review, 2) implementation, grant management, technical assistance, M&E, and 3) resource mobilisation, advocacy and communications - developed initial thinking on what it could mean to support a health intervention that cuts

[1] Extract from the Board minutes (November 2013): *The Board noted that based on the current assessment there is a reasonable case for GAVI support for a malaria vaccine, and that the Board will consider opening a window if and when the vaccine is licensed, recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts and the Malaria Programme Advisory Committee (expected in 2015) and WHO prequalified, taking into account updated projections of impact, cost and country demand as reviewed by the Programme and Policy Committee (PPC).*

across the missions of Gavi and the Global Fund, including alignment and possible integration of relevant policies and processes.

1.4. The Phase III clinical trial concluded in 2014 and upon review of data on the quality, safety and efficacy of the vaccine, the European Medicines Agency (EMA) provided a positive scientific opinion. According to the EMA assessment the risk-benefit balance of RTS,S is favourable, which opens the possibility for African national regulators to issue a local license. The EMA agreed with the manufacturer on a Risk Management Plan to be implemented in the post-licensure period. The plan includes a Phase IV study to further evaluate the safety, impact and effectiveness of the vaccine when used outside a trial setting.

1.5. In a joint meeting on 21 October 2015, two advisory bodies to WHO - the Strategic Advisory Group of Expert on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) - agreed on a set of recommendations regarding the use of RTS,S. They recommended pilot implementations of RTS,S in children of 5-17 months of age before considering wider scale-up, in order to provide information on the vaccine's protective effect when administered outside of a trial, as well as the feasibility of administering four doses of RTS,S in routine vaccination programmes.

1.6. Further information will also be provided in the pilots with regard to the impact of the vaccine on child mortality and with regard to meningitis and cerebral malaria, complementing the information that will become available through the post-licensure studies in the Risk Management Plan. Meningitis and cerebral malaria were reported more frequently in the vaccinated group in the clinical trial, but the significance of these findings in relation to vaccination with RTS,S was unclear.

1.7. The Independent Expert Committee (IEC) that supported the 2013 VIS process was reconvened in a teleconference on 29 October to advise on the potential future value of a malaria vaccine for Gavi's portfolio in light of the latest evidence and SAGE/MPAC recommendations and to advise on data and information needed to inform PPC and Board deliberations on a role for Gavi in the immediate next steps. The IEC advised that Gavi should continue to consider malaria a high priority disease area. Pilot implementations of RTS,S are a critical next step to establish whether the vaccine is suitable for broader use and to provide further information about the potential value of this vaccine for Gavi's portfolio. The IEC emphasised that clear leadership is critical in the next steps to ensure that the right questions are asked to inform future decision-making on implementation and that activities go ahead in a timely manner. IEC members agreed that it would be important for Gavi to be involved in the vaccine's assessment after its licensure and thus play a role in the next steps for this vaccine. This role could be in market shaping, in contributing to the questions to be addressed in the pilots, and in convening funding partners (see section 5). The Chair's summary of the IEC teleconference as well as the background document for this discussion are available in Annexes A and B.

1.8. Informed by the IEC discussions, the following options for Gavi engagement have been developed. The PPC is asked for guidance on whether this is the right range of options to present to the Board for consideration at its December meeting.

(a) **Option 1: Strategic engagement in pilot planning and market shaping, playing a role alongside other funding partners to support pilots and studies in the Risk Management Plan:** engage in pilot implementation planning with WHO - and in coordination with the Global Fund - with a view to inform future decision-making in case of a broader future rollout; in parallel, explore funding options with other potential donors with a view to develop an international cost-sharing strategy[2], and to minimise delays in the implementation of pilots and key studies in the Risk Management Plan. If the cost-sharing strategy includes a funding role for Gavi, a detailed investment proposal would be brought to the PPC in May 2016 for recommendation to the Board in June.

(b) **Option 2: Strategic engagement in pilot planning and market shaping, playing a role alongside other funding partners to support pilots**: As above, but without support for studies in the Risk Management Plan.

(c) **Option 3: Strategic engagement in pilot planning**: engage in pilot implementation planning with WHO - and in coordination with the Global Fund - with a view to inform future decision-making in case of a broader rollout. No role in funding or market shaping.

(d) **Option 4: No engagement**: no engagement in the next steps for RTS,S; monitor further developments and consider Gavi support for a broad rollout if and when the vaccine is recommended for broader use by WHO in the future.

2. Recommendations

2.1. The PPC is asked for guidance on whether this is the right range of options for potential Gavi engagement in the next steps for the RTS,S malaria vaccine to present to the Board for consideration at its December meeting.

[2] Resources for implementation of RTS,S must be additional to existing malaria financing and not detract from other key interventions for malaria control or immunisation

Section B: Content

3. Background on VIS, clinical trial results and regulatory review

3.1. **Assessment of the malaria vaccine in the 2013 Vaccine Investment Strategy (VIS):** In 2007, the Gavi Board initiated the Vaccine Investment Strategy process as a way to determine which vaccines to include in its portfolio for its next strategic period and which to exclude in light of limited resources and relative public health priorities. A new VIS is developed every five years. It prioritises Gavi's resources and helps to pre-empt first-come-first-serve decisions by the Board on which vaccines to include in Gavi's global portfolio. It creates predictability for governments in Gavi countries and for donors. Early decisions on Gavi's vaccine priorities give an important signal to the R&D community and vaccine manufacturers.

3.2. At the conclusion of the last VIS process in November 2013, the Board deferred a decision on the RTS,S malaria vaccine, which was still in Phase III clinical trials at the time. It concluded that "based on the current assessment there is a reasonable case for GAVI support for a malaria vaccine, and that the Board will consider opening a window if and when the vaccine is licensed, recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts and the Malaria Programme Advisory Committee (expected in 2015) and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the PPC."

3.3. **Final results from clinical studies and regulatory review by the European Medicine's Agency (EMA):** The large-scale Phase III trial to assess the efficacy and safety of the RTS,S malaria vaccine candidate concluded in January 2014 and published final results in April 2015.[3] Eleven research centres in seven African countries [4] conducted the trial and followed up more than 15,000 participants in two age categories over 3-4 years. A summary of the final trial results is provided in Annex C.

3.4. Vaccine efficacy against clinical malaria for children vaccinated at the age of 5-17 months was 39% after receiving four doses and 26% for those who only received three doses, over an average 46 months (~4 years) of follow-up. Statistically significant vaccine efficacy against severe malaria to the end of the study period was 29% for children receiving four doses. There was no efficacy against severe malaria in those who only received three doses.

3.5. The European Medicines Agency (EMA), under a process known as article 58[5], reviewed data on the quality, safety and efficacy of the vaccine and has

[3] Publication in the Lancet: RTS,S Clinical Trials Partnership, Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial, Lancet 2015; 386:31-45, available: http://dx.doi.org/10.1016/S0140-6736(15)60721-8

[4] Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania

[5] Article 58 of a European Community Regulation establishes a mechanism whereby the EMA may give a Scientific Opinion, in the context of cooperation with WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community

issued what is called "a European scientific opinion". The EMA's opinion was positive indicating a favourable assessment of the risk-benefit balance of RTS,S.

3.6. EMA concluded that the safety profile of this vaccine is acceptable and similar to others apart from a higher risk for febrile convulsions within 7 days after a vaccine dose. An increase in the number of cases of meningitis and cerebral malaria was found in the group receiving the RTS,S malaria vaccine compared to the control group. The significance of these findings in relation to vaccination is unclear. All identified potential safety issues (febrile convulsions, meningitis, cerebral malaria, auto-immune disorders, anaphylaxis, malaria rebound) will be evaluated further in post-licensure studies as part of the risk management plan agreed between EMA and the manufacturer.

4. SAGE/MPAC recommendations

4.1. Two advisory bodies to WHO - the Strategic Advisory Group of Expert on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) – agreed on a set of recommendations regarding the use of RTS,S during a joint meeting on 21 October 2015 [6] . They recommended pilot implementations of RTS,S in children of 5-17 months of age before considering a wider scale-up, in order to provide information on the vaccine's protective effect when administered outside of a trial, as well as the feasibility of administering four doses of RTS,S in routine vaccination programmes.

4.2. Further information will also be provided in the pilots with regard to the impact of the vaccine on child mortality and with regard to meningitis and cerebral malaria, which were reported more frequently in the vaccinated group in the clinical trial. This information will complement the Phase IV study agreed between the manufacturer and the EMA to further evaluate these findings post-licensure.

4.3. SAGE/MPAC recommended pilot implementations in 3-5 distinct settings in sub-Saharan Africa with moderate-to-high transmission of malaria to generate critical information on the issues described above. They strongly recommended that WHO coordinate these pilot implementations. SAGE/MPAC recommended that the population vaccinated in these pilot implementations be large enough to allow for an evaluation of the impact of RTS,S vaccination on mortality, and that there be ongoing coverage of other proven malaria control prevention, diagnostic and treatment measures. The Secretariat understands that each of the 3-5 pilots may target approximately 200,000 children, which could imply a total target population of up to one million with a need for approximately four million vaccine doses in the short term.

[6] All SAGE/MPAC background documents and presentations are available here: http://www.who.int/immunization/sage/meetings/2015/october/en/

4.4. SAGE/MPAC did not recommend the use of the malaria vaccine in the 6-12 weeks age group in view of the limited and short-term efficacy shown in this age group.

4.5. Pilot implementations may take 3-5 years. However, if favourable data from safety monitoring and implementation feasibility becomes available earlier, SAGE/MPAC may consider a recommendation for wider use sooner.

5. Review and advice by the VIS Independent Expert Committee

5.1. The VIS Independent Expert Committee was reconvened on 29 October 2015 to advise on the potential future value of a malaria vaccine for Gavi's portfolio in light of the latest evidence and SAGE/MPAC recommendations and to advise on data and information needed to inform PPC and Board deliberations on a role for Gavi in the immediate next steps for the RTS,S malaria vaccine. The background document for this call and the Chair's summary are available as annexes.

5.2. Using the 2013 VIS decision-making framework, the Secretariat presented an updated (preliminary) assessment of the potential future value of this vaccine, including projected health impact, if wider deployment would follow the pilot implementations. A range of malaria experts were consulted in order to inform the assumptions used for the updated assessment of potential demand and impact under a broad roll-out scenario post pilot implementations.[7] Committee members noted that malaria continues to be a high-burden disease in many parts of the world, in particular in Africa, causing millions of cases and hundreds of thousands of deaths each year and increasing children's vulnerability to other infectious diseases. A malaria vaccine could play a role, alongside other interventions, in addressing this burden. Given Gavi's mission to save children's lives in the poorest countries, the IEC advised that the Vaccine Alliance should continue to consider this disease area a priority. It noted that if a vaccine were to become recommended for wider use and supported by Gavi, coordination with the Global Fund would be critical as well as technical support to NITAGs to help governments decide how best to use the vaccine given competing demands on budgets and particularities of every system

5.3. The IEC emphasised the need for a robust design of pilot implementations to ensure that all outstanding questions can be effectively addressed during this critical next phase.

5.4. IEC members were in agreement that Gavi should play some role in supporting the next steps for this vaccine. Members expressed that clear leadership will be critical to ensure that the right questions are asked to inform future decision-making and to maintain momentum. Members agreed that Gavi should not be the sole funder but given its experience in resource mobilisation, the IEC felt that Gavi might be well positioned to play a

[7] Experts consulted: Vasee Moorthy (WHO), Scott Filler and Susan Nasr (GFATM), Andrew Jones (BMGF), Larry Barat and Misun Choi (USAID/PMI), Fred Binka (University of Health and Allied Sciences, Ghana), James Tibenderana (Uganda Malaria Vaccine Committee), Tracy Goodman, (WHO), Andrea Bosman (WHO), Robert Black (JHU), Dennis di Mascio (GSK), Carla Botting (PATH)

leadership role in convening funders around a shared goal. Finally, one IEC member expressed concern about the risk of the manufacturer pulling out and suggested that Gavi's expertise in market shaping could help in this area.

6. Likely needs, stakeholder roles and potential gaps in the next steps for the RTS,S malaria vaccine

6.1. The currently known next steps for the RTS,S malaria vaccine include:

(a) **Pilot implementations**: as per SAGE/MPAC recommendations, to provide information on implementation feasibility, as well as vaccine impact and safety, in order to inform future considerations of wider use.

(b) **Post-licensure studies**: as per the manufacturer's Risk Management Plan agreed with the EMA.

(c) **Vaccine production**: limited volumes of vaccine will be needed in the short term for the implementation of these studies and pilots, and larger volumes in the medium term, if WHO recommends the vaccine for wider use after pilot implementations.

6.2. To facilitate a discussion about a possible role for Gavi in these next steps, this section provides an overview of possible needs related to these steps, and known commitments by different stakeholders to contribute to these needs. Of note, the information presented here reflects a high-level, preliminary assessment by the Secretariat that is likely to change in the coming weeks and months as more information becomes available through the WHO-led process to prepare for pilot implementations and conversations with the manufacturer and other stakeholders.

6.3. **Pilot implementations**: Effective and efficient design and implementation of pilots will require:

(a) *Coordination* across relevant stakeholders (governments of malaria-endemic countries, technical and funding partners including PATH, the Global Fund, implementers, etc.). SAGE/MPAC strongly recommended that WHO coordinate the pilot implementations.

(b) *Scientific oversight* over the research component of trials and interpretation of findings will be provided by SAGE/MPAC.

(c) *Guidance on questions* to be addressed in pilots to inform future decision making by WHO (in view of a potential recommendation for larger deployment) and by Gavi and the Global Fund (on whether to support this vaccine if WHO was to recommend broader use after pilot implementations).

