SUBJECT:	**VACCINE INVESTMENT STRATEGY: SHORT LIST**
Agenda item:	07
Category:	For Decision

Section A: Introduction

- This report presents outcomes of the Phase II analyses for the Vaccine Investment Strategy (VIS) to seek Board approval of (1) a prioritised short list of vaccines for endemic disease prevention for investment case development and (2) the approach for Gavi to evaluate potential investments in vaccines for epidemic disease preparedness and response.
- In November 2017 the Secretariat presented to the Board a differentiated approach to evaluate (1) vaccines for endemic disease prevention, (2) vaccines for epidemic preparedness and response and (3) Gavi's engagement with inactivated polio vaccine (IPV) post-2020. The Board approved the evaluation criteria for the assessment of vaccines for endemic disease prevention and requested the Secretariat to develop an evaluation approach for vaccines for epidemic preparedness and response.
- This report includes that completed evaluation of vaccines for endemic disease prevention and the PPC-endorsed short list for investment case development (for decision in November 2018), and the PPC-endorsed evaluation framework and approach for review of potential investments for epidemic preparedness and response.
- Finally the Secretariat has developed a separate report on Gavi's engagement with IPV post-2020 (see Doc 08).

Section B: Vaccine Investment Strategy: short list

1. Methodology

1.1 Occurring every five years, the VIS is Gavi's prioritisation approach for new vaccine investments to inform Gavi's next strategic and funding cycle. The VIS 2018 has three phases: 1) development of an evaluation approach for vaccines for endemic disease prevention; 2) narrowing of these candidates to a short list, and development of an evaluation approach for vaccine investments for epidemic preparedness and response (for decision at this meeting); 3) final recommendations including details on the scope and nature of Gavi's future investments (for decision at the end of 2018).

1.2 To inform this report, consultations were conducted with in-country stakeholders (179 responses), including Ministries of Health, technical partners and civil society organisations. The consultation survey explored preferences and implementation challenges for VIS candidate vaccines. The VIS Steering Committee (SC) was convened twice in Phase II to validate the assessment of vaccines. Further information on the stakeholder consultations and VIS SC meetings is provided in Appendices1 and 2.

2. Vaccines for endemic disease prevention: analyses and short list

2.1 To assess each candidate vaccine against the Board-approved evaluation criteria, the Secretariat first identified a vaccination strategy (or multiple strategies) for each candidate based on disease epidemiology, vaccine product profiles, consultations with disease experts and WHO recommendations. This served as the basis to forecast demand in Gavi-supported countries and project health impact and cost implications of future potential Gavi investments for the period 2020-2035. Based on guidance from the VIS SC, each vaccine was evaluated against pre-defined thresholds corresponding to a 'traffic light' system of red/yellow/green scores for the indicators which comprised each evaluation criterion. This enabled relative comparison between candidates.

2.2 The Secretariat subsequently consulted with a subset of Board members representing 17 Board constituencies to determine how the vaccine 'traffic light' scores would be used to prioritise candidates. Among the 'ranking' criteria, Board members assigned the largest weight to the 'health impact' criterion, followed by 'value-for-money'[1]. The weights were then applied to the 'traffic light' scores for each 'ranking' criterion to develop overall scores for each candidate[2]. Further, Board members agreed that 'secondary' criteria, which were informed by country consultations, be considered to adjust the prioritisation of vaccines. The overall scores for each candidate were presented to the VIS SC in rank order for review at its 12-13 March 2018 meeting. See Appendices 3, 4 and 5.

2.3 Ultimately 9 potential investments in immunisation products were assessed through the endemic disease prevention framework: diphtheria, tetanus, pertussis-containing (DTP) boosters; hepatitis B birth dose; cholera (preventive immunisation); meningitis (multivalent conjugate vaccines[3]); hepatitis A; dengue; maternal influenza; respiratory syncytial virus (RSV) maternal vaccine and monoclonal antibody; and rabies post-exposure

