



Report to the GAVI Alliance Board

21-22 November 2013

Subject:	Vaccine Investment Strategy
Report of:	Nina Schwalbe, Managing Director, Policy and Performance
Authored by:	Judith Kallenberg, Senior Specialist, Vaccine Investment Strategy and Aurélia Nguyen, Director, Policy and Market Shaping
Agenda item:	08
Category:	For Decision
Strategic goal:	Affects all strategic goals

Section A Overview

1 Purpose of the report

- 1.1 This report seeks Board approval of the recommendations by the Programme and Policy Committee with regards to the Vaccine Investment Strategy. The paper discussed by the PPC at its meeting on 9-10 October 2013, which presents the outcomes from a 12-month long process of analysis and consultation, is attached.

2 Executive Summary – Update

- 2.1 The PPC reviewed the outcomes from the analyses and made the recommendations below to the Board. They also requested that the Secretariat include information for the Board on the on-going investment in current GAVI vaccines, in addition to new investments recommended as part of the VIS (see section 4 below).

3 Recommendations

- 3.1 The PPC, and where appropriate, the AFC and the EC recommended to the GAVI Alliance Board that it:
- (a) **Decide** to support new yellow fever vaccine campaigns and request the Secretariat to develop a process for the funding of individual campaigns on the basis of robust risk assessments.
 - (b) **Approve** a contribution to the global cholera stockpile for use in epidemic and endemic settings and to that end:

- i. Endorse a net increase in programme budgets for the global cholera stockpile by US\$ 114.5 million for the period 2014-2018. (This endorsement would constitute acknowledgement of such budget amounts as an indication of potential future expenditures but would not constitute a funding approval, decision, obligation or commitment of the GAVI Alliance or its contributors.);
 - ii. Approve a net increase of near-term programme liabilities for the global cholera stockpile (a sub-component of endorsed programme budgets) by US\$ 8.5 million for 2014;
 - iii. Note the opportunity for the GAVI Alliance to generate impact data based on the use of the cholera stockpile in emergency settings.
- (c) **Approve** an assessment of the feasibility of GAVI support for rabies vaccines (to be evaluated in the next Vaccine Investment Strategy process). A funding request for the outsourced assessment will be included as part of the Business Plan in 2015.
- (d) **Note** 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.
- (e) **Note** the potential public health impact of vaccinating pregnant women against seasonal influenza and the need to assess the emerging evidence of impact of vaccination on neonates, but decides not to open a funding window for influenza vaccines at this time.
- (f) **Approve** an amount up to US\$ 1.5 million to be added to the 2014 Business Plan to implement the Board's VIS decisions through Secretariat and partner activities as described in section 5.2 of Doc 07 to the PPC.

4 Additional information requested by the PPC

- 4.1 The Vaccine Investment Strategy is the outcome of an evidence-based prioritisation process, undertaken once every five years, to identify new vaccines with high priority for inclusion in the GAVI portfolio. Existing vaccine support programmes are not revisited. The projected cost and impact of GAVI's on-going investment in these programmes in the next strategic period will be presented in the replenishment process. Estimated, preliminary cost and impact projections for current vaccines (based on GAVI's strategic demand forecast version 7) are presented in table 1 below.

Table 1. Cost and impact estimates of current GAVI vaccines and VIS

Note: cost and impact estimates of current portfolio vaccines based on strategic demand forecast version 7

	Cost ¹ 2016-2020 (US\$ million)	Cost ¹ 2021-2030 (US\$ million)	Deaths averted / 100k vaccinated ²	Deaths averted 2016-2020	Deaths averted 2021-2030	Cost per death averted ³
HPV	453	1,552	1,479	0.5 million	2.2 million	1,200
Pneumo	2,919	4,568	668	1.3 million	2.8 million	2,600
HepB	1,582 (=penta)	2,588 (=penta)	768	2.5 million	3.7 million	700 (=penta)
Hib			576	1.6 million	3.0 million	
Rota	1,009	1,943	198	0.3 million	0.8 million	3,500
Other ⁴	679	147	24-63	0.3 million	0.0 million	2,600-12,000 ⁵
Cholera stockpile	89	-	-	-	-	-
YF campaigns ⁶	95	31	147	0.1 million		1,600
Malaria ⁷	287	2,274	541	0.1 million	1.0 million	3,100

1. Total cost to GAVI (procurement + vaccine introduction grant + operational cost support for campaigns)

2. Based on impact/coverage projections over 2015-2030;

3. Based on cost/impact projections over 2015-2030; takes into account full procurement and operational cost to GAVI and countries; rounded to nearest hundred

4. Other = Meningitis A, rubella campaigns, JE;

5. Rubella cost based on cost of MR

6. Campaigns considered in the VIS only

7. Subject to future Board approval

5 Risk and Financial Implications – Update

5.1 There are no additional implications other than those included in the PPC paper.



Report to the Programme and Policy Committee

9-10 October 2013

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Section A: Overview

1 Purpose of the report

- 1.1 In June 2013 the GAVI Alliance board reviewed an initial assessment of fifteen vaccine investment options and approved prioritisation of five vaccines for further evaluation by the Secretariat.
- 1.2 This report presents Secretariat recommendations for malaria, cholera, yellow fever, rabies and influenza vaccines. It provides an overview of the outcomes from a 12-month long process of analysis and consultation. It requests a Programme and Policy Committee recommendation on future vaccine investments for decision by the GAVI Board at its November meeting.

2 Recommendations

- 2.1 Taking into account recommendations by the Independent Expert Committee for the Vaccine Investment Strategy¹ the Secretariat requests the PPC to:

Recommend to the Board that it:

- (a) **Note** that based on the current assessment there is a strong case for GAVI support for a malaria vaccine, and that the Board expects to open a window if and when the vaccine is licensed, recommended for use by the WHO Strategic Advisory Group of Experts (expected in 2015) and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the PPC.

¹ See report in Annex D

- (b) **Decide** to support new yellow fever vaccine campaigns and requests the Secretariat to develop a process for the funding of individual campaigns on the basis of robust risk assessments.
- (c) **Approve** a contribution to the global cholera stockpile for use in epidemic and endemic settings and to that end:
 - i. Endorses, subject to confirmation by the Audit and Finance Committee that this is consistent with the Programme Funding Policy, a net increase in programme budgets for the global cholera stockpile by US\$ 114.5 million for the period 2014-2018. (This endorsement would constitute acknowledgement of such budget amounts as an indication of potential future expenditures but would not constitute a funding approval, decision, obligation or commitment of the GAVI Alliance or its contributors).
 - ii. Approves, subject to confirmation by the Audit and Finance Committee that this is consistent with the Programme Funding Policy, a net increase of near-term programme liabilities for the global cholera stockpile (a sub-component of endorsed programme budgets) by US\$ 8.5 million for 2014.
- (d) **Approve** an assessment of the feasibility of GAVI support for rabies vaccines (to be evaluated in the next Vaccine Investment Strategy process). A funding request for the outsourced assessment will be included as part of the Business Plan in 2015.
- (e) **Note** the potential public health impact of vaccinating pregnant women against seasonal influenza and the need to assess the emerging evidence of impact of vaccination on neonates, but decides not to open a funding window for influenza vaccines at this time.