(d) *Planning for implementation,* e.g. information, education and communication (IEC) activities, training of health care workers and EPI staff, integration and coordination with activities funded by the Global Fund and with the malaria control programme more broadly as well as integration with other relevant interventions (vaccine catch-up, nutrition, family planning, etc.), vaccination strategy planning potentially including campaigns, etc.[8] It is unclear at this stage how these elements would be taken forward and which actors may support such activities in coordination with the governments of countries identified for pilot implementations.

(e) *Funding* for all components of the pilots. No funding source has been identified. Key cost drivers may include design choices and the price of the vaccine.

6.4. **Post-licensure studies according to the Risk Management Plan**: The EMA agreed with the manufacturer on a risk management plan (RMP)[9] for RTS,S, which details the measures to be taken in order to ensure that the vaccine is used safely. None of these studies are a condition of the marketing authorisation. However, as is always the case at this stage, the positive opinion could be withdrawn if the plan is not implemented satisfactorily. Key components of the RMP include: 1) a baseline study to define incidence of diseases specified as potential adverse events prior to vaccine implementation, 2) a phase IV pharmacovigilance, impact and effectiveness study to estimate the incidence of these events in children vaccinated with RTS,S as well as to estimate the vaccine effectiveness on the incidence of any malaria, severe malaria, anaemia, hospitalisation and mortality, and 3) a malaria transmission intensity study to assess changes in parasite prevalence and malaria control measures in the areas where the two previously mentioned studies take place. The objectives, scope and timing of these studies are described in more detail in Annex C.

(a) *Funding*: these studies are currently partially funded by the Bill & Melinda Gates Foundation but gaps remain, and efforts by GSK and PATH to identify third party funders for these late stage studies have been unsuccessful to date.

6.5. **Vaccine supply:** RTS,S has been developed through a public-private partnership between GlaxoSmithKline and PATH's Malaria Vaccine Initiative (MVI) with investments from the manufacturer and a grant to MVI from the Bill & Melinda Gates Foundation.

[8] More information on this can be found in a background paper for the SAGE/MPAC review in which WHO has provided preliminary thoughts on programmatic options for implementation of the RTS,S malaria vaccine. See: http://www.who.int/entity/immunization/sage/meetings/2015/october/3_Programmatic_options_RTSS.pdf?ua=1

[9] EMA risk management Plan EMA's Summary of the risk management plan (RMP) for Mosquirix: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190200.pdf

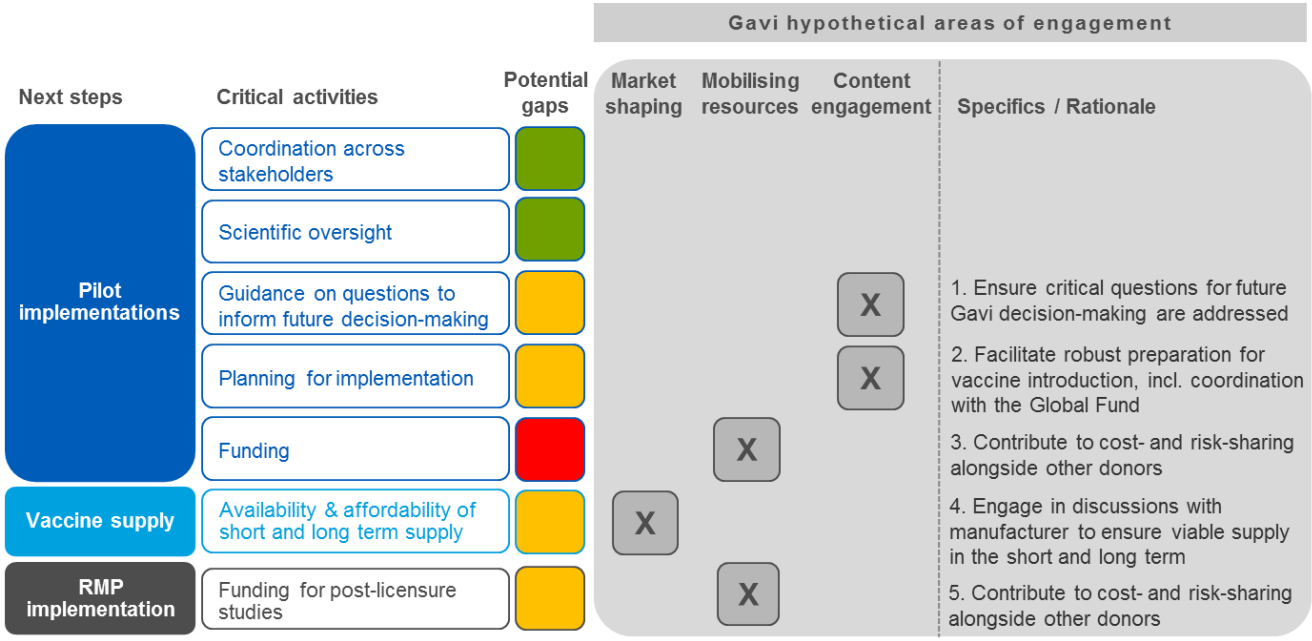
(a) *Availability and affordability of short and long term supply*: as part of its commitment to the fight against malaria, GSK has reiterated its previous commitment that the RTS,S vaccine would be made available, upon widespread use, at cost plus a 5% mark-up with any profits being reinvested in research and development for next generation malaria vaccines and vaccines against other neglected diseases. GSK has also committed to donating at least 12.5 million doses of RTS,S (if approved for use) to PATH. Donation doses could be made available to support pilot implementations, depending on the conditions under which the vaccine would be provided, including financial support for other aspects of the pilots and the RMP studies. For the longer term, in case WHO recommends wider deployment after pilot implementation, sufficient and reliable supply would have to be secured at a sustainable cost. Consideration will be required as to whether and how to address concerns about the ability of and cost implications for the manufacturer to maintain a dedicated production facility in the absence of larger volumes of supply being required in the next 3-5 years Since there is no dual high- and low-income country market for RTS,S, certainty around demand is critical for sustaining supply in the short and long term. Further discussions on risk-sharing around supply will likely be needed.

7. Potential Gavi role in support of the next steps for RTS,S following SAGE/MPAC recommendations

7.1. Figure 1 below presents an overview of the next steps, their related needs and potential gaps. For some areas a lead agency has already been identified (green), in others there are remaining questions about who would lead or what activities will be done and how (yellow), or there is a critical gap with no lead or source identified (red). The figure includes a preliminary assessment of hypothetical areas for Gavi engagement across three dimensions: market shaping, resource mobilisation and content engagement as identified by the IEC.

7.2. Any role for Gavi in supporting the next steps for RTS,S should be in line with its mission, strategic interests and competencies. Considerations may also take into account past experience. Section 8 provides additional background on these elements.

Figure 1. Overview of next steps, gaps and potential areas for Gavi engagement



7.3. The PPC is asked for guidance on whether this is the right range of options for potential Gavi engagement in the next steps for the RTS,S malaria vaccine to present to the Board for consideration at its December meeting (numbers refer to the hypothetical roles outlined under 'Specifics/Rationale' in Figure 1):

(a) **Option 1: Strategic engagement in pilot planning and market shaping, play a role alongside other funding partners to support pilots and studies in the Risk Management Plan (1-5):** engage in pilot implementation planning with WHO - and in coordination with the Global Fund - with a view to inform future decision-making in case of a broader future rollout; in parallel, explore funding options with other potential donors with a view to develop an international cost-sharing strategy[10], and to minimise delays in the implementation of pilots and key studies in the Risk Management Plan. If the cost-sharing strategy includes a funding role for Gavi, a detailed investment proposal would be brought to the PPC in May 2016 for recommendation to the Board in June.

(b) **Option 2: Strategic engagement in pilot planning and market shaping, playing a role alongside other funding partners to support pilots (1-4)**: As above, but without support for studies in the Risk Management Plan.

(c) **Option 3: Strategic engagement in pilot planning (1)**: engage in pilot implementation planning with WHO - and in coordination with the Global Fund - with a view to inform future decision-making in case of a future broader rollout. No role in funding or market shaping

[10] Resources for implementation of RTS,S must be additional to existing malaria financing and not detract from other key interventions for malaria control or immunisation

(d) **Option 4: No engagement**: no engagement in the next steps for RTS,S; monitor further developments and consider Gavi support for a broad rollout if and when the vaccine is recommended for broader use by WHO in the future.

7.4. Table 1 summarises potential opportunities and risks associated with each option. The likelihood of these risks materialising is unknown at this stage.

Table 1: Opportunities and risks relating to options for discussion

	Opportunities	Potential risks
Option 1	- Holistic engagement - Mitigates risks of delayed implementation of next steps - Helps ensure that pilots address critical questions to inform future Gavi decision-making - Provides more visibility of future supply situation in case of a broader Gavi supported roll out	- Mission creep for potential funding contribution to RMP studies - Crowding out of other funders more able to play in this space
Option 2	- Mitigates risks of delayed implementation of next steps - Helps ensure that pilots address critical questions to inform future Gavi decision-making - Provides more visibility of future supply situation in case of a broader Gavi supported roll out	- Crowding out of other funders more able to play in this space
Option 3	- Helps ensure that pilots address critical questions to inform future Gavi decision-making. - Immediate clarity for stakeholders on Gavi's position regarding funding and market shaping	- Uncertainty about funding of pilots and RMP studies delays planning and implementation
Option 4	- Immediate clarity for stakeholders on Gavi's position	- Critical questions to inform Gavi's future decision-making remain unanswered - Delay in execution or abandoning of pilot implementations if no other funders found

8. Additional background for consideration of options

8.1. Any role for Gavi in supporting the next steps for RTS,S should be in line with its mission, strategic interests and competencies in supporting vaccine introductions, market shaping, convening stakeholders and resource mobilisation. Considerations may also take into account Gavi's past experience in funding evidence generation activities:

8.2. Although Gavi has never had a stand-alone research funding program, over the years it has invested in different studies to strengthen the evidence base on vaccine-preventable disease burden, vaccine safety and effectiveness, cost-effectiveness and programmatic feasibility of new vaccines. This includes investments in a 'learning agenda' and post-licensure studies for selected vaccines ahead of inclusion in Gavi's portfolio as well as investments in studies and demonstration projects related to current Gavi vaccines.

(a) **Accelerated Development and Introduction Plans (ADIPs):** In 2003, Gavi launched the Accelerated Development and Introduction Plans (ADIPs) to put two new life-saving vaccines that had not yet been recommended by WHO for global use on the agendas in both donor and developing countries: PneumoADIP, led by Johns Hopkins University Bloomberg School of Public Health, which focused on pneumococcal vaccines; and RotaADIP, led by PATH, WHO and US CDC, which concentrated on rotavirus vaccines. The Gavi Board approved an initial envelope of US $30 million for each ADIP for the period 2003 – 2007, which was later extended to 2008. Amongst other things, the ADIPs supported clinical trials of rotavirus vaccines and effectiveness studies to assess the immunogenicity, safety, efficacy and effectiveness of pneumococcal and rotavirus vaccines in developing countries. In 2006, the Gavi Board approved US $15 million for the completion of clinical trials of rotavirus vaccines in Africa and Asia, which had previously only been tested in and recommended for use in North America, Latin-America and Europe. Data from these trials informed the 2009 WHO recommendation for universal introduction of rotavirus vaccines. Pneumococcal conjugate vaccines were recommended for global use by WHO in 2007 and Gavi started to support national introductions in 2010.

(b) **Learning agenda for rabies and oral cholera vaccines:** Following the 2013 VIS assessment of rabies and cholera vaccines, the Board decided not to add these vaccines to Gavi's portfolio at this time, but to invest in a 'learning agenda'. The aim is to identify, through the design, implementation and evaluation of field-based assessments, cost efficient settings and strategies where cholera vaccination can contribute to control endemic transmission while optimizing health impact. For rabies, the aim is to evaluate the feasibility and logistics requirements of increasing access to post-exposure prophylaxis rabies vaccination and to estimate rabies burden and vaccination impact in endemic Gavi countries. The objective of the learning agenda

investments of around US $6 million is to address evidence gaps to better inform consideration of potential Gavi support for these vaccines in the 2018 Vaccine Investment Strategy.

(c) **Impact assessments and other post-licensure research:** The Gavi-funded Hib Initiative (US$ 37 million) supported WHO estimation of the burden of Hib disease as well as development of a surveillance protocol; it funded surveillance and impact studies in Africa and a vaccine probe study in India (US$ 9 million) to assess impact of Hib vaccine in a country with unclear disease burden. The work of the Hib Initiative contributed to the revision of the WHO Position Paper on Hib vaccine. In 2009, Gavi launched the Accelerated Vaccine Introduction (AVI) initiative. Part of AVI's funding has been dedicated to "special studies" to support decision making and assess vaccine impact. A research budget of around US$ 60 million was committed for 2009-2015 to cover assessments of the health and economic impact of pneumococcal conjugate and rotavirus vaccines in early adopter countries; assessments of the risk of pneumococcal serotype replacement; and assessments of safety related to rotavirus (intussusception)[11] and rubella vaccines. In the past three years, Gavi has spent around US$ 11 million per year on these special studies.

(d) **Demonstration programmes for vaccine delivery outside the infant EPI schedule:** Countries without experience in delivering vaccines to school-age girls can apply for Gavi support to conduct small-scale demonstration programmes. The objective of these 2-year programmes is to support countries in developing and gaining experience with effective delivery strategies in order to prepare for a national rollout. Of note, in contrast to the RTS,S malaria vaccine, the HPV vaccine had already been recommended by WHO for inclusion in national immunisation programmes when Gavi support for national roll-out and demonstration programmes started. The HPV demonstration programmes primarily serve the applying Gavi eligible country to assess implementation feasibility and to help prepare for a subsequent national rollout. In contrast, the RTS,S pilot implementations will be primarily aimed at gathering further information to assess general feasibility and public health value of the vaccine in order to guide future recommendations by WHO on broader use of the vaccine.

