SUBJECT:	**VACCINE INVESTMENT STRATEGY: METHODOLOGY**
Agenda item:	12
Category:	For Decision

Section A: Introduction

- The Vaccine Investment Strategy (VIS) is Gavi's bespoke prioritisation approach for new investments in vaccines. It is developed every five years to inform Gavi's strategic and funding cycle. Twice before, Gavi has developed a VIS and as a result added new vaccines to its portfolio and committed to other types of vaccine investments.[1]

- The VIS 2018 has three phases: 1) development of an evaluation approach for vaccines for endemic disease prevention through routine immunisation (for decision at this meeting); 2) narrowing of these candidates to a shortlist, and development of an evaluation approach for vaccine investments for epidemic response; (for Board decision in June 2018); 3) final recommendations including details on the scope and nature of Gavi's investment (for decision at the end of 2018).

- A Steering Committee (SC)[2] provides scientific and technical input into the VIS process. The SC met on 11-12 September 2017 (meeting summary in Appendix 5) and provided guidance on the overall VIS methodology, the list of candidates and the evaluation approach as described below.

Section B: Vaccine Investment Strategy: methodology

1. Stakeholder consultations

1.1 The Secretariat conducted initial consultations with Gavi Board members and via a survey to Alliance stakeholders (160 responses). Summary findings from these consultations are in Appendix 2. Questions focused on the relative importance of different types of vaccine investments (e.g. routine immunisation versus outbreak response), strategic consideration of specific development objectives (e.g. global health security), evaluation

[1] In 2008, Gavi's Board prioritised Japanese encephalitis (JE), rubella, HPV and typhoid conjugate vaccines. In 2013, Gavi's Board made investment decisions for three vaccines: expanded yellow fever campaigns; support for a global stockpile of oral cholera vaccine, including the opportunity to generate impact data; and investment in a 'learning agenda' for rabies vaccine. The Board requested monitoring of new data on maternal influenza vaccine impact and a re-assessment of the RTS,S malaria vaccine once it had been recommended for use by SAGE, and subsequently in 2015 approved funding for implementation pilots conducted by WHO.
[2] List of members in Appendix 4

criteria, and if/how Gavi should signal its interest in vaccines that are still in early-stage development.

2. Apples, oranges, fish? A differentiated approach to assessment

2.1 WHO conducted a landscape analysis to identify candidates for the VIS 2018.[3] Agreed inclusion criteria included public health relevance to low- and middle-income countries and expected licensure by 2023. Following consultation with the SC, 20 candidates will be considered. The list of candidates (attached in Annex B) is longer and more diverse than in the last VIS.[4] In addition, the SC advised that Gavi monitor R&D of high-impact vaccines which are too early/uncertain to include in the VIS now, but are of potential future relevance for Gavi.[5]

2.2 The diversity of candidates mirrors a growing differentiation in Gavi's investments, which have evolved from a focus on universal introductions of new and underused vaccines at Gavi's inception to also include investments in outbreak response, 'learning agendas', and vaccines of regional importance. Given this diversity, it would be challenging to compare all the candidates in a standardised way. Therefore, based on consultations and SC guidance, the Secretariat proposes categorising candidates as follows:

a. *Vaccines for endemic disease prevention through routine immunisation*: candidates where disease is endemic and the intervention would be planned, preventive immunisation to reduce disease burden. The majority of VIS candidates are in this category.

b. *Vaccine investments for epidemic preparedness*: candidates for which the intervention is primarily a global stockpile or similar mechanism to prepare for and respond to disease outbreaks. The potential impact of Gavi's investment in these vaccines is harder to quantify precisely due to limited predictable mortality or morbidity of these diseases.

c. *IPV post-eradication*: Inactivated poliovirus vaccine (IPV) for polio post-eradication can be seen as a contribution to the 'global public good' of maintaining disease eradication. While the intended intervention would be planned, routine immunisation, it would be to reduce the risk of re-emergence of polio, rather than to reduce disease burden.

2.3 In consultations, stakeholders were asked about the relative importance they would place on vaccine investments in each of these categories and said that vaccines intended to prevent endemic disease through routine immunisation should be the highest priority for Gavi. Investments in

[3] The scope of candidates was limited to vaccines and passive immunisation products for prophylactic use with public health relevance.
[4] Two products were deprioritised: a) mumps, because it is currently of limited public health importance to Gavi countries due to low or unknown disease burden, and b) diphtheria antitoxin because it is a therapeutic product and thus falls outside the scope of the VIS.
[5] These include HIV, 2nd generation tuberculosis, Enterotoxigenic Escherichia coli (ETEC), and norovirus vaccines.

epidemic preparedness and disease eradication were also considered important, but secondary to investments in routine immunisation.