2.2 The PPC is requested to:

Recommend, subject to endorsement by the Audit and Finance Committee, to the Executive Committee that it, in turn, recommend to the Board to approve an amount up to US\$ 1.5 million to be added to the 2014 Business Plan budget to implement the Board's VIS decisions through Secretariat and partner activities as described in section 5.2 of Doc 07.

3 Executive summary

Disease	Scope of potential vaccine investment	Time period	Objective	Programme cost to GAVI in 2014	Estimated programme cost to GAVI 2014-2020*
Cholera	Five-year investment in global cholera stockpile	2014-2018	Respond to outbreaks; stimulate global supply; assess value and feasibility of routine vaccination campaigns in endemic settings	\$8.5M	\$115M ²
Yellow fever	Financing of additional mass campaigns (~10)	From 2015	Prevent outbreaks; prevent ~100,000 future deaths by 2030	\$0	\$109M ³
Total				\$8.5M	\$223M
Malaria⁴	Vaccine support window for African countries (~34) ⁵	From 2016/7	Prevent ~1M future deaths by 2030	\$0	\$287M ⁶
Total				\$8.5M	\$510M
<i>Est. business plan costs (incl. outsourced rabies study)</i>				<i>\$1.5M</i>	<i>up to \$14M</i>

*This VIS covers the period through 2018 at which point in time the vaccine landscape will be re-evaluated. Cost estimates are presented through 2020 to align with the next strategic period. Cost estimates for programmatic and business plan costs are presented in Annex A per year and strategic period (through 2030).

² Includes vaccine procurement cost only

³ Includes vaccine procurement cost and operational cost grants (per current policies)

⁴ Contingent on future board approval per recommendation 2.1 (a)

⁵ Both vaccine licensure and a WHO recommendation are highly likely to be restricted to Africa. A vaccine indication for use in Asia is not expected in the near term.

⁶ Includes vaccine procurement cost and introduction grants (per current policies)

4 Risk implication and mitigation

Risk implications of recommendations

- 4.1 There is a risk that insufficient **resources** are mobilised to finance new vaccines. However, the cost of new investments is relatively small compared with current expenditures and the bulk of these costs (for a possible malaria vaccine rollout) would not take full effect until after 2020 when expenditures for other GAVI vaccines are expected to come down. Of note, GAVI involvement in malaria may open up new partnership and fundraising opportunities.
- 4.2 There is a risk that new vaccine investments would detract from efforts to increase immunisation **coverage** of vaccines currently supported. To mitigate this risk, GAVI would not compromise on its commitment to help countries introduce and scale up coverage of current vaccines. The latter is the primary goal of GAVI's health systems strengthening programme. Work is underway to assess how further improvements in coverage can be achieved.
- 4.3 There is a risk that **co-financing** requirements for the potential addition of a malaria vaccine would pose a financial burden on countries. An analysis of country expenditure projections, based on the current co-financing policy, shows that because most of the countries that would adopt the malaria vaccine are in the lowest income tier, the incremental co-payment for a malaria vaccine would result in a limited reduction in overall fiscal space in these countries (see section 14.1).
- 4.4 Related to the above (section 4.3), there is also a risk that possible future GAVI support would incentivise countries to take on the malaria vaccine without appropriate consideration of the incremental public health benefits relative to the price. This risk would be mitigated by rigorous assessment on a country by country basis of the appropriate mix of interventions for malaria control as part of the application review process. Of note, a review of the co-financing policy to be conducted in 2014 will also re-explore if there are ways to link co-payments to cost and/or cost effectiveness of vaccines requested by countries as this risk applies to other GAVI supported vaccines as well.
- 4.5 There is a risk that the leading **malaria** vaccine candidate does not get licensed, and/or that based on final trial data the impact of a malaria vaccine is significantly lower than currently assumed and no longer merits rollout in endemic countries, and/or that assumptions underlying country demand projections are inaccurate and that true demand would be lower. This is mitigated by the fact that eventual implementation of a malaria country support window will be approved only if and when the vaccine is licensed, recommended for use by the WHO Strategic Advisory Group of Experts (expected in 2015) and WHO pre-qualified, taking into account updated projections of impact, cost and country demand as reviewed by the PPC.

- 4.6 Not committing to support maternal **influenza** vaccination - per VIS recommendations - could be a missed opportunity to introduce this vaccine in countries if the value of this intervention is confirmed (studies to be completed in 2014). However, it is likely that other activities would need to happen before a country support window could be opened in the event that influenza vaccine trials demonstrate substantial impact. For example, regulatory and logistical hurdles would need to be overcome and country demand would need to be generated. This might take several years and would thus be aligned with the timing of the next VIS.
- 4.7 Not committing to opening a **rabies** country support window - per VIS recommendations - risks maintaining the status quo of limited access to rabies vaccination (and rabies immunoglobulins) in GAVI-eligible countries. However, this is outweighed by the risk of failed or inefficient implementation as described in Section 11.4. Moreover, the proposed investment in a feasibility assessment through observational studies of rabies vaccination could accelerate investment decisions by GAVI (i.e. in the next VIS) or by other funders.