[11] Rotavirus vaccines are associated with an increased (up to 6-fold) risk of intussusception after the first dose of vaccine in some populations. Initially, WHO recommended an age restriction for administration of rotavirus vaccines, given a potentially higher risk of intussusception beyond the recommended age. Ultimately, in 2012, WHO removed the age restriction since the benefits of providing rotavirus vaccine to more children (including those that present beyond the recommended age range) far outweighed the risks of intussusception. WHO recommends active surveillance of intussusception in countries that plan to introduce rotavirus vaccines.

8.3. **Projected impact under a broad future roll-out scenario (post pilot implementations)**

(a) The Secretariat updated the 2013 VIS forecast of potential demand and received modelled impact estimates from four groups[12] in order to assess the potential future value of the malaria vaccine if a WHO recommendation for wider deployment would follow the pilot implementations. The updated impact estimates now take into account final Phase III clinical trial data to inform assumptions of vaccine efficacy after the 4th dose[13], which were not available in 2013. The outputs of this preliminary update were presented to the IEC and can be found in Annex B.

(b) Updated assumptions with regard to vaccine introduction timing, vaccine uptake in-country, wastage, etc. were developed by the Secretariat in consultation with experts. A key change compared with 2013 is the use of sub-national data on malaria parasite prevalence and the assumption that RTS,S would only be introduced in areas where the percentage of 2-10 year olds infected by the parasite (PfPR2-10) is above 10%, corresponding to medium to high transmission settings. This reduced the country scope from 34 Gavi-eligible countries in the 2013 VIS to 23, some of which would only introduce at sub-national level rather than nationwide. Of note, these scenarios assume (country-driven) vaccine use starting from 2018. Given the SAGE/MPAC recommendation for limited initial use in pilot implementations, the projected demand and impact would shift out by 3 to 5 years (everything else held constant) compared to what is presented here.

(c) The updated impact estimates suggest that the RTS,S vaccine could avert up to 100 million malaria cases and approximately half a million deaths in Gavi supported countries over the period 2018-2030. This translates into approximately 100,000 cases and, depending on the model used, between 410 to 570 deaths averted per 100,000 children vaccinated, as compared to a point estimate of 540 deaths averted per 100,000 vaccinated children estimated in 2013. The models predict that an additional 250,000 deaths could be averted in 5 countries not projected to qualify for Gavi support under current policy (over 90% of which is projected impact in Nigeria).

(d) The IEC background paper (Annex B) presents projected RTS,S mortality impact per vaccinated children compared to other vaccines in Gavi's portfolio (p.20).

9. Next steps

9.1. Following PPC guidance on whether this is the right range of options for consideration by the Board, at its December meeting the Board will provide

[12] Imperial College London; Swiss Tropical and Public Health Institute; Institute for Disease Modelling and GlaxoSmithKline Vaccines
[13] The models assume 20% drop-out from dose 3 to dose 4

guidance on a preferred option for Gavi engagement in the immediate next steps. Should the Board-preferred option include a potential funding role for Gavi, a detailed investment proposal would be brought to the PPC in May 2016 for recommendation to the Board in June.

Section C: Risk implication and mitigation and Financial implications

10. Financial implications

10.1. This paper is for guidance, hence there are no programmatic financial implications at this point. If Gavi was to play a role in the next steps for the RTS,S malaria vaccine, a subsequent paper will be brought to the PPC and Board in May and June 2016 that may include investment options for decision. The cost of pilot implementations has not yet been established as it will depend on design choices and cost of the vaccine. Preliminary estimates suggest that the total cost of pilots could be in the order of $75 - $150 million.

10.2. Financial implications for the Secretariat relating to engagement in the pilot planning process over the coming months (e.g. a consultant to support this work) would be covered under the current budget submission for 2016.

11. Risk implication and mitigation

Short-term risks:

11.1. The PPC and Board are not asked for a decision on funding RTS,S malaria pilots at this stage. There is a risk that the absence of commitments in the short term by Gavi and/or other funders may delay planning and implementation of pilots and RMP studies, and ultimately the potential wider availability of a malaria vaccine.

11.2. There is a risk that Gavi engagement in pilot planning raises expectations about future financial contributions by Gavi. This risk could be mitigated by clearly communicating the limited nature of Gavi's engagement in the coming months and the governance steps required to decide on a funding role later.

11.3. There is a risk that Gavi engagement in pilot planning for RTS,S raises expectations about Gavi's engagement in 'upstream' work on other (non-Gavi) vaccines. This is mitigated by clearly communicating the rationale for Gavi's involvement in this vaccine at this time.

11.4. If Gavi does not engage in the planning of RTS,S pilots, there is a risk that questions to inform Gavi's future decision-making are not taken into consideration for pilot design and remain unanswered. This could be mitigated by pursuing informal discussions with WHO through existing engagement to convey Gavi concerns and interests as relevant to a future investment decision.

Medium-long term risks:

11.5. There is a risk that absence of Gavi financial engagement causes delays in the execution of pilots. If no funders for pilot implementations are found, pilots may not be pursued which would prevent future WHO consideration of the vaccine for wider use. This risk may be mitigated by advocating for commitments by other stakeholders to support the next steps for this vaccine.

11.6. In the absence of a cost-sharing strategy among stakeholders and funding partners, there is a risk that the manufacturer is unable to sustain RTS,S production. Such a scenario may have implications for the prospects of future Product Development Partnerships (PDP) for products without a dual market in developing and high/middle income countries.

11.1. There is a risk that funding commitments by donors for the next steps for RTS,S reduce the overall available funding for other malaria interventions. Resources needed for RTS,S must be additional to existing malaria financing and not detract from other key interventions for malaria control or immunisation. To mitigate this risk, if the Board wanted to explore a funding role for Gavi, and if its contribution could not be covered with existing resources, resource mobilisation for RTS,S would be undertaken in coordination with the Global Fund so as to not interfere with their 2016 replenishment, likely occurring in summer/early fall 2016.

Section D: Implications

12. Impact on countries

12.1. There are no implications for countries in relation to the engagement options presented in this paper. Countries where pilots will be conducted will likely be identified as part of the WHO-led design process.

13. Impact on Gavi stakeholders

13.1. There are no implications for Gavi stakeholders at this stage.

14. Impact on Secretariat

14.1. Engagement in pilot planning, market shaping and exploring funding options with other donors may require limited additional human resource capacity. It is expected that this could be covered under the current Budget submission for 2016.

15. Legal, governance and gender implications

15.1. There are no legal, governance and gender implications in relation to the options presented in this paper.

16. Consultations (under options 1, 2 and 3)

16.1. The Independent Expert Committee would be consulted prior to the May PPC meeting on the options developed for PPC and Board decision.

16.2. Gavi stakeholders would be consulted in the course of Gavi's engagement in pilot planning to help inform Gavi's input into strategic questions.

16.3. Prior to the SAGE/MPAC recommendations, for over a year, Gavi has cooperated closely with the Global Fund to jointly prepare for the possible rollout of RTS,S. Under the current scenario of pilot implementations, Gavi would continue to coordinate closely with the Global Fund to ensure that: 1) RTS,S implementation in pilot settings is integrated with other malaria activities supported by the Global Fund, and 2) pilots are used to test joint approaches and document lessons for a potential wider roll-out in the future.

Annexes

Annex A: Chair's summary of the VIS Independent Expert Committee call

Annex B: Background document for the VIS Independent Expert Committee call

Annex C: Summary of Phase III clinical trial results, EMA regulatory review and Risk Management Plan

Annex B: Chair's summary of the VIS Independent Expert Committee call

GAVI
Independent Expert Committee - Vaccine Investment Strategy
Malaria Vaccine

29 Oct 2015, Teleconference

Members attending: Dr. Robert Black (Chair), Prof. Fred Binka, Dr. Melinda Moree, Prof. Helen Rees
Apologies: Dr. Kalipso Chalkidou (shared comments), Dr. Anne Schuchat, Dr. Jane Achan, Dr. Maharaj K Bhan

Documentation: A background document was provided in advance of the teleconference to inform the discussion

Chair's Summary

The purpose of the call was for the Independent Expert Committee (IEC) to advise on the potential future value of a malaria vaccine for Gavi's portfolio in light of the latest evidence and SAGE/MPAC recommendations and to advise on data and information needed to inform Board deliberations on a role for Gavi in the immediate next steps for the RTS,S malaria vaccine.

The Committee was presented with an update of the final RTS,S trial results, the scientific opinion provided by the European Medicine Agency (EMA) and the recent policy recommendations by the Strategic Advisory Group of Experts on Immunisation (SAGE) and the Malaria Policy Advisory Committee (MPAC). Using the 2013 VIS decision-making framework, the Gavi Secretariat presented an updated (preliminary) assessment of the potential future value of this vaccine, including projected health impact in Gavi countries if wider deployment would follow the pilot implementations. The estimates were shown for a baseline scenario in which (sub-national) areas with parasite prevalence levels above 10% would introduce the vaccine across Gavi countries over a seven-year period. Three additional, lower-uptake scenarios with a threshold imposed for coverage of bed net use were also shown. Next steps for RTS,S (pilot implementations; Phase IV post-licensure studies as part of a risk management plan agreed with the EMA; and sustainable supply of vaccines) were presented, as well as areas of potentially relevant Gavi expertise (vaccine introduction support; market shaping; convening power; resource mobilisation) and relevant past experience (Accelerated Development and Introduction Plans (ADIPs); learning agenda for rabies and oral cholera vaccines; vaccine impact assessments and other post-licensure research; demonstration programmes for vaccine delivery outside the infant EPI schedule).

The IEC was asked to advise on the following questions:

1. Using the 2013 VIS decision framework, what is the potential future value of a malaria vaccine for Gavi's portfolio in light of the additional evidence from the completed trials, the European Medicines Agency's assessment and SAGE/MPAC recommendations? Should this be a priority disease/vaccine area for Gavi?

2. What data and information about the next steps for RTS,S (following EMA approval and SAGE/MPAC recommendations) will help inform the Gavi Board's deliberations?

3. What aspects of Gavi's expertise and experience to date are most relevant to the next steps for RTS,S to be taken into account by the Board in considering a role for Gavi?

4. What risks and benefits of engagement or no engagement by Gavi should be considered? To what extent are other organisations better placed or complimentary to support the next steps for this vaccine?

Committee members noted that malaria continues to be a high-burden disease in many parts of the world, in particular in Africa, causing millions of cases and hundreds of thousands of deaths each year and increasing children's vulnerability to other infectious diseases. A malaria vaccine could play a role, alongside other interventions, in addressing this burden. Given Gavi's mission to save children's lives in the poorest countries, the IEC recommended that the Vaccine Alliance continues to consider this disease area a priority. If a vaccine were to become recommended for wider use and supported by Gavi, coordination with the Global Fund would be critical as well as technical support to NITAGs to help governments decide how best to use the vaccine given competing demands on budgets and particularities of every system.

With regards to the RTS,S malaria vaccine, the IEC emphasised that in light of the vaccine's partial efficacy, implementation would be highly context-specific. Projections of impact need to be contextualised and take into account other prevention and control measures, underlying epidemiology and whether the country is pursuing a control or elimination strategy. The IEC suggested that value for money estimates be explored for all four demand scenarios to help assess how this may vary with changing bed net coverage levels. The potential value of the vaccine in the context of increasing threats to existing prevention and treatment tools - parasite resistance to artemisinin and mosquito resistance to insecticides - should also be considered.

The IEC took note of the SAGE/MPAC assessment of the RTS,S malaria vaccine, which highlighted remaining questions related to the vaccine's safety, its impact on mortality when used outside a trial setting, and the feasibility of administering four doses in routine vaccination programmes. The recommended pilot implementations are expected to provide more insight into these questions and, as a consequence, will help to assess whether the RTS,S malaria vaccine would be a valuable addition to Gavi's portfolio.

In terms of the immediate next steps for this vaccine, the IEC emphasised the need for a robust design of pilot implementations to ensure that all outstanding questions can be effectively addressed during this critical next phase. It will be important to find the right balance in design choices to assess feasibility and mortality impact in real-life settings while also being able to detect potential safety signals. IEC members called for more clarity on how safety monitoring will be done in the Phase IV study conducted by the manufacturer to better understand what information this study will generate and what additional information should be pursued in the pilots. Collectively these Phase IV studies and pilots must document the level of adverse events because this will be a paramount consideration for a preventive intervention, especially when there are alternative preventive measures. The pilots should also contribute to a better understanding of how RTS,S introduction may strengthen or weaken the performance of the national immunisation programme, including its effect on coverage of other vaccines. Achieving

high coverage with this vaccine could be challenging in countries that are still struggling to ensure high coverage and low drop-out rates in the existing routine EPI schedule (e.g. measles second dose). The pilots should also be used to collect data on the cost to countries and integration of the vaccine with other malaria control interventions.

IEC members were in agreement that Gavi should play some role in supporting the next steps for this vaccine. There were diverging views, however, on the nature of this engagement, especially on Gavi's role as a potential funder of pilots. Some members suggested that such an investment would be different from what Gavi has historically been funding, through the ADIPs for example, since the outstanding safety questions imply that this vaccine is more 'upstream' in its lifecycle; other donors who typically support these types of research questions might be better placed to cover the cost. Members agreed, however, that it would be important for Gavi to be involved in the vaccine's assessment after its licensure. One member noted that there was some prior expectation that these studies be supported by different parties than those involved in the trials and that Gavi would bring neutrality into this important last phase. Members expressed that clear leadership is critical in the next steps to ensure that the right questions are asked to inform future decision-making on implementation and that activities go ahead in a timely manner. Given its experience in resource mobilisation, Gavi might also be well positioned to play a leadership role in convening funders around a shared goal. IEC members agreed, however, that Gavi should not be the sole funder. There would be a risk of crowding out other potential funding if Gavi was to commit to covering costs. One member highlighted that one of the biggest risks now was to lose momentum and to miss the opportunity of making a malaria vaccine available as soon as safety, feasibility and impact were found to be favourable. Having been at the forefront of preparing for new vaccine implementation, Gavi could inform the questions to be addressed in the pilots and keep the momentum high to ensure implementation of pilots without unnecessary delays. Finally, one IEC member expressed concern about the risk of the manufacturer pulling out and suggested that Gavi's expertise in market shaping could help in this area.