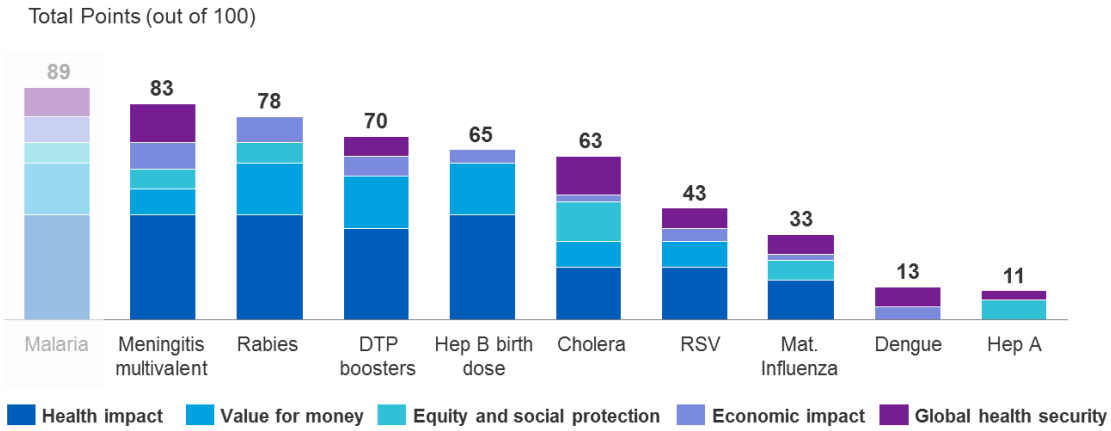
[1] Board members also reported a preference for measuring health impact based on deaths averted rather than cases averted. Based on this feedback, the Secretariat has only taken into consideration the metrics 'total future deaths averted' and 'deaths averted per 100,000 vaccinated' in the ranking of vaccines but more heavily weighted towards the former, also based on Board member preferences.

[2] Out of 100 total points: maximum of 40pts for health impact (30pts for total deaths averted, 10pts for deaths averted per 100,000 vaccinated), 20pts for value for money (cost per death averted), 15pts for equity and social protection impact, 10pts for economic impact and 15pts for global health security impact.

[3] Conjugate vaccines including A, C, W, Y, or X serogroups.

prophylaxis (vaccine and immunoglobulin). Figure 1 details the scoring of each candidate vaccine against all of the ranking criteria.

Figure 1: Vaccine scores based on assessment against ranking criteria[4]



2.4 Three short list options for development of vaccine investment cases were proposed. Option A included all 6 vaccines with the highest cumulative score on ranking criteria, while Options B and C deprioritised rabies; and rabies, DTP boosters and RSV, respectively, based on considerations of secondary criteria.

2.5 The PPC endorsed **Option A**, prefering further analysis of each candidate to allow greater discernment of potential vaccine investments. PPC members also felt that using lack of 'fit' with existing Gavi programmes (e.g. rabies vaccine is not a traditional childhood vaccine) to deprioritise vaccines suggested a narrower scope than Gavi programmes currently encompass. and limits Gavi from addressing new challenges. They noted that Gavi has already moved beyond traditional EPI to new immunisation timepoints (e.g. HPV) and to new programme designs (e.g. pilots for the malaria vaccine).

2.6 *Key findings and conclusions from the Phase II analyses for each vaccine from Option A and the recommendations from the PPC*

2.7 **Multivalent conjugate meningitis** vaccines were assessed to have high health impact and global health security impact by addressing the burden of Neisseria meningitidis serogroups C and W, the main causes of outbreaks in recent years, in addition to continuing to control NmA burden. The SC requested the Secretariat to explore an additional risk-based vaccination scenario given heterogeneous serogroup risk and disease burden in endemic countries.

2.8 **Hepatitis B birth dose** showed high health impact and value for money, due to lower vaccine costs. However, despite a strong WHO recommendation, it has thus far not been broadly implemented by Gavi-supported countries, presenting an opportunity to catalyse introductions

[4] Malaria is included only as a comparator and is not considered for an investment decision in the VIS 2018.

(e.g. potentially through support for introduction and short-term vaccine funding), as well as strengthen the health system by supporting an important service delivery platform and encouraging institutional births. The PPC also felt it was important to consider reaching babies born outside health facilities with this vaccine and recommended that the Secretariat further explore the feasibility and impact of this expanded strategy.