Risk implications of not approving the recommendations

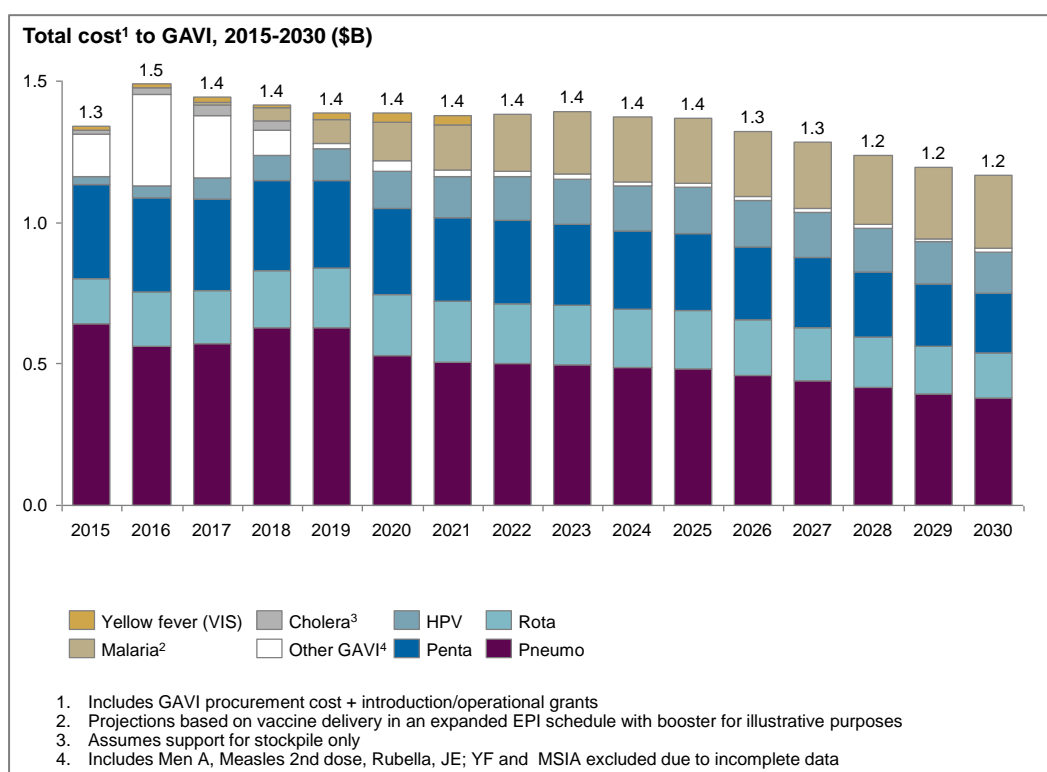
- 4.8 If the GAVI Board does not open a country support window once a **malaria** vaccine becomes available and recommended for use, GAVI-eligible countries are likely to maintain their interest in the vaccine but may not be able to afford introduction. Other agencies such as the Global Fund to fight Aids, TB and Malaria (GFATM) may consider funding the vaccine to meet country demand. Such agencies would also have to raise resources for this initiative and may have more limited expertise and/or experience in supporting new vaccine introduction.
- 4.9 By withholding support for the global **cholera** vaccine stockpile GAVI may miss an important opportunity to leverage its market shaping power to improve the global response and preparedness for cholera outbreaks.
- 4.10 In the absence of GAVI support for new **yellow fever** campaigns countries may not be able to implement such campaigns and would face an increased risk of yellow fever outbreaks.

5 Financial implications: Business plan and budgets

- 5.1 Estimated **programme costs** of new investments in cholera, yellow fever and malaria are presented in Annexes A and B. These costs will be included in GAVI's long-term financial projection updates to the Board. The endorsement of multi-year programme budgets and the approval of near-term programme liabilities will be sought through programme funding requests presented to the Board/EC for their approval and in line with the Programme Funding Policy.
- (a) Programme costs in 2014 amount to US\$ 8.5 million for the cholera stockpile (see funding request in 2.1.c.ii).

- (b) Programme costs in 2015 would amount to US\$ 17 million for the cholera stockpile and an estimated US\$ 14 million for the yellow fever campaign funding window.
- (c) If a malaria window is approved, programme expenditures for new investments (cholera, yellow fever, malaria) through 2020 would amount to approximately US\$ 510 million or 7% of total vaccine expenditures planned for this period. Malaria would become GAVI's fourth largest expenditure after pneumo, penta and rota in 2015-2030.

The figure below presents total vaccine programme costs through 2030, including for a possible malaria country support window.



5.2 Business plan costs for the period through 2020 are estimated to amount up to US\$ 14 million and would cover the following:

- (a) GAVI Secretariat management of programme design, demand forecasting, country communication, vaccine introduction support and M&E activities related to cholera stockpile contributions, yellow fever campaigns, and potentially a malaria country support window.
- (b) Partner support for the implementation, management and M&E of the cholera stockpile, yellow fever risk assessments and stockpile management, and potential support for a malaria window.

Cost for 2014 would require up to US\$ 1.5 million.

Section B: Content

6 Background

- 6.1 GAVI's mission is to save children's lives and protect people's health by increasing access to immunisation in poor countries. At the heart of GAVI's business model is the provision of new and under-used vaccines for use in national immunisation programmes. Support for a selected menu of vaccines is offered and awarded in response to requests from eligible country governments. In 2007, the Board initiated the Vaccine Investment Strategy (VIS) process as a way to determine which vaccines to include in this menu and which to exclude in light of limited resources and relative public health priorities.
- 6.2 Prior to 2007 the Board decided to open 'country support windows' on the basis of investment cases for individual vaccines⁷. Through the VIS approach the Secretariat undertakes a similar evidence-based assessment of potential new investments, within an overall strategic framework for decision-making on a comprehensive set of options reviewed once every five years. This approach helps to prioritise GAVI's resources and pre-empt first-come-first-serve decisions. In addition, predictable programming helps countries understand what vaccines may and may not be feasible to introduce and inform planning by Ministries of Health and Finance. Upfront decisions on future vaccine support also give an important signal to vaccine manufacturers, which helps to accelerate development timelines and boost investments in expanding production capacity. Finally, planning and projecting ahead allows GAVI to provide donors with a predictable forecast of GAVI's future financial needs.
- 6.3 The 2008 VIS process led to the GAVI Board's decision to include Japanese Encephalitis (JE), typhoid, human papillomavirus (HPV), and rubella vaccines in the GAVI portfolio. Support windows for HPV and rubella vaccines have since been opened. Now that a suitable vaccine is highly likely to be pre-qualified by the World Health Organization (WHO) by the end of 2013, the Secretariat will recommend to the PPC that a support window for JE vaccines be opened for eligible countries in Asia at the GAVI Board meeting in November. A support window for typhoid vaccines will be opened once a suitable conjugate vaccine is pre-qualified. Cost estimates of the rollout of JE and typhoid vaccines are included in current financial projections.
- 6.4 Resources committed to help countries increase coverage of these and other vaccines in national immunisation programmes (through GAVI's health systems strengthening support window) will not be diverted to finance new vaccines. The Secretariat will undertake to raise additional resources to finance successful applications for new vaccine support.

⁷ Support for pneumococcal, rotavirus and meningococcal A vaccines as well as time-limited support for the polio stockpile and campaigns with yellow fever, measles and tetanus vaccines was decided in this way.

- 6.5 Non-immunisation commodities such as antibiotics, oral rehydration solution (ORS), zinc and nutritional supplements have not been evaluated in the VIS. Possible GAVI support for such interventions will be explored as part of the 2016-2020 Strategy development process. However, the context of existing preventive or therapeutic interventions in the disease areas being reviewed (e.g. cholera, malaria) is considered in the respective vaccine assessments.