Annex C: Background document for the VIS Independent Expert Committee call

Independent Expert Committee – Vaccine Investment Strategy

Malaria Vaccine
Background paper for teleconference 29 October 2015

1. Background

1.1. The Vaccine Investment Strategy

Gavi's mission is to increase access to new and under-utilised vaccines in lower-income countries. The Alliance offers support for selected vaccines for use in national immunisation programmes in response to applications from eligible country governments. Gavi currently offers support for 11 vaccines: human papillomavirus, inactivated polio, Japanese encephalitis, measles, meningitis A, meningitis ACYW (emergency stockpile), oral cholera, DTP/Hepatitis B/Hib as pentavalent, pneumococcal conjugate, rubella, rotavirus, and yellow fever.

In 2007, the Gavi Board initiated the Vaccine Investment Strategy (VIS) process as a way to determine which vaccines to include in its portfolio and which to exclude in light of limited resources and relative public health priorities. A new VIS is developed every five years. It prioritises Gavi's resources and helps to pre-empt first-come-first-serve decisions by the Board on which vaccines to include in Gavi's global portfolio. It creates predictability for governments in Gavi countries and for donors. Early decisions on Gavi's vaccine priorities give an important signal to the R&D community and vaccine manufacturers.

The VIS[1] entails, for each vaccine under consideration, a detailed assessment of the available evidence, modelling exercises to project future demand, impact, and cost under hypothetical Gavi-supported implementation scenarios, assessments of Gavi's market shaping potential for that vaccine, the programmatic feasibility of rolling it out in Gavi countries, and other factors of relevance for Gavi decision-making. Alliance partners, including Gavi country representatives, and a wide range of experts are consulted in the process. Outcomes from analyses and consultations are assessed against pre-agreed evaluation criteria to allow for vaccine-by-vaccine comparisons.

Gavi countries have diverse needs. The VIS aims to identify vaccine investments with significant benefits for a significant number of countries (e.g. HPV vaccines), or with special benefits for a particular region (Japanese Encephalitis) or vaccine areas for which Gavi support fills a unique gap (e.g. support for the oral cholera vaccine stockpile for emergency use to help fight outbreaks and to ensure supply security). It considers local implementation feasibility as well as global factors such as Gavi's ability to influence supply security, affordability and innovation. A key consideration for decisions to expand the portfolio is whether Gavi has a comparative advantage in helping to overcome barriers to accessing a vaccine of public health importance.

[1] More information on the VIS can be found here: http://www.gavi.org/about/strategy/vaccine-investment-strategy/

1.2. Vaccine investments prioritised through the VIS

The 2008 VIS identified human papilloma virus (HPV), rubella, Japanese encephalitis (JE) and typhoid conjugate vaccines as priorities. The first three vaccines have since been added to Gavi's portfolio, and countries can apply for support for these vaccines. No typhoid conjugate vaccines have been prequalified to date.

The 2013 VIS resulted in the following investment decisions:

1. Support yellow fever mass preventive campaigns in countries at risk (projected cost $109 million through 2020)
2. Finance the global stockpile of oral cholera vaccine to increase access to cholera vaccine in outbreak situations and increase global supply (capped at $115 million for 2014-2018)
3. Invest in a 'learning agenda' for rabies and cholera vaccines (estimated at $6 million):
    a) Studies to address evidence gaps around rabies vaccine (disease burden, risk factors, access to post-exposure vaccination, unmet demand, etc.).
    b) An assessment of strategies for cost-effective use of oral cholera vaccine in endemic settings

Vaccines considered but not prioritised in the VIS 2013 included dengue, DTP (booster), EV71 (Hand, Foot, Mouth disease), hepatitis A, hepatitis B (birth dose), hepatitis E, seasonal influenza (maternal), measles (for children between 5-15Y), meningococcal disease (serogroups CYW), and mumps vaccines.

1.3. Board discussion on malaria vaccine in 2013

The Board deferred a decision on the RTS,S malaria vaccine, which was still in phase III clinical trials at the time. It concluded, in November 2013, that "based on the current assessment there is a reasonable case for GAVI support for a malaria vaccine, and that the Board will consider opening a window if and when the vaccine is licensed, recommended for use by the joint meeting of the WHO Strategic Advisory Group of Experts and the Malaria Programme Advisory Committee (expected in 2015) and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the PPC."

A demand forecast developed in 2013 assumed that 34 Gavi-eligible countries in Africa would introduce the vaccine over the course of ten years starting with a first introduction in 2017. Based on the available data at the time and assumptions on the vaccine's efficacy, RTS,S had the highest potential among vaccines considered to increase Gavi's impact on public health, as measured by morbidity and mortality reduction. The cost of Gavi support for uptake of this vaccine in eligible countries during 2016-2020 was estimated at US $287 million.Preliminary updated estimates of demand, impact and cost under a broad roll-out scenario are presented in section 4.1.

2. SAGE/MPAC recommendations on malaria vaccine

Two advisory bodies to WHO - the Strategic Advisory Group of Expert on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) – agreed on a set of recommendations regarding the use of RTS,S during a joint meeting on 21 October 2015[2]. They recommended pilot implementations of RTS,S in children of 5-17 months of age before considering a wider scale-up, in order to provide information on the vaccine's protective effect

[2] All SAGE/MPAC background documents and presentations are available here: http://www.who.int/immunization/sage/meetings/2015/october/en/

when administered outside of a trial, as well as the feasibility of administering four doses of RTS,S in routine vaccination programmes.

Further information will also be provided in the pilots with regard tothe impact of the vaccine on child mortality and with regard to meningitis and cerebral malaria, which were reported more frequently in the vaccinated group in the clinical trial. This information will complement the Phase IV study agreed with the EMA to further evaluate these findings post-licensure. Overall, the EMA concluded that the safety profile of RTS,S is acceptable.

SAGE/MPAC recommended pilot implementations in 3-5 distinct settings in sub-Saharan Africa with moderate-to-high transmission of malaria to generate critical information on the issues described above. They strongly recommended that WHO coordinate these pilot implementations. SAGE/MPAC recommended that the population vaccinated in these pilot implementations be large enough to allow for an evaluation of the impact of RTS,S vaccination on mortality, and that there be ongoing coverage of other proven malaria control prevention, diagnostic and treatment measures. SAGE/MPAC did not recommend the use of the malaria vaccine in the 6-12 weeks age group in view of the limited and short-term efficacy shown in this age group.

Pilot implementations may take 3-5 years. However, if favorable data from safety monitoring and implementation feasibility becomes available earlier, SAGE/MPAC may consider a recommendation for wide use sooner.

3. Gavi policy process for malaria vaccine

WHO recommendations on RTS,S will be presented to the Board's Programme and Policy Committee (PPC) during a special call on 12 November 2015. The PPC will be asked to provide guidance on options for potential Gavi engagement to be presented to the Board. At its meeting on 2-3 December 2015, the Gavi Board will review these options and provide directions as to the desired level of Gavi engagement in the next steps towards implementing the forthcoming WHO recommendations. Unless the Board opts for no further Gavi engagement at this stage, more refined investment options would likely be presented to the Board for decision in June 2016.

It will be important for the Board to consider whether the assessment of the potential long-term value of this malaria vaccine has changed since the 2013 Vaccine Investment Strategy in light of the final trial results and SAGE/MPAC recommendations.

4. Assessing the evidence for a decision on a potential Gavi role

As SAGE/MPAC does not recommend a broad roll-out of RTS,S at this stage, it is clear that Gavi will not consider opening a funding window in the near term. Pilot implementations are the next step with this vaccine, and the Gavi Board upon advice from the PPC needs to decide what role, if any, it wants to play in this. To help inform Secretariat recommendations for guidance by Gavi's PPC and Board, the VIS Independent Expert Committee (IEC) is asked for their views on the following questions:

QUESTIONS:

1. Using the 2013 VIS decision framework, what is the potential future value of a malaria vaccine for Gavi's portfolio in light of the additional evidence from the completed trials, the European Medicines Agency's assessment and SAGE/MPAC recommendations? Should this be a priority disease/vaccine area for Gavi?

2. What data and information about the next steps for RTS,S (following EMA approval and SAGE/MPAC recommendations) will help inform the Gavi Board's deliberations?

3. What aspects of Gavi's expertise and experience to date are most relevant to the next steps for RTS,S to be taken into account by the Board in considering a role for Gavi?

4. What risks and benefits of engagement or no engagement by Gavi should be considered? To what extent are other organisations better placed or complimentary to support the next steps for this vaccine?

4.1. Preliminary update to VIS assessment

The VIS assessed (candidate) vaccines against a range of criteria, vetted with Gavi stakeholders through consultations, and grouped in four categories: health impact (quantitative), additional impact considerations (qualitative), implementation feasibility, cost and value for money. Scores on individual indicators were given a red/yellow/green colour code based on predefined thresholds to show how the vaccine performed against each criterion relative to other vaccines considered. The complete 'scorecard' formed a framework to help facilitate prioritisation.

Figure 1 shows the scorecard that was developed for RTS,S in 2013[3], including a preliminary 2015 update. The following sections provide a preliminary assessment of changes, if any, to this assessment in light of the final results from the phase 3 trial and other information that has since become available.

[3] 2013 data reflect final estimates presented to the PPC in October 2013 and are based on the 'Expanded EPI with booster' scenario (i.e. 5-17 months old receiving 4 doses)

Figure 1. VIS Scorecard for RTS,S malaria vaccine, 2013 assessment and 2015 updates

Category	VIS Criteria	Indicator showing 2013 estimates*	2013 Evaluation	2015 update (draft)
health impact	Impact on mortality	Future deaths averted, 2015-2030: 960,000 (STPH) – 1.3M (Imperial)		440,000 (STPH) 520,000 (Imperial)
		Future deaths averted per 100K vaccinated: 470 (STPH) – 640 (Imperial)		410 (STPH) – 570 (Imperial)
	Impact on morbidity	Future cases averted, 2015-2030: 195M (STPH) – 292M (Imperial)		86M (STPH) – 99M (Imperial)
		Future cases averted per 100K vaccinated: 95,000 (STPH) – 145,000 (Imperial)		81K (STPH) – 109K (Imperial)
		No long term sequelae		Unchanged
Additional impact considera-tions	Epidemic potential	High epidemic potential		Remains high
	Global or regional public health priority	No global or regional elimination or eradication goals (Millennium Development Goal 6c to 'reverse incidence' of malaria)		New GTS for malaria 2016-2030 adopted
	Herd immunity	Herd immunity threshold 80-99%		Unchanged
	Availability of alternative interventions	Alternative disease control interventions exist (e.g. LLINs, IRS, SMC, artemisinin-based combination treatment)		Unchanged
	Socio-economic inequity	Highly disproportionate risk for the rural poor. Vectors prosper in rural settings		Unchanged
	Gender inequity	Pregnant women are at higher risk and have more severe outcomes		Unchanged
	Disease of regional importance	Burden concentrated in Africa		Unchanged
Implementa-tion feasibility	Capacity and supplier base	Planned capacity to meet <100% of GAVI demand; 1 manufacturer		Remains a risk
	GAVI market shaping potential	GAVI has good potential to influence the market		Unchanged
	Ease of supply chain integration	Packed volume / dose expected between 3 and 12 cm3 (9.9 cm3)		9.7 cm3 - Unchanged
	Ease of programmatic integration	Partially outside EPI schedule: up to 3 additional visits required		Unchanged
	Vaccine efficacy and safety	55.8% against clinical malaria in 5-17 months old receiving 4 doses; no evidence of causal link to serious adverse events		39% against clinical malaria, Safety to be further assessed in Ph IV study and monitored in pilot
Cost and value for money	Vaccine procurement cost[1]	Total procurement cost to GAVI and countries, 2015 – 2030: ~$3.4B		~$2B
	In-country operational cost	Likely higher incremental costs compared to infant vaccines due to additional visits		Unchanged
	Procurement cost per death averted	Procurement cost / death averted: $2,600 (Imperial) - $3,500 (STPH)		$3600 (Imperial) -$4300 (STPH)

*2013 data reflect final estimates presented to the PPC in October 2013 and are based on the 'Expanded EPI with booster' scenario (i.e. 5-17 months old receiving 4 doses); 1. Procurement cost includes vaccine, syringe, safety box, and freight

Health impact

Four modelling groups have been working together with WHO since 2010 in an effort to compare and harmonise assumptions, including on demography, access to effective malaria treatment, and a range of transmission intensities.[4] Figure 1 reflects updated health impact estimates from Swiss Tropical and Public Health Institute and Imperial College London whose earlier estimates of RTS,S impact were used in the 2013 VIS. The updated estimates now include Phase 3 clinical trial data to inform assumptions of vaccine efficacy after the 4th dose, which were not available in 2013.

Updated assumptions with regard to vaccine introduction timing, vaccine uptake in-country, wastage, etc. were developed by the Secretariat in consultation with experts.[5] A key change compared with 2013 is the use of sub-national data on malaria parasite prevalence and the assumption that RTS,S would only be introduced in areas of $PfPR_{2-10}$ above 10%.[6] This reduced the country scope from 34 Gavi-eligible countries in the 2013 VIS to 23, some of which would only introduce at sub-national level rather than nationwide. Of note, these scenarios assume (country-driven) vaccine use starting from 2018. Given the SAGE/MPAC recommendation for much more limited initial use in pilot implementations, projected impact would shift out by 3-5 years compared to what is presented here.