3. Vaccines for endemic disease prevention through routine immunisation

3.1 Fifteen **candidates** (13 vaccines and 2 passive immunisation products[6]) fall in this category

(a) *Vaccines with a link to current Gavi investments*: diphtheria booster, tetanus booster, pertussis booster, hepatitis B birth dose, oral cholera vaccine, meningitis C, Y, W, X, malaria (RTS,S), rabies (post-exposure prophylaxis), and rabies immunoglobulin/mAb.

(b) *Other vaccines*: hepatitis E, hepatitis A, dengue, maternal influenza, maternal respiratory syncytial virus (RSV), and RSV monoclonal antibodies (mAb).

3.2 Each candidate will be evaluated against a standardised set of criteria. The proposed **criteria** (Annex C) reflect alignment with Gavi's mission, strategic and global priorities identified in consultations. They also incorporate lessons learned in the 2013 VIS and SC guidance. The table includes preliminary indicators which will be further refined in consultation with the SC and other experts.

3.3 Once all vaccines have been evaluated against these criteria, prioritisation would be done as follows:

(a) First, candidates will be ranked based on: *health impact; value for money; equity and social protection; economic impact;* and *global health security impact* (including antimicrobial resistance impact). The specific weighting of these individual **ranking criteria** will be determined through consultations in early 2018.

(b) Second, an analysis against **secondary criteria** - *implementation feasibility, availability of alternative interventions, broader health system benefits* (e.g. integration opportunities), and *Gavi's comparative advantage* in supporting the vaccine (e.g. unique market shaping needs) – may adjust a vaccine's ranking up or down if it scores strongly on any of these criteria. Additionally, cost implications, both to Gavi and to countries, will be estimated and may also be used to adjust a vaccine's initial ranking.

(c) The Secretariat will highlight how different priorities affect the vaccine shortlist and, if relevant following consultations, propose different options for weighting for consideration by the PPC and Board.

[6] Passive immunisation products directly provide antibodies to protect against infection whereas vaccines enable the immune system to develop its own protective response to infection. Passive immunisation products are given when the time needed for immunity to naturally develop is too short (e.g., in the event of a potential rabies infection) or inhibited (e.g. the immune systems of newborns are not fully developed).

3.4 The PPC endorsed the criteria and their proposed application toward prioritisation of candidates. PPC members suggested the Secretariat further explore potential indicators relating to long-term sequellae and potential to avert medical costs and productivity loss due to illness.

4. Vaccine investments for epidemic preparedness

4.1 Four **candidate vaccines** primarily intended for epidemic response will be considered in the VIS 2018. Chikungunya, Zika and Ebola vaccines are all in late-stage clinical trials. A fourth, pandemic influenza, will also be considered, but the SC recommended it be treated separately since potential investments towards pandemic flu preparedness would be of a different nature and may require a different evaluation approach.[7]

4.2 Many of the **criteria** for assessing vaccines for endemic disease prevention will also apply to vaccines for epidemic response. However in some cases, different indicators will need to be identified, e.g. rather than estimating health impact, magnitude of risk could be more meaningful since the future impact of outbreaks is inherently uncertain. Preliminary draft evaluation criteria and illustrative indicators reflecting initial SC guidance are in Appendix 3. These will further refined and submitted to the PPC and Board for decision in mid-2018.

4.3 The Secretariat posed three specific questions to the PPC about Gavi's role in epidemic preparedness vaccines:

(a) Given the unpredictable nature of outbreaks, shifting disease epidemiology and rapidly evolving vaccine landscape, should this be monitored more regularly outside the 5-year VIS cycle? The PPC asked that the Secretariat first focus on further defining evaluation criteria and indicators, in consultation with WHO and other experts. These would be considered at the next PPC meeting together with an appropriate process for investment decision-making.