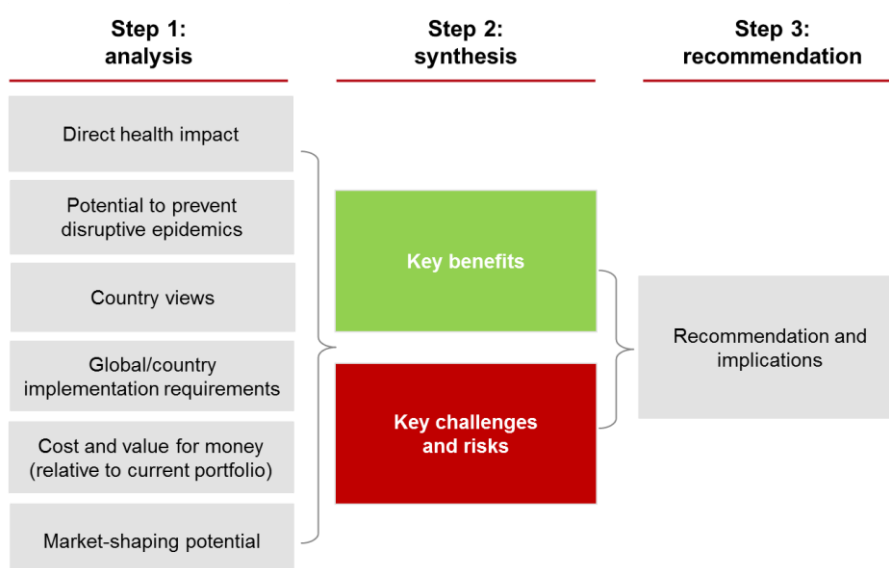
7 Process

- 7.1 The VIS process was led by a Secretariat project team assisted by the Boston Consulting Group, and involved literature reviews, quantitative and qualitative analyses, and numerous consultations with a large number of disease and vaccine experts, GAVI Alliance partners and stakeholders (see section 18). Regular review meetings were held with a Technical Consultation Group (TCG) comprised of technical partners and stakeholders and with an Independent Expert Committee (IEC). The TCG provided advice on the scope and content of vaccine evaluations and consultations, evolving vaccine-specific questions, and the relative importance of different strategic considerations for decision-making (see section 18.2). The IEC validated data inputs and methodologies, including modelled vaccination strategies, impact modelling assumptions and assessments of implementation feasibility (see section 18.3). A report by IEC Chair Professor Bob Black with vaccine-by-vaccine recommendations to the Secretariat is attached as Annex D.
- 7.2 VIS recommendations have been developed in a two-step process; in **phase I** - from November 2012 to June 2013 - the Secretariat assessed an initial list of vaccine investment options, provided by WHO⁸. This 'long list' included available vaccines not yet in the GAVI portfolio (e.g. cholera and rabies), vaccines for which there was a potential case for additional GAVI investment (e.g. yellow fever campaigns), and 'pipeline' vaccines in late stages of development (e.g. malaria). The GAVI Alliance Board in June 2013 endorsed a prioritisation approach for phase I, focusing on 1) health impact (deaths and cases averted), 2) epidemic potential, and 3) value for money (procurement cost per death averted) and requested the Secretariat to further assess five vaccine investment options in phase II: cholera, influenza for maternal vaccination, malaria, rabies vaccine and yellow fever campaigns. Separately, the Board agreed that the GAVI Alliance should play a lead role in the introduction of Inactivated Polio Vaccine (IPV) into routine immunisation services in countries where GAVI currently works, as recommended by WHO and as part of the Polio Eradication Endgame Strategic Plan. IPV is therefore no longer considered as part of the VIS and related investment decisions will be taken separately by the GAVI Board (see paper 11 for this meeting).

⁸ Cholera, dengue, DTP (booster), EV71 (Hand, Foot, Mouth disease), hepatitis A, hepatitis B (birth dose), hepatitis E, seasonal influenza (maternal), malaria, measles (for children between 5-15Y), meningococcal disease (serogroups CYW), mumps, poliomyelitis (IPV), rabies (post-exposure prophylaxis) and yellow fever (mass campaigns).

- 7.3 The Board in June highlighted the importance of **dengue**. However, (pipeline) dengue vaccines were not prioritised because of a relative lack of evidence on the burden of dengue in GAVI eligible countries, especially in Africa, and the likelihood of an effective vaccine becoming available in this time period. Dengue remains an important area for monitoring, and data gaps will need to be addressed to facilitate future decision-making. In the meantime GAVI will continue to be engaged in the evolving dengue vaccine pipeline.
- 7.4 Whereas phase I focused on relative measures, in **phase II**, the Secretariat evaluated the absolute merits of each shortlisted vaccine and reviewed these in the context of the current GAVI portfolio. For each vaccine the Secretariat conducted detailed assessments of mortality impact, potential to reduce epidemics, country views, implementation feasibility, cost, cost per death averted ('value for money') and GAVI market-shaping potential (see figure below). Five separate **vaccine presentations** (available on myGAVI) summarise the analytical approaches and findings from these assessments. These presentations include information on: modelled scenarios; estimates of impact, cost and cost per death averted; impact modelling method(s) and demand forecasting assumptions; sensitivity analyses of impact and cost estimates; findings from country consultations; implementation challenges and implications for GAVI policies, EPI programmes, surveillance; key benefits and challenges of GAVI support for this vaccine; investment recommendations; and implications of a GAVI decision not to invest in this vaccine.

Vaccine assessments and framework for decision-making in VIS phase II



- 7.5 Also available on request⁹ are detailed methodologies used for analyses of demand, cost, health impact, operational cost and cold chain capacity,

⁹ Please request any or all of these materials through: vis@gavialliance.org

fiscal space, and a literature review of the cost-effectiveness of vaccines and alternative interventions.

8 Malaria

- 8.1 Antimalarial interventions such as insecticide-treated bednets (ITNs) and indoor residual spraying (IRS) have seen a massive scale up in the last decade. Despite this success the remaining burden is still high, and malaria continues to a leading killer of children in GAVI-eligible countries. In some places malaria has resurged, underlining the fragility of success achieved to date. The World Malaria Report 2012 estimates that malaria caused 660,000 deaths in 2010, including 596,000 deaths in Africa¹⁰, 91% of these in children under five. In addition to its impact on health malaria poses a heavy economic burden on countries. Drug and insecticide resistance are major emerging threats to malaria control.
- 8.2 A candidate vaccine (RTS,S) is currently in phase III clinical trials in eight African countries. RTS,S will be the world's first vaccine against a parasite and will likely have lower efficacy and/or duration of protection than 'traditional' vaccines. However, due to the heavy burden of malaria and continued high death rates in young children, the impact of a partially efficacious vaccine is likely to be substantial in terms of cases and hospitalizations prevented. As such, it is not vaccine efficacy in and of itself but public health impact that would drive decision-making. The impact of RTS,S is incremental to the impact projected from ITNs and IRS and the vaccine would be a complement to these and other existing interventions as part of comprehensive malaria control programmes.
- 8.3 Licensure of RTS,S is expected in 2015. A WHO recommendation on the use of RTS,S is expected in 2015 and pre-qualification potentially in 2015-2016. Both vaccine licensure and the WHO recommendation are highly likely to be restricted to Africa given that all clinical trial data is from Africa. A vaccine indication for use in Asia is not expected in the near term although consultations indicate that several Asian countries have a strong interest in malaria vaccines relevant to their region. As such, GAVI will continue to monitor and encourage product development for this region. Development timelines for other malaria vaccine candidates are ten years or so behind RTS,S.
- 8.4 RTS,S is being tested in two age groups and appears to have the highest impact in children between 5-17 months of age. SAGE has strongly supported investigation of various immunisation schedules.¹¹ This could include a scenario with one new visit for consideration if the 5-17 months age group becomes the focus of WHO recommendations, with other visits being combined with vitamin A administration and the existing 9 month visit for measles. This ties in with on-going work by WHO to expand the EPI schedule in order to reduce the number of child injections per visit and to allow for delivery of additional interventions and longer follow-up, e.g. to

¹⁰ Down from 682,000 deaths in Africa in 2000

¹¹ SAGE meeting report from April 2013 (<http://www.who.int/wer/2013/wer8820.pdf>)

reinforce nutrition and hygiene messages at the transition from exclusive breastfeeding.