The impact data presented in this paper further assume that Gavi's current Eligibility & Transition policy would be applied to the malaria vaccine. As highlighted in the 2013 analysis, an important source of uncertainty influencing demand (and therefore impact and cost) is whether or not Nigeria - representing around one quarter of total demand - would be eligible to apply for Gavi support by the time the vaccine becomes available. While included in the 2013 VIS estimates, based on updated projections and assuming strict application of the eligibility rules Nigeria would not introduce (with Gavi support) in this updated scenario.

An overview of impact projections for all countries forecasted to introduce, including those without Gavi support, is presented in Annex 3. Annex 3 also reflects several alternative demand scenarios with lower vaccine uptake if a threshold of insecticide treated bed net (ITN) use coverage were to be imposed. Under these scenarios, countries would only introduce the vaccine if they have achieved more than 60%, 70%, or 80% bednet coverage.

The updated point estimates of the mortality impact of RTS,S through 2030 indicate the potential to avert 86 - 99 million malaria cases and 440,000 - 520,000 deaths in the 23 countries forecasted to introduce with Gavi support. This translates into 81,000-109,000 cases and 410-570 deaths averted per 100,000 children vaccinated, which is of similar order of magnitude as estimated in 2013. An additional 220,000-250,000 deaths would be averted in the 5 countries that would not qualify for Gavi support under current policy (28% of which is projected impact in Nigeria). The models assume 20% drop-out from dose 3 to dose 4.

The estimated impact on mortality reduction is not derived from trial data, but based on mathematical modelling – it is among the objectives of the pilot implementations to assess the impact of the vaccine on child mortality in a real-life setting.

[4] These are Imperial College London; Swiss Tropical and Public Health Institute; Institute for Disease Modelling and GlaxoSmithKline Vaccines

[5] Experts consulted: Vasee Moorthy (WHO), Scott Filler and Susan Nasr (GFATM), Andrew Jones (BMGF), Larry Barat and Misun Choi (USAID/PMI), Fred Binka (University of Health and Allied Sciences, Ghana), James Tibenderana(Uganda Malaria Vaccine Committee), Tracy Goodman, (WHO), Andrea Bosman (WHO), Robert Black (JHU), Dennis di Mascio (GSK), Carla Botting (PATH)

[6] Recently updated MAP (Malaria Atlas Project, the most extensive effort to map malaria parasite prevalence in Africa) estimates show that in many African regions the transmission of Plasmodium falciparum malaria has been reduced to $PfPR_{2-10}$ levels below 10% in recent years. In these low transmission settings, RTS,S is predicted to be less cost effective than in settings with more intense malaria transmission.

Additional impact considerations

Additional considerations of the impact of a malaria vaccine have not changed fundamentally since the assessment in 2013:

- **Epidemic potential**: malaria continues to have high epidemic potential.
- **Global public health priority**[7]: there is no internationally agreed elimination objective for Africa although an increasing number of countries have a national elimination goal. In its advice to SAGE/MPAC, the Joint Technical Expert Group (JTEG) recommends that there is an evaluation of the malaria vaccine in the context of elimination. A high priority area for such an evaluation is South-East Asia in areas of artemisinin resistance. The 2000 Millennium Development Goals (MDG 6 target C) called for halting and beginning to reverse the incidence of malaria by 2015. According to a September 2015 WHO/UNICEF report, this target has been met "convincingly", with a 37% decline in global malaria incidence since 2000. The World Health Assembly in May 2015 adopted WHO's Global Technical Strategy for Malaria 2016-2030, which targets to reduce malaria incidence and mortality rates globally by at least 90% by 2030, to eliminate the disease in at least 35 new countries, and to prevent its re-establishment in countries that were free of malaria in 2015.
- **Herd effects**[8]: given the relatively modest efficacy of RTS,S and the fact that only a small proportion of the infectious reservoir (i.e. young children) are considered for vaccination it is not expected that there will be any substantial transmission reduction effect from paediatric vaccination with RTS,S.[9]
- **Alternative malaria control interventions**[10] continue to exist and there is a continued need to further scale up the use of these interventions. Modelling of the comparative cost-effectiveness of different control measures (by the Imperial College, publication forthcoming) showed that use of long-lasting insecticidal bed nets (LLINs) is the most cost-efficient intervention to reduce burden in children under 5 years of age across all transmission settings in Africa. In areas where seasonal malaria chemoprevention (SMC) is recommended, this is predicted to be the second most cost-effective intervention. In settings in which low incidence could not be achieved with the first two interventions alone, the RTS,S vaccine could be considered once the use of the other two interventions had been optimised. In absolute terms, RTS,S is predicted to be cost-effective (at price assumptions of US $2, $5 and $10 per dose) in areas with current parasite prevalence of 10% or higher. Emerging drug- and insecticide-resistance continues to pose a major threat to malaria control[11] and variation in these factors could alter the conclusions about comparative cost-effectiveness.
- **Inequity**: malaria continues to disproportionally affect poor people in rural areas, including pregnant women for whom the disease has more severe outcomes as compared with men (of note: RTS,S is not indicated for pregnant women).
- **Regional importance**: the burden of malaria is still largely concentrated in Africa. According to the latest WHO estimates there were 438,000 malaria deaths in 2015, with over 90% of these in sub-Saharan Africa, mostly in children younger than 5 years.

[7] Yellow score = No global or regional UN resolutions
[8] Yellow score (2013) = Herd immunity threshold above 70% or unknown
[9] JTEG report on the RTS,S/AS01 malaria vaccine, September 2015
[10] Yellow score (2013) = Yes, alternative interventions for effective disease control (prevention and treatment) are used and can be scaled up
[11] World Malaria Report 2014

Implementation feasibility

Phase III trial data provided certainty on vaccine efficacy and SAGE/MPAC subsequently recommended vaccination of the older age group only. The trial data also raised questions about safety signals. Other aspects of implementation feasibility are mostly unchanged.

- **Supply capacity**: the sole source situation is expected to remain for some time. While other malaria vaccine candidates are in the pipeline, they are at least 5-10 years behind RTS,S in their clinical development and testing. Vaccine needs for the immediate next steps (pilot implementations) will be limited. However, if WHO recommends broader use in several years, supply capacity of the manufacturer may be insufficient to meet demand.
- **Market shaping**: demand for this vaccine would come almost exclusively from (current) Gavi countries. For this reason, the 2013 VIS evaluated Gavi's market shaping potential as high. If WHO recommends broader use in the future, and if the Gavi Board subsequently decides to open a funding window, it is unclear at this stage if Gavi would finance and/or procure vaccines for malaria-endemic countries that would no longer be eligible by then (e.g. Ghana and Nigeria).
- **Ease of supply chain integration**: the cold chain volume per dose of RTS,S is now confirmed as 9.7 cubic centimeter, which is within the range of other vaccines such as pneumococcal conjugate and DTP-HepB-Hib vaccines.
- **Ease of programmatic integration**: as anticipated in 2013, the recommended schedule for RTS,S requires four doses including several outside the current EPI schedule. In its recommendation, WHO highlights this as a key challenge and primary reason for conducting pilots before broader use. It also highlights that successful expansion of the schedule with additional visits presents an opportunity to strengthen the immunisation programme and primary health care delivery more broadly.
- **Vaccine efficacy**: Phase III data from the RTS,S trial were published in April 2015[12]. Vaccine efficacy against clinical malaria for children vaccinated at the age of 5-17 months was 39% after receiving four doses and 26% for those who only received three doses, over an average 46 months (~4 years) of follow-up. Statistically significant vaccine efficacy against *severe* malaria to the end of the study period was 29% for children receiving four doses. There was no efficacy against severe malaria in those who missed the fourth dose. The assumptions in 2013 (56% efficacy waning over three years for a four dose regimen in the older age group) were based on the then available data set related to 12-months of follow up after the 3rd dose. Current modelling assumptions use the efficacy data after the 4th dose and over the full study period of the completed trial.
- **Vaccine safety:** the EMA concluded that the safety profile of this vaccine is acceptable and similar to others apart from a higher risk for febrile convulsions within 7 days after the 3rd dose. An increase in the number of cases of meningitis and cerebral malaria was found in the group receiving the RTS,S malaria vaccine compared to the control group. The significance of these findings in relation to vaccination is unclear and will be further evaluated in a Phase IV study agreed with the manufacturer, as well as in the pilot implementations recommended by SAGE/MPAC.

[12] RTS,S Clinical Trials Partnership, Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial, Lancet 2015; 386:31-45, see http://dx.doi.org/10.1016/S0140-6736(15)60721-8

Cost and value for money

Changes in assumptions related to vaccine uptake ('demand') have led to a decrease in the expected number of vaccine doses needed and imply lower procurement cost over the 2015-2030 timeframe. Value for money indicators remain within the range of other new vaccines supported by Gavi.

- **Vaccine procurement cost:** The projected total cost of vaccine procurement to Gavi and countries over the 2015-2030 timeframe has decreased from $3.4 billion in 2013 to approximately $2 billion. The main reason for this reduction is the decrease in the number of countries – and the number of sub-national units within countries – projected to introduce with Gavi support based on the assumption that the vaccine would not be used in low transmission settings where Plasmodium falciparum parasite prevalence is below 10%. To facilitate comparison with VIS 2013 numbers and in the absence of new insights at this stage, vaccine price assumptions were kept unchanged.
- **In-country operational cost**: SAGE/MPAC do not recommend use of the malaria vaccine in the 6–12 weeks age group in view of the limited and short-term efficacy shown in this age group. Vaccination will target children of 5–17 months of age, with the first three doses given one month apart followed by an 18-month pause before the fourth dose. While the third dose could be administered together with measles vaccine at the age of 9 months, the other three doses would require additional immunisation visits outside the current schedule. Studies are currently underway to estimate the incremental costs of adding this vaccine to the routine vaccination programme.
- **Value for money:** The lower vaccine efficacy results in an increase in the procurement cost per death averted relative to 2013. Current estimates of $3,600 (Imperial College) and $4,300 (Swiss TPH) per death averted remain within the range of other new vaccines in Gavi's portfolio.

QUESTION 1

Using the 2013 VIS decision framework, what is the potential future value of a malaria vaccine for Gavi's portfolio (in light of the additional evidence from the completed trials, the European Medicines Agency's assessment and SAGE/MPAC recommendations)? Should this be a priority disease/vaccine area for Gavi?

4.2. Needs, stakeholder roles and gaps in the next steps for RTS,S

Next steps for RTS,S include:

- **Pilot implementations:** as per SAGE/MPAC recommendations, to provide information on implementation feasibility, as well as vaccine impact and safety, in order to inform future considerations of wider use.
- **Post-licensure studies**: as per the manufacturer's Risk Management Plan agreed with the EMA
- **Vaccine production**: limited volumes of vaccine will be needed in the short term for the implementation of these studies and pilots, and larger volumes in the medium term, if WHO recommends the vaccine for wider use.

To facilitate a discussion about a possible role for Gavi in these next steps, this section provides an overview of possible needs related to these steps, and known commitments by different stakeholders to contribute to these needs. Of note, the information presented here reflects a high-level, preliminary assessment by the Secretariat that is likely to change in the coming weeks and months when more information becomes available through the WHO-led process to prepare for pilot implementations and conversations with the manufacturer and other stakeholders.

4.2.1. Pilot implementations

Effective and efficient design and implementation of pilots will require:

a) **Coordination** across relevant stakeholders (governments of malaria-endemic countries, technical and funding partners including the Global Fund, implementers, etc.). SAGE/MPAC strongly recommended that WHO coordinate the pilot implementations.

b) **Scientific guidance and oversight** to ensure robust design, implementation and interpretation of findings will be provided by SAGE/MPAC.

c) **Implementation support** may include support for information, education and communication (IEC) activities, vaccine delivery potentially including campaigns, training of health care workers and EPI staff, revision of reporting tools and forms, strengthened routine surveillance, integration and coordination with the malaria control programme and other relevant interventions (vaccine catch-up, nutrition, family planning, etc.), monitoring and evaluation.[13] It is unclear at this stage which actors would provide such support to the governments of countries identified for pilot implementations.

d) **Funding** for all components of the pilots. No funding source has been identified. Key cost drivers may include design choices and the price of vaccines used.

4.2.2. Phase IV post-licensure studies (Risk Management Plan)

The EMA agreed with the manufacturer on a risk management plan (RMP) [14] for RTS,S, which details the measures to be taken in order to ensure that the vaccine is used safely. None of these studies are a condition of the marketing authorisation. However, the positive opinion could be withdrawn if the plan is not implemented satisfactorily. Key components of the RMP include:

[13] This draws in part on a background paper for the SAGE/MPAC review in which WHO has provided preliminary thoughts on programmatic options for implementation of the RTS,S malaria vaccine.
[14] EMA risk management Plan EMA's Summary of the risk management plan (RMP) for Mosquirix: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190200.pdf

- **A baseline study (study 002)** to define the incidence of diseases specified as protocol-defined potential adverse events of specific interest (AESI) and serious adverse events (SAE) in infants and children in Africa prior to implementation of the RTS,S/AS01 candidate vaccine. Enrollment has started in one site in Burkina Faso in September 2015 and work in up to six additional sites will commence shortly[15].
- **A phase IV pharmacovigilance, impact and effectiveness study (study 003)** to estimate the incidence of AESI, and other AEs leading to hospitalisation or death, and meningitis and cerebral malaria in children vaccinated with RTS,S as well as to estimate the vaccine effectiveness on the incidence of any malaria, severe malaria, anaemia, hospitalisation and mortality. This study requires local licensure of the vaccine.
- **A malaria transmission intensity study (study 005)** to assess *Plasmodium falciparum* parasite prevalence and malaria control measures in catchment areas of the two epidemiological surveillance studies (Studies 002 and 003). This study is currently underway in 7 sites.[16]
- **Additional planned studies** will evaluate the timing of the 4th dose, impact of additional boosters and efficacy against clinical disease of a fractional dose of RTS,S.