2.9 Regarding **cholera** vaccine for preventive immunisation, the VIS SC emphasised the importance of shifting from emergency response to a comprehensive immunisation strategy, including proactive vaccination in targeted endemic 'hot spots' to supplement scale-up of water, sanitation and hygiene (WaSH) interventions. There is also a continued market shaping role for Gavi to ensure supply can meet increasing demand, building on gains made through Gavi's initial stockpile investment in 2013.

2.10 While **rabies** showed high health impact, the VIS SC raised concerns about the operational complexity of post-exposure prophylaxis. It was also viewed as having limited synergies with other Gavi programmes. While some PPC members acknowledged that implementation challenges are likely to be significant, others felt that, due to the compelling public health need for rabies vaccine, this should not be a reason to deprioritise and noted that many of the existing issues with countries' rabies programmes stem from their financing. The PPC requested a clarification of the proposed investment in 'implementation pilots', which was intended to describe a phased approach to introductions based upon comprehensive rabies programming being available to ensure operational success. The PPC felt that the term 'implementation pilots' was restrictive and subject to misinterpretation and requested its removal from the decision point.

2.11 **DTP boosters** were projected to have high value for money given medium health impact and low vaccine procurement costs. DTP boosters could also contribute to strengthening the 2nd year of life, school entry and adolescent immunisation timepoints to help address missed doses in the EPI schedule. However, the VIS SC raised questions regarding the role for Gavi given the low price implies that financing should not be a barrier to country introductions. The PPC recommended inclusion, due to the importance of DTP boosters in addressing coverage and equity gaps, particularly in light of current diphtheria outbreaks globally.

2.12 Analyses showed **RSV** to have medium health impact compared with other candidates, with disease burden most highly concentrated in neonates and children under the age of five. The VIS SC further acknowledged the benefits of leveraging RSV vaccination to establish the maternal immunisation timepoint, which may be increasingly important with additional vaccines in the future (e.g. group b streptococcus). However, while the VIS SC considered potentially deprioritising RSV vaccine given that it was not projected to be introduced until towards the end of the next strategic period, it saw value in signalling intent to manufacturers to ensure capacity planning, including in Gavi supported countries. The PPC acknowledged the universal burden of RSV in both high and low income settings and noted

Gavi's role in ensuring equitable access to the vaccine, thereby recommending RSV for inclusion on the short list. The PPC also noted that new developments in the clinical trial indicate that the lead pipeline candidate might become available sooner than anticipated. The Secretariat will incorporate this potential revised timeline in further analyses for the investment case.

2.13 Due to low overall scores on the ranking criteria, the VIS SC did not include dengue, hepatitis A or maternal influenza on any short list option for PPC consideration. **Dengue**[5] was recognised as an important disease but due to uncertainties in the pipeline and disease burden, the SC recommended to continue to monitor developments. **Hepatitis A** was not highly prioritised by stakeholders and has limited health impact. **Maternal influenza** was also viewed as having uncertain burden and health impact, but may be further considered as part of the pandemic flu investment case. The PPC endorsed the exclusion of these vaccines from the short list.

2.14 Finally, PPC members also raised broader points regarding the VIS process and considerations for future investments, noting the importance of aligning with Gavi's strategy for the next period (2021-2025). The PPC requested the Phase III analyses include links to the ongoing work on developing Gavi's next strategy. They also recommended that the investment cases include a view to research and implementation gaps that might be relevant for Gavi or other stakeholders to mitigate risk and ensure successful uptake of new vaccines.

3. Vaccines for epidemic preparedness and response

3.1 At the Board's request in November 2017, the Secretariat has developed an evaluation framework for vaccine investments for epidemic preparedness and response, namely vaccine stockpiles or similar approaches. The proposed framework (Figure 2) draws from the criteria and indicators used in the evaluation of vaccines for endemic disease prevention. It also includes criteria related to epidemic risk reduction that are unique to these vaccine investments and recognises that classic metrics (e.g. deaths averted, value-for-money) may not apply. It reflects feedback from the Gavi PPC and Board, the VIS SC, WHO and other expert consultations and builds on the work of other initiatives, particularly the WHO R&D Blueprint.