- 8.5 The current demand forecast assumes that 34 GAVI-eligible countries in Africa would introduce the vaccine over the course of ten years from the first year of introduction in 2017 (detailed forecast in the malaria presentation on myGAVI). Based on currently modelled estimates, RTS,S has the highest potential among vaccines considered in this investment strategy period to increase GAVI's impact on public health. Modelling by the Swiss Tropical and Public Health (STPH) Institute and Imperial College suggests that approximately one million child deaths could be prevented in GAVI-eligible countries in Africa¹². This impact is incremental to the impact of existing prevention measures such as bednets. For every 100,000 children vaccinated with the malaria vaccine, 550 deaths could be prevented, compared with 600 for Hib and 200 for rotavirus vaccines. Sensitivity analyses show that if efficacy wanes faster than assumed, impact will be lower but still similar to that of rotavirus vaccines (see Annex C, figure 1)¹³.
- 8.6 The cost per death averted by malaria vaccines is estimated around \$3,000, which falls within the range of other GAVI vaccines (see Annex C, figure 2). As the primary buyer of malaria vaccines, GAVI would have important market-shaping opportunities and would develop a supply and procurement roadmap to guide engagement in this area.
- 8.7 A review of the literature on cost-effectiveness of malaria interventions (available on request¹³) shows that insecticide-treated bednets, indoor residual spraying, treatment and intermittent preventive treatment are cost-effective interventions. Donors have invested heavily in these in the last decade, which has resulted in substantial scale-up since 2000. However, coverage and use of these interventions is highly variable, often inequitable and has plateaued in many GAVI-eligible countries despite strong, continued commodity support¹⁴. Challenges in further scale up of bednets and other interventions are linked to demand issues and weaknesses in delivery systems. In addition, increasing resistance to antimalarial drugs and insecticides used in bednets is of great concern.

¹² For illustrative purposes, assumes vaccine administration in children 5-17 months old ('expanded EPI') with booster scenario; with vaccine efficacy of 56% and 3 years to half initial efficacy (exponential decay rate) based on publicly available trial results. Estimates for additional scenarios are available in the malaria presentation on MyGAVI.

¹³ Please request this document through: vis@gavialliance.org

¹⁴ The proportion of households in Sub-Saharan Africa owning at least one insecticide treated net (ITN) increased from 3% in 2000 to 53% in 2011, and remained at 53% in 2012. The proportion of the population at risk that sleeps under an ITN was 33% in 2012. In the majority of countries in Sub-Saharan Africa only 25-50% of the population at malaria risk is protected by ITNs or indoor residual spraying (IRS) and coverage has reached a plateau (source: World Malaria report 2012)

- 8.8 Based on a comprehensive assessment of the available evidence¹⁵ and a positive recommendation by the IEC, there is a strong case for adding malaria vaccines to the GAVI portfolio. This is based on:
- (a) the substantial impact that can be achieved by preventing a significant portion of malaria deaths in young children (based on currently modelled estimates endorsed by the IEC);
 - (b) strong country demand linked to a high-burden and high-visibility disease and;
 - (c) an important market-shaping opportunity for GAVI.
- 8.9 The actual opening of a country support window will be subject to:
- (a) vaccine licensure and a WHO SAGE recommendation on use (expected in 2015)
 - (b) vaccine prequalification (expected in 2015-2016)
 - (c) confirmation of the current positive assessment of malaria vaccines, taking into account updated projections of impact, cost and country demand (based on final trial results expected in 2014), as reviewed by the PPC.
- 8.10 Sending a signal now is critical for market-shaping activities and will enable the Secretariat and partners to explore preparatory and fundraising activities in order to ensure efficient implementation as soon as conditions are met. Malaria vaccines would be GAVI's fourth largest expenditure in 2015-2030 at a cost of roughly US\$ 2.6 billion, after pentavalent, pneumococcal and rotavirus vaccines. Expenditures in the upcoming strategic period 2016-20 would amount to approximately US\$ 287 million.
- 8.11 A malaria vaccine cannot replace other interventions and must be viewed as part of a comprehensive approach to malaria control. Countries would need to weigh and demonstrate in their application consideration for the relative cost-effectiveness and scalability of different interventions to maximise impact on malaria. Conditionalities of malaria vaccine support such as minimum required bed net coverage could be explored as part of the development of application guidelines.
- 8.12 At the community level, malaria vaccine administration could bring important indirect benefits as it offers an opportunity to deliver and reinforce compliance with other malaria control interventions. Because of high awareness and likely strong community demand, consultations indicate that introduction of this vaccine may also boost coverage of EPI vaccines more broadly¹⁶.

¹⁵ Detailed malaria assessment available on MyGAVI

¹⁶ Source: consultations with malaria control experts and country stakeholders

9 Yellow fever

- 9.1 GAVI has provided support for routine yellow fever vaccination since 2000. Following approval of a yellow fever investment case in 2005 and a subsequent one in 2008, GAVI also supported mass, preventive campaigns in twelve “A” risk countries (identified by WHO¹⁷) between 2006-2012. In addition, GAVI helped create the international stockpile and has supported ~20M doses for yellow fever outbreaks. WHO currently recommends new yellow fever campaigns in nine GAVI-eligible “B” risk countries and in previously unvaccinated districts in one GAVI-eligible “A” risk country, to be implemented during 2015-2021¹⁸. Previous GAVI support for campaigns was capped based on the original investment case plan and budget. More recent WHO assessments indicate that the projected need for mass campaigns was underestimated previously. In light of the depletion of funds allocated for campaigns in the original investment case and in the absence of an existing funding mechanism for yellow fever campaigns, the Board asked the Secretariat to review this additional investment in the context of the VIS.
- 9.2 Yellow fever is an acute viral disease transmitted by mosquitoes, for which there is no specific treatment. WHO estimates yellow fever causes around 30,000 deaths each year, mainly in Africa. In recent years, WHO has reported a resurgence of the disease. Vaccination is the most important preventive measure; a single dose of vaccine is sufficient to confer life-long protection against yellow fever disease. Additional mass campaigns between 2015-2021 are estimated to prevent 100,000 deaths (on top of the impact from routine vaccination in these countries). Importantly, this strategy would significantly reduce the risk of future outbreaks by covering those who have been missed or are not targeted through routine vaccination.
- 9.3 An emergency stockpile would also be maintained to be able to respond to epidemics. Such epidemics would most likely occur in the countries targeted for mass campaigns. Areas covered by reactive vaccination would not need to be re-vaccinated during subsequent preventive campaigns. At the end of each year, any doses left in the stockpile would be used for preventive campaigns in targeted countries.
- 9.4 In light of the public health value of yellow fever vaccination, a relatively low cost per death averted and low projected total cost of additional campaigns, the Secretariat recommends that GAVI continues to fund yellow fever campaigns as needed. This investment is also expected to strengthen GAVI’s market shaping power towards stabilising global yellow fever supply. Due to the changing nature of yellow fever epidemiology robust risk assessments are of critical importance to guide resource allocation. The Secretariat recommends that a robust process for planning

¹⁷ WHO defines “A” risk countries as countries reporting multiple YF outbreaks (≥ 2) in the previous 30 years; “B” risk countries are countries reporting at least one YF event in the previous 50 years and with evidence of YF circulation.