These studies are currently partially funded by the Bill & Melinda Gates Foundation but gaps remain and efforts to identify 3rd party funders for these late stage studies have been unsuccessful to date.

4.2.3. Vaccine supply

SAGE/MPAC recommended that the population vaccinated in pilot implementations be large enough to allow for an evaluation of the impact of RTS,S vaccination on mortality. We understand that each of the 3-5 pilots may target approximately 200,000 children, which could imply a total target population of up to 1 million with a need for approximately 4 million vaccine doses in the short term. Donation doses may be made available to support pilots, depending on the conditions under which the vaccine would be provided, including financial support for other aspects of pilot implementations and the RMP studies.

For the longer term, in case WHO recommends wider deployment after pilot implementation, sufficient and reliable supply would have to be secured at a sustainable cost. The manufacturer has reiterated its previous commitment to offer the vaccine, upon widespread use, at cost plus a 5% mark-up with any profits being reinvested in research of underfunded tropical diseases.

In the short term, consideration will be required as to whether and how to address concerns about the ability of and cost implications for the manufacturer to maintain a dedicated production facility that would allow sufficient supply being available until wider deployment of the vaccine may be recommended. Since there is no dual market for RTS,S, certainty around demand is critical for sustaining supply in the short and long term. Further discussions on risk-sharing around supply will likely be needed.

QUESTION 2:

What data and information about the next steps (following EMA approval and SAGE/MPAC recommendations) will help inform the Gavi Board's deliberations?

[15] Additional sites have been confirmed in Burkina Faso, Kenya and Ghana, with up to three further sites yet to be identified.
[16] In Ghana (1 site), Senegal (2), Burkina Faso (2), Tanzania (1), Kenya (1)

5. What role could Gavi play, if any, in the next steps for RTS,S?

If the RTS,S malaria vaccine continues to be of interest to the Gavi Board for potential future inclusion in its portfolio, it would have to establish what role, if any, it will play in supporting the implementing of next steps for this vaccine. Any such role should be in line with Gavi's mission and competencies, and take into account historical precedents.

5.1. Gavi mission and mandate

Gavi's mission for its next strategic period 2016-2020 is "to save children's lives and protect people's health by increasing equitable use of vaccines in lower-income countries".

In 2014, the Board adopted a 'risk appetite statement' in order to articulate its risk appetite in relation to Gavi's four strategic goals (SG1-4) and to key functional areas. With regard to 'accelerating the equitable uptake of vaccines' in lower-income countries (SG1) Gavi has a *higher risk appetite*[17] relative to other areas of work. "Achieving rapid access to new, life-saving vaccines is at the heart of Gavi's mission. The Alliance is willing to be bold and take some risk in pursuing this important goal."

5.2. Gavi competencies

Supporting vaccine introductions
Supporting and facilitating vaccine introductions is at the core of the Alliance's operations. Gavi has put in place a coherent set of policies to guide its support and operates a coordinated system for managing the full life-cycle of a new introduction: from application guidance, proposal review, implementation support through partners, to monitoring and evaluation.

Market shaping expertise
Over the past 15 years, Gavi has gained experience in influencing the vaccine markets to achieve its supply and procurement objectives: to ensure sufficient and uninterrupted supply of high-quality vaccines, promote low and sustainable costs for developing countries, and foster an environment for innovation. A recent review found that the Alliance has increased supply security and reduced prices in several key vaccine markets. Through demand forecasting and transparency on the availability of funding, Gavi has increased visibility of demand, which has been particularly important in markets with limited supply.

Convening power
As an Alliance, Gavi brings together a range of global public and private partners in immunisation. The Alliance has become a platform for exchanging views and aligning stakeholders around common goals. Gavi's role in Inactivated Polio Vaccine introduction and the accelerated development of an Ebola vaccine are recent examples where the Alliance's convening power in a complex stakeholder landscape was critical to drive action.

Resource mobilisation
Over the past 15 years, Gavi has built a strong base of sovereign donors as well as foundations and private sector funders. Gavi mobilises resources using a 'replenishment model', seeking funding commitments in advance of projected expenditures for vaccines which enable it to make long-term, predictable commitments to countries. To date, Gavi has mobilised nearly US$20 billion, including $9.5 billion for projected expenditures in the period 2016-2020. Of note, this does not include potential future expenditures for malaria vaccine.

[17] A higher risk appetite signals a willingness to accept more risk to achieve certain end goals or benefits with the belief that if risks were to crystallise, the downside is moderate or acceptable in light of the benefits that will accrue.

5.3. Past experience: funding evidence generation activities

Although Gavi has never had a stand-alone research funding program, over the years it has invested in a range of studies to strengthen the evidence base on vaccine-preventable disease burden, vaccine safety and effectiveness, cost-effectiveness and programmatic feasibility of new vaccines. This includes investments in a 'learning agenda' and post-licensure studies for selected vaccines ahead of inclusion in Gavi's portfolio as well as investments in studies and demonstration projects related to current Gavi vaccines.

Accelerated Development and Introduction Plans (ADIPs)

In 2003, Gavi launched the Accelerated Development and Introduction Plans (ADIPs) to put two new life-saving vaccines that had not yet been recommended by WHO for global use on the agendas in both donor and developing countries: PneumoADIP, led by Johns Hopkins University Bloomberg School of Public Health, which focused on pneumococcal vaccines; and RotaADIP, led by PATH, WHO and US CDC, which concentrated on rotavirus vaccines. The Gavi Board approved an initial envelope of $30 million for each ADIP for the period 2003 – 2007, which was later extended to 2008. Amongst other things, the ADIPs supported clinical trials and effectiveness studies to assess the immunogenicity, safety, efficacy and effectiveness of pneumococcal and rotavirus vaccines in developing countries. In 2006 the Gavi Board approved $15 million for the completion of clinical trials of rotavirus vaccines in Africa and Asia, which had previously only been tested in North America, Latin-America and Europe. Data from these trials informed the 2009 WHO recommendation for universal introduction of rotavirus vaccines. Pneumococcal conjugate vaccines were recommended for global use by WHO in 2007 and Gavi started to support national introductions in 2010.

Learning agenda for rabies and oral cholera vaccines

Following the 2013 VIS assessment of rabies and cholera vaccines, the Board decided not to add these vaccines to Gavi's portfolio at this time, but to invest in a 'learning agenda'. The aim is to identify, through the design, implementation and evaluation of field-based assessments, cost efficient settings and strategies where cholera vaccination can contribute to control endemic transmission while optimizing health impact. For rabies, the aim is to evaluate the feasibility and logistics requirements of increasing access to post-exposure prophylaxis rabies vaccination and to estimate rabies burden and vaccination impact in endemic Gavi countries. The objective of the learning agenda investments of around $6 million is to address evidence gaps to better inform consideration of potential Gavi support for these vaccines in the 2018 Vaccine Investment Strategy (VIS).

Impact assessments and other post-licensure research

The Gavi-funded Hib Initiative (US$37 million) supported WHO estimation of the burden of Hib disease as well as development of a surveillance protocol; it funded surveillance and impact studies in Africa and a vaccine probe study in India (US$9 million) to assess impact of Hib vaccine in a country with unclear disease burden. The work of the Hib Initiative contributed to the revision of the WHO Position Paper on Hib vaccine.

In 2009, Gavi launched the Accelerated Vaccine Introduction (AVI) initiative. Part of AVI's funding has been dedicated to "special studies" to support decision making and assess vaccine impact. A research budget of around $60 million was committed for 2009-2015 to cover assessments of the health and economic impact of pneumococcal conjugate and rotavirus vaccines in early adopter countries; assessments of the risk of pneumococcal serotype replacement; and assessments of safety related to rotavirus (intussusception)[18] and

[18] Rotavirus vaccines are associated with an increased (up to 6-fold) risk of intussusception after the first dose of vaccine in some populations. Initially, WHO recommended an age restriction for administration of rotavirus vaccines, given a potentially higher risk of intussusception beyond the recommended age. Ultimately, in 2012, WHO removed the age restriction since the benefits of providing rotavirus vaccine to more children (including

rubella (congenital rubella syndrome) vaccines. In the past three years, Gavi has spent around $11 million per year on these special studies.

Demonstration programmes for vaccine delivery outside the infant EPI schedule

Countries without experience in delivering vaccines to school-age girls can apply for support to conduct small-scale demonstration programmes. The objective of these 2-year programmes is to support countries in developing and gaining experience with effective delivery strategies in order to prepare for a national rollout. Of note, in contrast to the RTS,S malaria vaccine, the HPV vaccine had already been recommended by WHO for inclusion in national immunisation programmes when Gavi support for national roll-out and demonstration programmes started. The HPV demonstration programmes primarily serve the applying Gavi eligible country to assess implementation feasibility and to help prepare for a subsequent national rollout. In contrast, the RTS,S pilot implementations will be primarily aimed at gathering further information to assess general feasibility and public health value of the vaccine in order to guide future recommendations by WHO on broader use of the vaccine.

QUESTION 3:

What aspects of Gavi's expertise and experience to date are most relevant and should be taken into account by the Board in considering a role for Gavi in the next steps for RTS,S?

QUESTION 4:

What risks and benefits of engagement or no engagement by Gavi should be considered? To what extent are other organisations better placed or complimentary to support the next steps for this vaccine?

6. Independent Expert Committee mandate and objective

In 2013, the mandate of the Independent Expert Committee (IEC) was to review and validate the analyses undertaken for the VIS, including analyses of impact, implementation feasibility and other VIS criteria for all vaccines considered, in order to inform vaccine portfolio recommendations to the PPC. The task at hand following the SAGE/MPAC recommendation for pilot implementations is different in that a portfolio decision is not yet in scope. Therefore, the updated estimates of (longer term – post pilot) impact presented in this paper are meant to situate the discussions in the Gavi context and current portfolio, rather than as to support an immediate investment decision. The IEC is thus not asked to undertake a detailed review of demand forecasting, health impact or value for money modelling methods and outputs at this stage. Rather, the IEC is asked to advise primarily on how the data and information available today may inform deliberations by the PPC and Gavi Board on a role, if any, in support of the next steps for this vaccine.

Annexes

- Annex 1: List of Independent Expert Committee members
- Annex 2: Summary of clinical trial results and regulatory review
- Annex 3: Summary of preliminary updated demand and impact estimates

those that present beyond the recommended age range) far outweighed the risks of intussusception. WHO recommends active surveillance of intussusception in countries that plan to introduce rotavirus vaccines.

Annex 1: List of Independent Expert Committee members

Name	Affiliation
Robert Black (Chair)	Bloomberg School of Public Health, Johns Hopkins University
Jane Achan	Uganda Paediatrics Association
Raj Bhan	University of Delhi, India
Fred Binka	University of Health and Allied Sciences, Ghana
Kalipso Chalkidou	National Institute for Health and Care Excellence (NICE), UK
Melinda Moree	Global Health Consultant
Helen Rees	Wits Reproductive Health and HIV Institute, South Africa; TAG/TFI AFRO
Anne Schuchat	Centers for Disease Control and Prevention, USA

Annex 2: Summary of clinical trial results and regulatory review

Phase 3 clinical trial of approximately 15 000 infants and young children were conducted in 7 sub-Saharan African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania) representing a range of malaria transmission settings. The trial included 2 age groups:

- Infants aged 6–12 weeks, who received the malaria vaccine together with other routine childhood vaccine.
- Young children, who received their first dose of the malaria vaccine between 5 and 17 months of age.

Efficacy

The EMA published the following numbers in its Summary of Product Characteristics for Mosquirix:

Table 1. Vaccine efficacy against all episodes of clinical malaria and severe malaria by age group over the full trial period*. According-to-protocol (ATP) cohort.

	Vaccine efficacy against all episodes of **clinical malaria** (95% CI)		Vaccine efficacy against **severe malaria** (95% CI)	
	3 doses	4 doses	3 doses	4 doses
Infants aged 6-12 weeks at first dose	18% (11;25)	27% (21;32)	*13% (-17;35)*	*21% (-7;42)*
Children aged 5-17 months at first dose	26% (21;31)	39% (34;43)	*-6% (-35;17)*	29% (6;46)

Note: *The follow-up period from dose 3 to study end was not the same for all subjects. The median follow-up period from dose 3 to study end is 36 months in infants and 46 months in children.
Italic VE numbers are not statistically significant

Among infants, vaccine efficacy against clinical malaria was 27% in the group that received 4 doses for the full duration of the trial. In this age group, no significant efficacy was noted against severe malaria, with or without a fourth dose.

Among children aged 5–17 months who received 4 doses of RTS,S, vaccine efficacy against clinical malaria was 39% over the full duration of the trial. The efficacy against severe malaria in this age group was 29% with a 4-dose schedule. Without a fourth dose of the vaccine, no protection was seen against severe malaria. Three doses still protected against clinical malaria with statistically significant efficacy of 26%.

Safety

According to the EMA report, the most serious and confirmed side effect reported in clinical studies with Mosquirix was febrile seizures, which occurred in 1 child in 1,000. These febrile seizures resolved without long-term consequence and are not unique to this vaccine. The most common side effects were fever, irritability and injection site reactions such as pain and swelling.