3.2 The Secretariat recognises that many diseases may be categorised as having both epidemic and endemic characteristics. Assessment against one or the other framework will depend on the public health goal and the type of investment (i.e. planned preventive immunisation versus a stockpile or similar).

3.3 The evaluation framework for epidemic preparedness and response is intended to structure the assessment and decision-making process around

[5] Dengue-specific analysis (Annex 3b in May 2018 PPC meeting book) updated following PPC to include revised information regarding vaccine characteristics.

four critical questions (aligned with the four categories of criteria and indicators in the framework):

a) **Disease Risk and Burden**: Is the epidemic potential of the disease sufficient to prioritise a stockpile or similar investment?
b) **Vaccine Impact and Feasibility**: Would the vaccine be feasible to use and impactful as part of epidemic preparedness and response?
c) **Fit for Gavi and Partners**: What is Gavi's comparative advantage and how can Gavi's expertise contribute to the funding and delivery of this vaccine?
d) **Financial Implications**: What is the appropriate scale of the stockpile (or related intervention) and what would be the financial implications of an investment?

3.4 Given the greater uncertainty around emerging infectious diseases, there are likely to be data gaps and the methodology will need to be refined as the framework is used. The PPC supported the proposed framework and approach in principle but noted that the approach may evolve with experience and in the context of broader discussions on Gavi's role in epidemic preparedness and response.

Figure 2: Evaluation framework for vaccines for epidemic preparedness and response

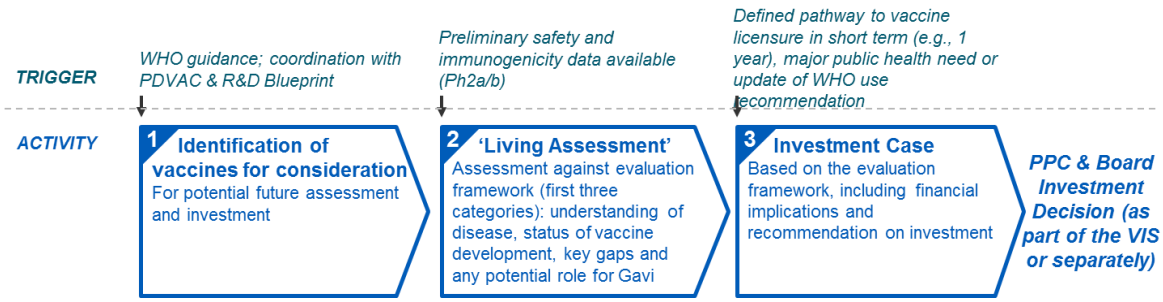
	Criteria	Indicators
Disease Risk & Burden	Epidemic potential of disease	Transmission route
		Reproductive rate (R0) and generation time
		Timing of symptoms and infectivity
		Disease transmissibility and human transmission
		Human/ animal interface
		Global risk
		Frequency of outbreaks
	Endemic potential	Risk of the disease becoming endemic
	Disease burden	Total cases/ year
		Total deaths/ year
		Case fatality rate or severity of disease
		Cases of long-term disability
	Disease impact on equity, society and economy	Disproportionate burden of disease in vulnerable groups
		Special benefits of vaccination for women and girls
		Health system impact – health care workers and services
		Social disruption – impact on vital services Economic impact – cost of epidemics (direct & indirect)
	Additional factors to be considered in disease risk and burden scenarios include: evolutionary potential of the pathogen; vector burden, impact of climate change and demographic changes	
Vaccine Impact and Feasibility	Epidemic risk reduction/ mitigation	Efficacy of vaccine
		Time to immunity
		Indirect effects (herd protection/transmission blocking)
	Implementation feasibility	Ease of storage
		Dosing schedule
		Acceptability in the target population

		Considerations relating to timely delivery and use (composition of stockpile and factors influencing timely case detection and verification, including surveillance and the availability of rapid, effective diagnostics)
	Long term benefit	Cross strain protection
		Duration of protection
	Stockpile attributes	Availability of medical countermeasures/ alternative interventions
		Stockpile turnover and value
Fit for Gavi & Partners	**Gavi comparative advantage**	Burden in Gavi countries as a proportion of global burden
		Need for Gavi financing and market shaping
		Complementarity with other initiatives
Financial Impli-cations	**Vaccine stockpile cost**	Annual cost of global stockpile
	Operational cost	Incremental in-country operational costs per outbreak response