¹⁸ More details in yellow fever assessment on myGAVI

and monitoring campaigns is put in place and that funding for individual campaigns be released on the basis of country applications and risk assessments, reviewed by the Independent Review Committee.

10 Cholera

- 10.1 Cholera is a severe diarrhoeal disease that can kill within hours if left untreated. It affects the most vulnerable in urban slums and rural areas without access to clean water. WHO estimates that the burden of cholera is around 100,000-120,000 deaths per year. Many cases go unreported and most deaths occur in the poorest populations without rapid access to health services due to the quick progression of disease. Cholera can be treated effectively with timely rehydration therapy. Further, ensuring safe water and adequate sanitation are critical for preventing the disease. However, these needs are often not met in impoverished areas. The majority of cases reported to WHO are outbreak-related with 40 to 50 confirmed outbreaks each year. Epidemics can be a significant burden on health systems and divert national resources. Based on reported cases in recent years, the estimated population at risk in countries that suffered outbreaks ranged from 5 to 15 million.
- 10.2 Cholera vaccines were evaluated but not prioritised in the VIS 2008 because the available (~~injectable~~) vaccine product was not considered suitable for use in GAVI countries. Since then a safe and efficacious, relatively low-cost, oral cholera vaccine has come onto the market and has been pre-qualified by WHO in 2011. Due to the wide target age-group and relatively short duration of protection, periodic mass vaccination campaigns are the most practical option for delivering cholera vaccines. WHO recommends that oral cholera vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic and should be considered for outbreaks in areas at risk. Where resources are limited, immunisation should be targeted at high-risk children¹⁹. Oral cholera vaccines can thus be used in pre-emptive mass vaccination campaigns to prevent outbreaks in endemic countries, or in “reactive” campaigns after reported cases of cholera.
- 10.3 Based on an assessment of disease burden and country consultations, we estimate that roughly twenty endemic GAVI-eligible countries would apply for GAVI support for periodic, pre-emptive campaigns in 2015-2030. Such campaigns would be implemented in high risk areas in a sub-set of the population (e.g. between 1-15 years old). The projected impact of such campaigns in terms of deaths averted is unclear due to uncertainty about several input variables (e.g. target populations, underlying disease burden, case fatality rates and herd effects).
- 10.4 There is limited experience with periodic, preventive cholera campaigns and there are significant uncertainties around appropriate implementation strategies and, related to this, the projected impact of a GAVI investment.

¹⁹ WHO. Meeting of the Strategic Advisory Group of Experts on immunization, October 2009 – conclusions and recommendations. Weekly epidemiological record 2009; 50: 526-528.

In addition, implementation would come with relatively high operational costs linked to recurring campaigns²⁰. This increases the cost per death averted relative to other GAVI vaccines and raises questions about the sustainability of a long-term investment in periodic campaigns, in particular in the absence of a co-financing requirement for countries (per GAVI's current policies on campaign financing). In light of these considerations the Secretariat recommends that GAVI does not open a funding window for periodic ('routine') cholera vaccine campaigns.

- 10.5 Instead, the Secretariat recommends an investment in the global cholera vaccine stockpile, which was created in 2013 and is managed by WHO.²¹ This would serve three important objectives: 1) break the current cycle of low demand – low supply and significantly increase global supply, 2) reduce disruptive epidemics in a significant number of GAVI-eligible countries, 3) strengthen the evidence base for periodic, pre-emptive campaigns to facilitate reconsideration of a country support window in the next VIS process. This last objective would be achieved by using a small number of doses from the stockpile in pre-emptive campaigns in endemic countries with appropriate monitoring and evaluation activities to establish the public health value and operational feasibility of this approach.²² The Secretariat recommends an initial contribution of approximately US\$ 115 million over 2014-2018 (see Annex B) to gradually increase the stockpile to 20 million doses per year. Some of these costs may be reimbursed by countries under a revolving fund mechanism. All GAVI-eligible countries would be eligible to apply for stockpile support in case of an outbreak.

11 Rabies

- 11.1 Rabies is a fatal, vaccine-preventable infection. The disease is usually transmitted by dog bites and mostly affects poor children in rural areas. WHO estimates that rabies causes around 60,000 human deaths per year. Once symptoms appear, several weeks after an infectious bite, rabies cannot be treated and is almost invariably fatal within days. The terminal stage of the disease is characterised by increasing anxiety, agitation, hydrophobia (abnormal fear of water) or paralysis due to progressive inflammation of the brain.
- 11.2 Modern rabies vaccines have been in the market for more than 30 years. If given to bite victims rapidly after exposure to a rabid animal, rabies vaccines can effectively prevent death by triggering an immune response against the infection; so-called 'post-exposure prophylaxis' (PEP). For bites that break the skin WHO additionally recommends 'passive' immunisation by injection of immunoglobulins in the wound to strengthen the body's immune response.

²⁰ Currently estimated at approximately \$2.00 and \$1.15 per target person in campaigns in African and non-African countries respectively

²¹ Currently the stockpile holds 2 million doses, which is significantly below current demand

²² GAVI-supported rotavirus surveillance sites may be leveraged for cholera surveillance

- 11.3 Most rabies deaths occur in low-income countries where access to rabies PEP is limited. The vaccine is often only available in the private sector at a cost commonly exceeding \$50 per course. Importantly, rabies vaccine is often not available at peripheral levels where most bites occur and lack of access is cited as a key reason for rabies mortality. Rabies immunoglobulin is even more scarce and usually only available at a high cost to the patient (approximately \$60-80 per course)²³.
- 11.4 The severe nature of rabies, the fact that it is fully vaccine-preventable and the significant number of global deaths make for a compelling public health case; support for rabies vaccine in GAVI-eligible countries could potentially avert an estimated 200,000 deaths over 2015-2030²⁴. However, while the vaccine itself is 100% effective, it is unclear how GAVI could plan, fund and scale up rabies PEP provision programmatically. There are critical gaps in knowledge about existing levels of rabies vaccine (and immunoglobulin) provision, treatment-seeking behaviour, treatment compliance, user fees and barriers to access.
- 11.5 In light of these questions and potentially complex implementation requirements the Secretariat recommends that GAVI does not open a funding window for rabies vaccines at this time. These same questions were highlighted five years ago when rabies was also shortlisted for potential GAVI support in the previous VIS process. Annual rabies deaths have persisted since. To avoid that the same uncertainties around implementation feasibility prevent GAVI from making an informed investment decision in the next VIS, the Secretariat recommends that GAVI invests in an outsourced assessment to address key questions around the feasibility of potential future GAVI support, and to catalyse progress in this vaccine-preventable disease area. Such an assessment is estimated to cost up to US\$ 3 million and would be implemented in advance of the next VIS process in 2018.