In the clinical trial, meningitis was reported more frequently among the 5-17 month old participants who received the vaccine (21 cases out of 5949 vaccinees) compared to participants in the control group (1 case out of 2974 vaccinees).[19] The significance of these

[19] Background paper on RTS,S for the SAGE/MPAC meeting, p.50-51. Available here: http://www.who.int/immunization/sage/meetings/2015/october/1_Final_malaria_vaccine_background_paper_v2015_09_30.pdf?ua=1

findings in relation to the vaccination is unclear. WHO's Global Advisory Committee on Vaccine Safety considered that meningitis should therefore be regarded as a potential signal which requires further assessment post-licensure.[20]

Among children aged 5-17 months, an increase in the number of cases of cerebral malaria was found in the group receiving the malaria vaccine compared to the control group (43 cases among 5948 participants who received RTS,S and 10 cases among 2974 participants in the control group) 21.

The significance of these findings in relation to the vaccination is unclear and will be further evaluated in a Phase IV study agreed with the manufacturer, as well as in the pilot implementations recommended by SAGE/MPAC.

http://www.who.int/entity/immunization/sage/meetings/2015/october/1_Final_malaria_vaccine_background_paper_v2015_09_30.pdf?ua=1

[20] WHO's Weekly epidemiological record July 2015
http://www.who.int/vaccine_safety/committee/topics/communication/wer9029.pdf?ua=1

[21] Background paper on RTS,S for the SAGE/MPAC meeting, p.32

Annex 3: Summary of preliminary updated demand and impact estimates

The following section presents updated assumptions on demand and resulting impact estimates for the RTS,S malaria vaccine under a broad roll-out scenario. This update was produced in Q3 2015 prior to the SAGE/MPAC meeting.

Demand forecasting assumptions

Element	Assumptions[1]	Rationale / source
Country scope	• 43 malaria endemic countries in Africa[2] • 28 countries have subnational areas with parasite prevalence > 10% that are expected to introduce • 26 are in the Gavi73, of which 23 projected to introduce with Gavi support • Generally forecasted at the admin1 (e.g. province) subnational level*	Plasmodium falciparum malaria burden concentrated in Africa. No clinical trials outside of Africa
Introduction dates	• First introduction in 2018	Assumed a WHO recommendation for use in late 2015 and pre-qualification of RTS,S in 2016**
Within country uptake	• Most countries 2 years; larger countries up to 4 years	Standard Gavi uptake assumptions for new vaccines
Population	• Surviving infants. Based on UN WPP 2012 Medium Variant at national level and then distributed to admin1 level based on Malaria Atlas Project distribution of population.	Per SAGE/MPAC recommendation. Surviving infant cohort used as a proxy for the malaria vaccine routine target population
Schedule	• 4 doses (4 week intervals between doses 1-3, then dose 4 at ~20 months)	Per SAGE/MPAC recommendation
Wastage factor	• Wastage factor 1.11	WHO wastage factor recommendations for 2-dose lyophilised presentation
Other	• Buffer: 25% of change in demand between years	n/a

1. In the "Scenario 1 Baseline" case
2. Comoros and São Tomé and Príncipe are included in the 43 countries, but lack of data prevented inclusion in subsequent figures.

* An exception is vaccine coverage, as data was only widely available at the national level

** Given the SAGE/MPAC recommendation for more limited initial use in pilot implementations, projected demand would shift out by 3-5 years compared to what is presented here if all other variables were held constant.

Scenarios selected for demand forecasting and impact modelling

	Scenario 1 Baseline	Scenario 2 60% ITN threshold	Scenario 3 70% ITN threshold	Scenario 4: GTS alignment
Parasite prevalence threshold	10%: *most input from consultations suggested high likelihood of 10% being a critical threshold below which vaccine may not be recommended*			
Parasite prevalence change	**Constant at 2014 levels:** *Views expressed that it is difficult to project parasite prevalence trends*			**Decline (as modeled for GTS)** *Alignment with key global malaria plan modelling*
Insecticide-treated bed net (ITN) usage requirement	**None**	**60 %** *Area of high uncertainty but a very rough centering of consultation input around 60%*	**70%** *Primarily used to create a range for extrapolation if WHO recommendation not based on 60%*	**80%** *Alignment with key global malaria plan target for 2020*
ITN usage change	**Constant (at 2014 level)** *Differing views expressed as to whether constant or increasing is most reasonable*			**Rapid Increase (as modeled for GTS)** *Alignment with key global malaria plan modelling*
Country Uptake	**4 per year** *Area of uncertainty; 4 is rough average across widely different experiences with selected prior vaccines in this set of countries*			
Coverage, doses 1-3	**100-90-80% of MCV1, respectively for doses 1-3** *Area of uncertainty with differing views expressed as to difficulty with new visits contrasted with interest in vaccine*			
Dose 4 coverage (dropout from dose 3)	**20%** *Area of high uncertainty with differing views expressed with some focused on programmatic difficulty, while others suggested assuming large effort is applied to ensure 4th dose given its importance*			

Italics = rationale summary. GTS: Global Technical Strategy for Malaria 2016–2030

Data sources: Scenarios 1-3: parasite prevalence and ITN usage through 2014 at admin1 level from Oxford Malaria Atlas Project. Scenario 4: parasite prevalence and ITN usage from Imperial College aligned with GTS "Accelerate 2" scenario modelling. Coverage uses the national level WUENIC estimates released July 2014 and SDF projection assumptions for v10-11.

Country scope in hypothetical introduction sequence

- 43 malaria endemic countries in Africa
- 28 countries forecasted to introduce in 2018-2030*
- 23 countries would be eligible for Gavi support under current policy

Not forecasted to introduce given parasite rate <10%

Botswana*
Djibouti
Eritrea
Ethiopia
Gambia
Guinea-Bissau
Mauritania
Namibia*
Rwanda
Senegal
Somalia
Sudan: North
Zimbabwe

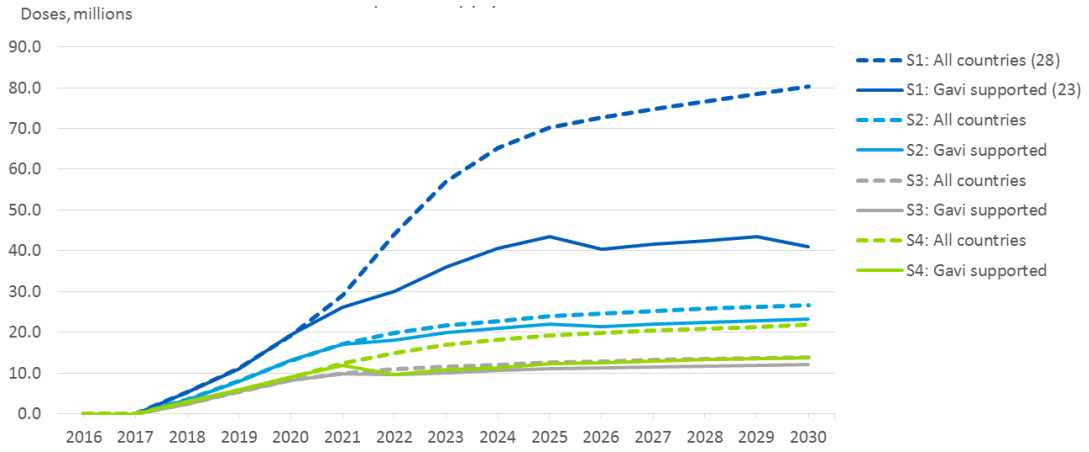
2018	2019	2020	2021	2022	2023	2024
Ghana	Burkina Faso	Benin	Cote d'Ivoire	Cameron	**Angola**	Chad
Malawi	Burundi	Congo, DR	**Nigeria**	**Congo, Rep.**	CAR	**Eq. Guinea***
Uganda	Kenya	Mali	Sierra Leone	Liberia	Madagascar	**Gabon***
Zambia	Tanzania	Mozambique	Togo	Sudan: South	Niger	Guinea

Gavi eligible at time of introduction
Part of Gavi73 but no longer eligible for new vaccine support by the time of introduction due to growth in GNI/capita
Never been Gavi eligible

*Comoros and São Tomé and Príncipe are not included in demand forecast due to lack of data.
Note: the year refers to when a country is forecasted to want an introduction. Depending on the parasite prevalence and ITN usage thresholds assumed in the scenario, there may be in fact no admin1 areas that qualify for introduction for a given country. Similarly in a scenario where prevalence and ITN usage is dynamic, introduction in a given admin1 area could come after the year specified above.

Forecast of required supply for a hypothetical roll-out in 28 countries

Note: Given SAGE/MPAC recommendations for pilot implementations before potential broader roll-out, projected demand would shift out by 3-5 years compared to what is presented here, if all other variables were held constant



Note: 28 countries forecasted to introduce in 2018-2030. 23 countries projected to introduce with Gavi support if current Eligibility and Transition policy were to be applied. For more information, see demand forecast assumptions and scenario explanation slides

Health impact estimates 2018-2030 for Scenario 1:

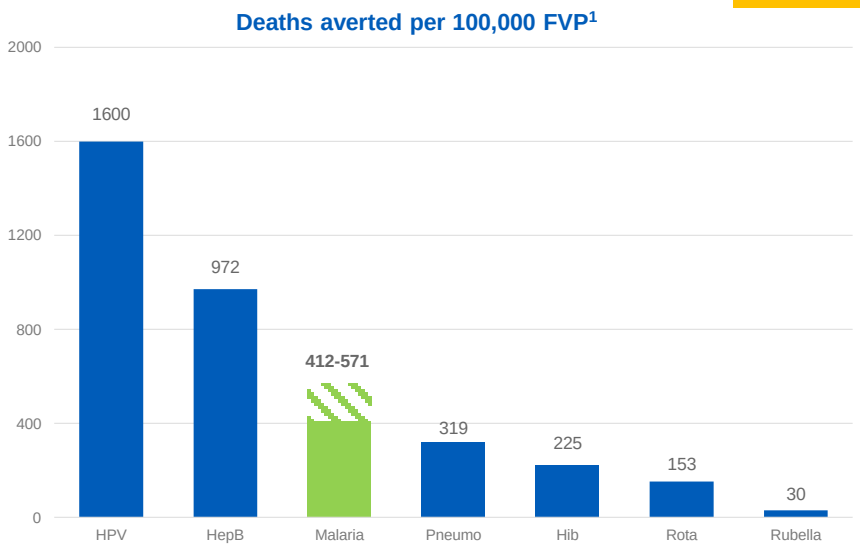
Introduction in admin 1 units where the $PfPR_{2-10}$ ≥10% with no ITN threshold

Routine administration in 6-9m olds wit 4 doses	Swiss TPH	Imperial College
All countries (28)	Mean (min-max)	
Children vaccinated	158,748,000	135,414,000
Deaths averted	660,000 (430,000 - 800,000)	770,000 (280,000 - 1,600,000)
Cases averted	129.3 million (103.3 - 144.3)	144.7 million (64.0 - 248.9)
Deaths averted per 100,000 FVC*	420 (270 - 510)	570 (210 - 1,180)
Cases averted per 100,000 FVC	81,500 (65,100 - 90,900)	106,900 (47,300 - 183,800)
Gavi supported countries (23)**		
Children vaccinated	106,221,000	90,784,000
Deaths averted	440,000	520,000
Cases averted	86.2 million	98.5 million
Deaths averted per 100,000 FVC	412	571
Cases averted per 100,000 FVC	81,100	108,500

*A Fully Vaccinated Child (FVC) is a child that has received at least 3 doses for the purposes of this slide deck
** Includes all countries expected to be eligible to apply according to Gavi's current Eligibility and Transition policy. Of note, according to current projections, Nigeria would no longer be eligible to apply for new Gavi support

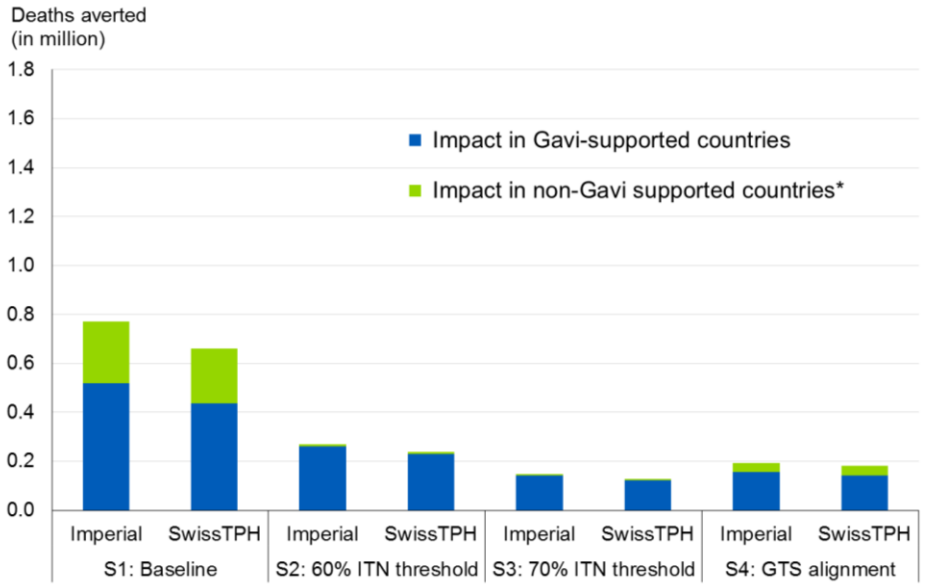
RTS,S may have impact per vaccinated person comparable to other Gavi supported vaccines

Preliminary draft



1. Based on estimated future deaths averted over 2015-2030
Note: Malaria model outputs shown for Scenario 1, with current Gavi Eligibility & Transition policy applied. Value range for malaria reflects Scenario 1 point estimates of deaths averted per 100k FVP from Swiss TPH and Imperial models; Please refer to previous slides to see uncertainty range of impact estimates.
Portfolio impact source: Gavi Strategic Demand Forecast v11, 2014 impact analysis