(b) What role, if any, should Gavi have in epidemic vaccines pre-licensure? Given that clinical efficacy trials can only be conducted during an outbreak, it may sometimes be necessary to establish stockpiles of such vaccines that have demonstrated immunogenicity in early clinical trials but are not yet licensed.[8] In line with SC guidance, PPC members broadly agreed that it is not Gavi's mandate to fund pre-licensure vaccines, keeping in mind that the Board can always take exceptional decisions, as it did for Ebola.

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[7] Stockpiling is not an effective solution with current vaccines given rapid mutation of flu viruses. In addition, other initiatives have already been established to address challenges around vaccine availability for developing countries in case of a pandemic (e.g., WHO's Pandemic Influenza Preparedness framework). The SC suggested that Gavi work with WHO and other stakeholders to understand the gaps and potential complementary roles Gavi could play. Routine immunisation of pregnant women for seasonal influena will also be considered within the VIS 2018 and is one way to strengthen country preparedness for pandemic influenza.

[8] The environment for use of experimental vaccines is complex given the scientific, ethical and regulatory requirements, and liability and indemnification contexts.

(c) How should Gavi treat vaccines developed by the Coalition for Epidemic Preparedness Innovations (CEPI)? The Secretariat noted that SC members had raised concern regarding potential gaps in the global health financing architecture, which could arise if organisational mandates are not aligned. PPC members agreed that vaccines for epidemic response would need to be assessed on a case by case basis for potential Gavi support, and that this applies to CEPI as well as any other vaccine funding initiative.

5. IPV post-eradication

5.1 Following eradication of polio, continued use of IPV would serve as 'insurance' against the re-emergence of the disease. Gavi's support for IPV is currently funded by the Global Polio Eradication Initiative (GPEI). However, it is anticipated that GPEI will close following global certification of polio eradication (currently projected for end of 2020). Therefore alternative funding would be needed for if Gavi is to continue to invest in IPV and related areas such as polio outbreak response, surveillance, etc. Most PPC members felt that there is likely a role for Gavi in post-2020 IPV support. One PPC member highlighted the need to consider hexavalent vaccines, which may become available in several years.

5.2 Based on consultations with donors and other key stakeholders, the Secretariat will develop a set of scenarios for Gavi's support for IPV post-2020 for PPC guidance in May 2018. This will include evaluating how the Eligibility, Transition and Co-financing policies would apply given that Gavi's current support for IPV makes specific exceptions to these policies.

6. Future priorities (beyond 2023)

6.1 The VIS considers candidates with expected licensure within five years (by 2023) to help guide vaccine priorities for the next strategic period. Some stakeholders have asked whether there is a role for Gavi in providing non-binding guidance on future vaccine priorities beyond this timeframe. As vaccine development occurs on a longer time horizon (10-20 years), this could help focus R&D priorities at earlier stages of clinical development and provide greater visibility for future cycles of the VIS. Some PPC members suggested that providing guidance on R&D prioritisation is a core role for WHO rather than Gavi, and questioned the usefulness of a non-financial commitment from Gavi.

Section C: Actions requested of the Board

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

a) **Approve** the evaluation criteria for potential new investments in vaccines and other immunisation products primarily intended for endemic disease prevention; these include ranking criteria (health impact, economic impact, equity and social protection impact, global health security impact, and value

for money), secondary criteria (other impact, Gavi's comparative advantage, broader health systems benefits, implementation feasibility, and alternate interventions) and cost criteria (vaccine cost, operational cost, and additional implementation costs) as further described in Table 1 and Section 4 of Doc 07 to the PPC *[as included in Annex C to Doc 12 to the Board];*

b) **Request** the Secretariat, in consultation with WHO and other experts, to develop evaluation criteria for potential new investments in vaccines for epidemic response for PPC review and Board approval.

Annexes

Annex A: Implications/Anticipated impact

Annex B: VIS candidates

Annex C: Criteria for vaccines for endemic disease prevention through routine immunisation

Additional information available on BoardEffect

Appendix 1 ***(in October 2017 PPC meeting book):*** Report to the Gavi Alliance Programme and Policy Committee: Vaccine Investment Strategy: Methodology

Appendix 2: Summary of stakeholder consultations

Appendix 3: Preliminary draft criteria for vaccines for epidemic preparedness

Appendix 4: List of Steering Committee Members

Appendix 5: SC meeting summary (September 2017) and terms of reference

Appendix 6: SC meeting background document (September 2017)

Additional reference materials online:

VIS internet page: http://www.gavi.org/about/strategy/vaccine-investment-strategy/