12 Influenza

- 12.1 Influenza is an acute viral infection that spreads easily, affects all age groups, and causes annual epidemics worldwide due to its mutating strains. Most people recover without needing treatment but influenza can cause severe illness and death in high risk populations, in particular in children <2 years of age, pregnant women and elderly people. The great majority of deaths from influenza occurs in developing countries. In pregnant women, who have increased risk of severe disease and death from influenza, the infection may also lead to complications such as stillbirth, neonatal death, preterm delivery, and decreased birth weight²⁵.
- 12.2 WHO recommends that for countries considering or implementing seasonal influenza vaccination, pregnant women should have the highest priority. Maternal influenza vaccination could have an impact on the

²³ Source: expert and stakeholder interviews

²⁴ See rabies assessment on myGAVI for more details

²⁵ Source: WHO Weekly epidemiological record, No. 47, 23 November 2012

mother and newborn through continued circulation of maternal antibodies in the infant up to 6 months after birth. Few mothers currently receive the vaccine in GAVI-eligible countries.

- 12.3 The secretariat reviewed a potential GAVI investment in funding seasonal influenza vaccines for pregnant women. If implemented across a broad range of GAVI-eligible countries, this could potentially prevent 210,000 deaths in women and infants. This estimate does not take into account possible additional benefits to the foetus. There is initial evidence of such benefits which could significantly increase the overall impact.
- 12.4 There is a high degree of uncertainty around the estimates of influenza vaccination impact. Evidence of vaccine efficacy in the under-6 month old population is currently based on a single randomised controlled trial with a small sample size from Bangladesh and observational studies from developed countries. Evidence of effects on the foetus is even more limited and therefore these effects are not currently included in the deaths averted estimates presented. The potential effects on the foetus and infants under 6 months are the subject of three large on-going randomised controlled trials with results expected in 2014.
- 12.5 Global supply capacity of influenza vaccines greatly exceeds potential demand from GAVI-eligible countries. However, other supply challenges exist. Manufacturers supply season-specific influenza vaccines to each hemisphere with an indicated shelf life of 6-12 months; only to be used in the current season. To maximise the benefits to mothers and infants, manufacturers would need to adapt to year-round supply cycles. This would require a change of 'business as usual' for influenza vaccine manufacturers and/or changes in in-country stock management if the vaccine is released only once a year.
- 12.6 Based on limitations in the current data the Secretariat recommends that the Board does not open a funding window at this time. If currently ongoing studies confirm a substantial impact on fetal, neonatal and infant mortality, there could be a strong case for future GAVI support to be reviewed in the next VIS process in 2018. In that case, the Board may want to consider preparatory activities to facilitate re-evaluation of influenza vaccine support in the next VIS process. Such preparatory activities could focus on acquiring additional data on implementation feasibility and addressing questions relating to the logistics of seasonal vaccine supply, surveillance and strain matching, and optimal delivery strategies for pregnant women.
- 12.7 The importance of a vaccination platform for pregnant women may further increase when other maternal vaccines (e.g. RSV²⁶) become available in the future. Other benefits of potential future support for maternal influenza vaccination include increased country preparedness for a pandemic.

²⁶ Respiratory syncytial virus

13 Next steps

- 13.1 Following the GAVI Alliance Board meeting in November 2013, the Secretariat will include the projected cost of approved new vaccine investments in its financial projections for donors. In addition, the Secretariat will work with partners through the business plan to start implementing the recommendations as specified below.
- (a) Malaria: the Secretariat will actively monitor regulatory and technical review developments and closely coordinate with WHO and other partners on the outcomes from these processes. If conditions specified in 2.1 (a) are met, the Secretariat will recommend the opening of a country support window to the Board. The Secretariat would also build on its initial engagement with the Global Fund to Fight Aids, Tuberculosis and Malaria (GFATM) to coordinate the introduction of new vaccines as part of integrated malaria control programmes and to explore opportunities for harmonised global procurement strategies (e.g. for GAVI eligible and non-eligible countries).
 - (b) Yellow fever: as described in paragraph 9.4 the Secretariat will revisit the yellow fever campaign funding process to guide the planning and funding of future risk assessments and campaigns.
 - (c) Cholera: the Secretariat will set up appropriate structures and processes for GAVI funding of the global stockpile. This would include agreement with WHO on the management of an enlarged global stockpile, monitoring and evaluation of the use of stockpile doses in outbreaks, and monitoring and evaluation of the use of stockpile doses in pre-emptive campaigns in endemic countries for learning purposes, as described in paragraph 10.5.
 - (d) Rabies: the Secretariat will issue a request for proposals in 2014 for an observational study to address gaps in knowledge about the feasibility of GAVI support for rabies vaccines as described in paragraph 11.5.

Section C: Implications

14 Impact on countries

- 14.1 Fiscal space: an analysis of country expenditure projections shows that the possible introduction of a malaria vaccine would not create significant fiscal space limitations. On average in low-income countries, the share of government health budgets that is allocated to vaccine procurement (GAVI-supported and 'traditional' vaccines) would increase from 0.7% to 0.8% with the introduction of a malaria vaccine, as per current co-financing policies. For countries in the intermediate group this share would go from 1.2% to 1.3%. More detail on this analysis is available on request²⁷.

²⁷ Please request this document through: vis@gavialliance.org

- 14.2 Operational costs have been quantified for each vaccine as the incremental immunisation-specific, non-vaccine cost associated with the introduction and recurrent delivery of routine vaccines and the administration of campaigns. Incremental costs reflect financial costs mainly (rather than economic costs)²⁸ and are shown to be quite small in the case of routine vaccines based on preliminary new data from country studies. Estimated operational costs are presented in the individual vaccine assessments. Cold chain implications have been assessed as the incremental volume requirement of new vaccines as compared with other GAVI vaccines. Malaria vaccines would require a modest incremental increase in cold chain capacity (smaller than cold chain capacity required for pentavalent and rotavirus vaccines). A description of the operational cost and cold chain analyses is available on request²⁹.

15 Impact on GAVI stakeholders

- 15.1 Financial projections relating to VIS recommendations will be included in the annual financial forecast update that will be provided to the Board in November 2013. Resource needs for the next strategic period, including a potential malaria country support window, will be included in financial projections for donors in the upcoming replenishment round.
- 15.2 GAVI's technical partners will be involved in different components of the implementation of VIS recommendations, including but not limited to yellow fever risk assessments, cholera stockpile management and related M&E activities, and support for the possible opening of a country support window for malaria vaccines (e.g. possible initiation of an expanded EPI schedule if recommended by SAGE on the use of malaria vaccine).