Health impact estimates: Total deaths averted 2018-2030 by demand scenario and model

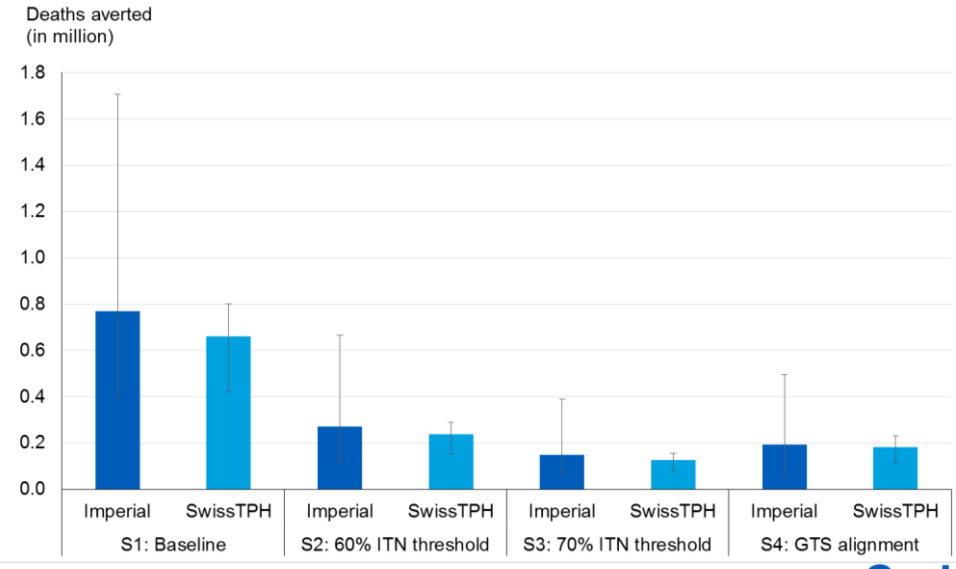


* Includes impact in: 1) countries not eligible for Gavi support (Equatorial Guinea, Gabon); 2) countries included in Gavi73, but projected not to be eligible to apply by the time of introduction (Angola, Congo Rep. Nigeria); 3) Post-Gavi impact in countries that introduced with Gavi support, but transition out of Gavi support before 2030 (Ghana, Zambia, Cote d'Ivoire, Kenya, Cameroon)

Health impact estimates: Total deaths averted 2018-2030 by demand scenario and model

In all 28 countries projected to introduce (irrespective of Gavi support)

Point estimate represents the mean, error bars give the absolute upper and lower bounds



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Annex D:Summary of Phase III clinical trial results, EMA regulatory review and Risk Management Plan

Phase III clinical trial results

The efficacy and safety of the RTS,S malaria vaccine candidate was assessed through a phase 3, double-blind, individually randomised, controlled trial that started in 2009. The trial enrolled over 15 000 infants and young children across eleven research sites in seven sub-Saharan African countries (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique, and the United Republic of Tanzania) representing a range of malaria transmission settings. The trial included two age groups:

- Infants aged 6–12 weeks at the time of first vaccination, who received the malaria vaccine together with other routine childhood vaccines.
- Young children, who received their first dose of the malaria vaccine between 5 and 17 months of age.

Participants were randomly assigned at first vaccination to receive three doses of RTS,S/AS01 at months 0,1,and 2 and a forth dose at month 20; three doses of RTS,S/AS01 and a dose of comparator vaccine at month 20; or a comparator vaccine at all four visits. In line with the WHO malaria vaccine technology roadmap of 2006, the primary objective of the trial was to demonstrate vaccine efficacy after the first 12 months of follow-up. Participants were however followed until January 2014, i.e. for three to four years, and the final results of the trial were published in the Lancet in April 2015. [1]

Vaccine efficacy

The European Medicine Agency (EMA) published the following vaccine efficacy numbers in its Summary of Product Characteristics for RTS,S[2]:

Table 1. Vaccine efficacy against all episodes of clinical malaria and severe malaria by age group over the full trial period*. According-to-protocol (ATP) cohort.

	Vaccine efficacy against all episodes of **clinical malaria** (95% CI)		Vaccine efficacy against **severe malaria** (95% CI)	
	3 doses	4 doses	3 doses	4 doses
Infants aged 6-12 weeks at first dose	18% (11;25)	27% (21;32)	*13% (-17;35)*	*21% (-7;42)*
Children aged 5-17 months at first dose	26% (21;31)	39% (34;43)	*-6% (-35;17)*	29% (6;46)

Note: *The follow-up period from dose 3 to study end was not the same for all subjects. The median follow-up period from dose 3 to study end is 36 months (3 years) in infants and 46 months (about 4 years) in children. *Italic VE numbers are not statistically significant, implying that no effect (neither positive nor negative) could be established regarding the outcome in question*

[1] RTS,S Clinical Trials Partnership, Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial, Lancet 2015; 386:31-45, see: http://intranet/sites/HT/Malaria/Pages/Home.aspx

[2] EMA Summary of Product Characteristics, Table 2 and 3, see: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500194574.pdf

Among infants, vaccine efficacy against clinical malaria was 27% in the group that received 4 doses for the full duration of the trial. In this age group, no significant efficacy was noted against severe malaria, with or without a fourth dose.

Among children aged 5–17 months who received 4 doses of RTS,S, vaccine efficacy against clinical malaria was 39% over the full duration of the trial. The efficacy against severe malaria in this age group was 29% with a 4-dose schedule.

Among those participants who only received three doses of RTS,S, there was an initial reduction in severe malaria, but this was balanced by an increase in severe malaria around 18 months after the initial vaccine course. Such an effect is sometimes referred to as rebound. On the whole, the incidence of severe malaria declined in all groups over the course of the 4-year follow-up period in the trial.

Rebound refers to higher susceptibility to severe malaria among recipients of a malaria-control intervention when the intervention is withdrawn (or when vaccine-induced immunity wanes in the case of a vaccine) as compared to individuals in the same population who did not receive the intervention. This effect can be seen for a vaccine and other preventative malaria interventions, including bed nets. According to the Joint Technical Expert Group on Malaria Vaccines (JTEG), this rebound effect for severe malaria was most marked in higher transmission settings, possibly because participants in the control group developed immunity through natural infection more rapidly – the malaria vaccine reduced the number of infections with the *P. falciparum* parasite, which resulted in a reduction in the number of clinical malaria episodes, but also in a delayed acquisition of naturally acquired immunity.[3] A rebound effect for severe malaria was not observed among children vaccinated at 5-17 months of age who received four doses of vaccine up to the end of follow-up, or in the group vaccinated at 6-12 weeks in whom vaccine efficacy was lower and prevented fewer episodes of malaria.

Vaccine safety

According to the EMA report, the most serious and confirmed side effect reported in clinical studies with RTS,S was febrile seizures.[4] The incidence of generalized convulsions within the seven days following any of the first three vaccinations in the 5-17 month age category was 1 per 1000 doses. Following a fourth dose of RTS,S, the incidence of generalized convulsions increased to 2.5 per 1000 doses.[5] These febrile seizures resolved without long-term consequence and are not unique to this vaccine. The most common side effects were fever, irritability and injection site reactions such as pain and swelling.

In the clinical trial, meningitis was reported more frequently among the 5-17 month old participants who received the RTS,S vaccine (21 cases out of 5949 vaccinees) compared to participants in the control group (1 case out of 2974 vaccinees).[6] The significance of this finding in relation to vaccination is unclear. WHO's Global Advisory Committee on Vaccine Safety considered that meningitis should therefore be regarded as a potential signal which requires further assessment post-licensure.[7]

Among children aged 5-17 months, an increase in the number of cases of cerebral malaria was found in the group receiving the malaria vaccine compared to the control group (43 cases

[3] Background paper on RTS,S for the SAGE/MPAC meeting prepared by the Joint Technical Expert Group on Malaria Vaccines (JTEG) and the WHO Secretariat, p.66. Available here: http://www.who.int/immunization/sage/meetings/2015/october/1_Final_malaria_vaccine_background_paper_v2015_09_30.pdf?ua=1

[4] EMA, EPAR summary for the public, p.2. See: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500194576.pdf

[5] Background paper on RTS,S for the SAGE/MPAC meeting, op. cit. p.49

[6] Ibid, p.50-51.

[7] WHO's Weekly epidemiological record July 2015 http://www.who.int/vaccine_safety/committee/topics/communication/wer9029.pdf?ua=1

among 5948 participants who received RTS,S and 10 cases among 2974 participants in the control group)[8].

The significance of these findings in relation to vaccination is unclear and will be further evaluated in a Phase IV study agreed with the manufacturer, as well as in the pilot implementations recommended by SAGE/MPAC.

European Medicines Agency (EMA) review of RTS,S

EMA positive scientific opinion

The quality, safety and efficacy of the RTS,S malaria vaccine was reviewed by the European Medicines Agency (EMA) using a procedure known as article 58 that allows the agency to review medicines that will be used exclusively outside the EU.[9] When assessing these medicines, the same rigorous standards as for medicines intended for patients in the EU applies. This procedure allows access to essential medicines for countries with limited regulatory capacity for assessing new medicinal products for their markets. After WHO makes its policy recommendation - considering additional aspects such as the feasibility of implementation, affordability and cost-effectiveness, and the public health value of the product - it will be up to national regulators in countries where the product will be used to register the product.

On 23 July 2015, the EMA's Committee for Medicinal Products for Human Use adopted a positive opinion, recommending the granting of a marketing authorisation for the RTS,S malaria vaccine. This implies that it considers the risk-benefit balance of RTS,S for active immunisation of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* as favourable.

The EMA concluded that the safety profile of this vaccine is acceptable and similar to others apart from a higher risk for febrile convulsions within 7 days after a vaccine dose. An increase in the number of meningitis and cerebral malaria cases was observed in the malaria vaccine group compared to the control group, however no clear relationship has been established with the vaccine.

Risk Management Plan

A risk management plan (RMP) is a document submitted as part of the dossier that is evaluated by regulatory authorities before a medicine can be authorised and which is regularly updated as new information becomes available. RMPs include information on a medicine's safety profile and explain the measures that are taken in order to prevent or minimise the medicine's risks in patients. The EMA indicates that all medicines have both benefits and risks; in order for a medicine to be authorised, the benefits have to outweigh the risks.[10] It further explains that at the time a medicine is first authorised, it is impossible to know everything about its safety as the medicine will only have been tested in a relatively small number of patients for a limited length of time. Some side effects are very rare, or only occur in patients with other conditions or particular genetic backgrounds. The RMP details the known safety concerns with the medicine and how they can be managed. The RMP will also include details of any additional studies that have been recommended at the time of licensing to provide more

[8] Background paper on RTS,S for the SAGE/MPAC meeting, op. cit., p.32

[9] Article 58 of a European Community Regulation establishes a mechanism whereby the EMA may give a Scientific Opinion, in the context of cooperation with WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community, for more see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp

[10] EMA Questions and Answers on the Risk Management Plan (RMP) Summary. See http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/05/WC500166101.pdf

information on the medicine's safety profile. Medicines are then carefully monitored after marketing (pharmacovigilance), so that new side effects can be detected quickly, and regulatory authorities can ensure that the benefits outweigh the known risks at all times.

All identified risks with RTS,S (febrile convulsions) and potential risks (including meningitis, and cerebral malaria) will be evaluated further in post-licensure studies as part of the risk management plan (RMP)[11] agreed between EMA and the manufacturer. The RMP details the measures to be taken in order to ensure that the vaccine is used safely. While none of these studies are a condition of the marketing authorisation, the positive opinion could be withdrawn if the plan is not implemented satisfactorily.

Below is a description of the studies included in the Risk Management Plan:

- **A baseline study (study EPI MAL 002)** to define the incidence of diseases specified as protocol-defined potential adverse events of specific interest (AESI), serious adverse events (SAE), aetiology confirmed meningitis and severe malaria, including cerebral malaria in infants and children in Africa prior to implementation of the RTS,S/AS01 candidate vaccine. Approximately 40,000 children will be under active surveillance. Enrollment has started in one site in Burkina Faso in September 2015 and work in up to six additional sites will commence shortly[12].
- **A phase IV pharmacovigilance, impact and effectiveness study (study EPI MAL 003)** to estimate the incidence of AESI, and other AEs leading to hospitalisation or death, and the incidence of aetiology confirmed meningitis and severe malaria, including cerebral malaria in children vaccinated with RTS,S as well as to estimate the vaccine effectiveness on the incidence of any malaria, severe malaria, anaemia, hospitalisation and mortality. Approximately 45,000 children will be under active surveillance. This study requires local (national) licensure of the vaccine. It is an observational cohort, implying that the same infrastructure for vaccine delivery will be used as during a normal vaccine roll-out.
- **A malaria transmission intensity study (study EPI MAL 005)** to assess *Plasmodium falciparum* parasite prevalence and malaria control measures in catchment areas of the two epidemiological surveillance studies (Studies EPI MAL 002 and 003). The study is expected to provide insights into the potential behavioural changes regarding usage of other malaria preventive measures and *Plasmodium* species replacement. This study is currently underway in 7 sites.[13]
- **A co-administration study (Malaria-073)** to assess the immunogenicity of RTS,S when co-administered with measles, rubella and yellow fever vaccines during the current EPI immunisation visit at 9 months of age, and to describe the antibody response to the human catalase after administration of a 3-dose course of RTS,S. The protocol for this study is in draft.

[11] EMA risk management Plan EMA's Summary of the risk management plan (RMP) for Mosquirix: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/07/WC500190200.pdf
[12] Additional sites have been confirmed in Burkina Faso, Kenya and Ghana, with up to three further sites yet to be identified.
[13] In Ghana (1 site), Senegal (2), Burkina Faso (2), Tanzania (1), Kenya (1)