3.5 Figure 3 illustrates how the framework would be applied to candidate vaccines. The Secretariat would identify candidate vaccines with WHO for 'living assessments' once preliminary safety and immunogenicity data is available (usually Phase 2a/b). A living assessment would include preliminary information on disease risk and burden, vaccine impact and feasibility and fit for Gavi. A full investment case would be triggered by one of the following: a clear timeframe and pathway to licensure, a WHO recommendation, or an urgent public health need. Recommendations on investment could be taken to the PPC/Board for decision as part of the VIS or separately.

3.6 The intention is that living assessments and investment cases would leverage existing analyses from partners particularly WHO, UNICEF, and the research community.

Figure 3: Development of 'living assessments' and full investment cases



3.7 Based on the process presented in Figure 3, it is proposed that the Secretariat would develop a full investment case for pandemic influenza for consideration by the PPC/Board in October/November 2018. The

Secretariat would begin to develop living assessments for Chikungunya, 2nd generation Ebola, Hepatitis E and Zika vaccines from 2019.[6]

3.8 For investment in pandemic influenza preparedness, the diversity and rapid evolution of influenza strains limits the value of a conventional stockpile. Recognising WHO's leadership and ongoing efforts in this area, the Secretariat has begun consulting with WHO and other experts to identify gaps and opportunities that leverage Gavi's comparative advantage. Amongst potential opportunities, two possible short-term investment options have been identified for detailed exploration by the Secretariat:

a) Support for seasonal immunisation in select high priority groups identified by WHO (such as pregnant women or healthcare workers) to help countries prepare for vaccination in a pandemic;
b) Complement existing efforts to increase vaccine supply to Gavi-supported countries in a pandemic.

3.9 The PPC highlighted the challenges and complexity of pandemic influenza preparedness and emphasised the need to continue to work in close collaboration with WHO.

3.10 Beyond the scope of this VIS, the VIS SC also encouraged Gavi to consider how existing investments in surveillance, immunisation and health systems support could contribute to pandemic preparedness, and commented on the importance and potential value of next generation influenza vaccines as and when they become available.

Section C: Actions requested of the Board

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

a) **Approve** narrowing the choice of possible vaccine investment options for further analysis within the endemic disease prevention category of the Vaccine Investment Strategy 2018 to meningitis (multivalent conjugate); hepatitis B birth dose; cholera; DTP boosters; RSV; rabies;

b) **Approve** the evaluation criteria for potential new investments in vaccines for epidemic preparedness and response and the approach for applying the criteria towards living assessments and investment cases as further described in Figures 2 and 3;

c) **Request** the Secretariat, in consultation with WHO and other experts, to develop an investment case for Gavi to support pandemic influenza preparedness for PPC and Board review.

[6] These four vaccines were selected based on WHO's May 2017 landscaping. If the approach is approved this list could be refreshed by WHO and may encompass relevant vaccines in earlier stages of development (such as R&D Blueprint and CEPI priority pathogens) as living assessments.

Annexes

Annex A: Implications/Anticipated impact

Additional information available on BoardEffect

Appendix 1 (in PPC Library – Additional materials for May 2018 meeting): Appendix 1 to Doc 10 *Stakeholder consultation summary*

Appendix 2 (in May 2018 PPC meeting book): Annex B to Doc 10 *Steering Committee meeting summaries*

Appendix 3 (in May 2018 PPC meeting book): Annex C to Doc 10 *Summary of key assumptions and analysis outcomes for vaccines for endemic disease prevention*

Appendix 4 (in PPC Library – Additional materials for May 2018 meeting): Appendix 2 to Doc 10 *Methodology for assessment of vaccines for endemic disease prevention*

Appendix 5 (in PPC Library – Additional materials for May 2018 meeting: Appendices 3a-3j to Doc 10 *Vaccine-specific summary analysis for each of 10 candidate vaccines for endemic disease prevention*