16 Impact on Secretariat

- 16.1 Secretariat implications of VIS recommendations are described in section 13.

17 Legal and governance implications

- 17.1 Once the Board approves the recommendations, appropriate legal and grant arrangements will be made with partners such as WHO and countries to implement the recommendations.

18 Consultation

- 18.1 The VIS process involved numerous and inclusive consultations with experts, GAVI Alliance partners and stakeholders. Over one hundred expert and manufacturer consultations were conducted through in-person meetings, telephone interviews or in writing using structured questionnaires. A full list of institutions and individuals who provided

²⁸ Economic costs reflect the opportunity cost of resources used to deliver an intervention, whether or not they incur a financial expenditure

²⁹ Please request this document through: vis@gavialliance.org

advise and input into the VIS process is available on myGAVI. In addition, regular review meetings were held with a Technical Consultation Group and Independent Expert Committee as described in paragraphs 18.2 and 18.3. Finally, a significant effort was made to seek the views of GAVI-eligible countries as described in paragraphs 18.4 and 18.5. The Secretariat is grateful for the many contributions received through these consultations.

- 18.2 A Technical Consultation Group (TCG) for the VIS provided advise on the scope and content of vaccine evaluations and consultations, evolving vaccine-specific questions, and the relative importance of different strategic considerations for decision-making. The TCG consisted of stakeholders and representatives of GAVI Board constituencies including WHO, UNICEF, the Bill and Melinda Gates Foundation, eligible countries, donors, civil society organisations, and technical and research institutes.
- 18.3 An Independent Expert Committee (IEC) for the VIS was established to validate data inputs and methodologies used, with a focus on modelled vaccination strategies, impact modelling assumptions and implementation feasibility assessments. Members served in their personal capacity with expertise in a variety of areas including but not limited to epidemiology, immunisation, vaccine development, infectious disease control, health systems, economic analysis and health financing. The committee was chaired by Professor Robert Black (Chairman, Johns Hopkins Bloomberg School of Public Health) with membership of Dr. Helen Rees, Dr. Anne Schuchat, Dr. Fred Binka, Dr. Melinda Moree, Dr. Jane Achan, Dr. Raj Bahn and Dr. Kalipso Chalkidou. The Chair's summary of the IEC's recommendations is attaced as Annex D.
- 18.4 In-depth interviews have been conducted with Ministry of Health officials and Inter-agency Coordinating Committee members from a subset of GAVI countries. In addition, EPI managers and other in-country stakeholders in immunisation in all GAVI-eligible countries were invited to complete an online survey. The objective of these consultations was to better understand country vaccine priorities, potential introduction timing and possible implementation challenges. 182 stakeholders from different countries completed the survey, including respondents from 43 (currently eligible) GAVI countries. The majority of respondents represented the Ministry of Health, followed by Civil Society Organisations, UNICEF, Technical/Research institutes and WHO. Survey results are presented in the individual vaccine assessments and a summary report is available on request³⁰.
- 18.5 The Secretariat had initial conversations with the malaria team at the Global Fund to fight Aids, TB and Malaria to discuss potential implications and opportunities for both agencies in case GAVI were to open a country support window for malaria vaccines. Follow-up conversations are planned following the PPC and Board review of VIS recommendations.

³⁰ Please request this document through: vis@gavialliance.org

19 Gender implications

- 19.1 The potential for vaccine impact on gender equity (due to higher disease prevalence and/or suffering in one gender, eg Hep E, malaria, influenza) was assessed for each disease and vaccine as one of the considerations for prioritisation.
- 19.2 Malaria infection during pregnancy brings substantial risks for the pregnant woman, her fetus, and the newborn child and is a significant public health problem. Support for infant vaccination with malaria vaccines is unlikely to have direct benefits for women. However, a possible indirect benefit from child vaccination with malaria vaccines could be achieved by using the opportunity of the immunisation visit for a malaria vaccine to deliver other antimalarial interventions and messages around the importance of bednets and intermittent preventive treatment in pregnancy. Investments in the cholera stockpile and additional yellow fever campaigns are not expected to bring unique benefits for one gender.

Section D: Annexes

Annex A: Summary of cost and impact estimates

Annex B: Projected annual programme and business plan costs

Annex C: Impact and cost estimates benchmarked against GAVI vaccines

Annex D: Independent Expert Committee for the VIS – Chair's Summary

Available on MyGAVI:

1. Cholera vaccine assessment
2. Influenza vaccine assessment
3. Malaria vaccine assessment
4. Rabies vaccine assessment
5. Yellow fever vaccine assessment
6. List of experts consulted

Available on request³¹

1. Demand forecasting and cost assumptions
2. Models and methodologies used for health impact calculations
3. Operational cost methodology and cold chain capacity analysis
4. Fiscal space analysis
5. Literature review of (alternative) intervention cost-effectiveness
6. Summary of country consultations

³¹ Please request any or all of these documents through: vis@gavialliance.org

Annex A: Summary of cost and impact estimates

Vaccine investment:	Rollout timing and projected scope		Vaccine impact and value for money		2014-2020		2014-2030	
	Introductions / stockpile contributions from year:	# country introductions / campaigns expected	Deaths averted per 100,000 vaccinated ¹	Cost per death averted (US\$) ²	Deaths averted (thousands)	Total cost (US\$)	Deaths averted (thousands) ³	Total cost (US\$)
Yellow fever campaigns	2015	10	147	1,600	Not available	109M	104	140M
Cholera stockpile (reactive campaigns)	2014	Multiple per year ⁴	Not applicable ⁵	Not applicable ⁶	Not applicable ⁶	115M	Not applicable ⁶	115M
Malaria^{6,7}	2017	34	201-640	2,700-6,800	36-71	287-379M	592-1,290	2.2-3.4B

¹ Comparison with GAVI vaccines in Annex C, figure 1

² Comparison with GAVI vaccines in Annex C, figure 2

³ Comparison with GAVI vaccines in Annex C, figure 3

⁴ In recent years 40-50 outbreaks have been reported to WHO each year. The number of reactive campaigns implemented through the global stockpile will depend on the size of individual outbreaks prioritized for vaccination.

⁵ Impact estimates for the use of oral cholera vaccines in planned campaigns in endemic settings are presented in the cholera assessment on MyGAVI (note these estimates are highly uncertain). The impact of a stockpile investment cannot be confidently predicted due to the reactive nature of campaigns for which the stockpile is used. In trials and previous campaigns OCV has shown to be a highly effective vaccine with significant herd effects.

⁶ Contingent on future board approval per recommendation 2.1 (a)

⁷ Ranges reflect impact estimates from two different models (Swiss TPH and Imperial College) for four different vaccination scenarios. More details can be found in the malaria assessment on MyGAVI.

Annex B: Projected annual programme and business plan costs

Projected programme and business plan costs (Secretariat and partners), US\$ Millions

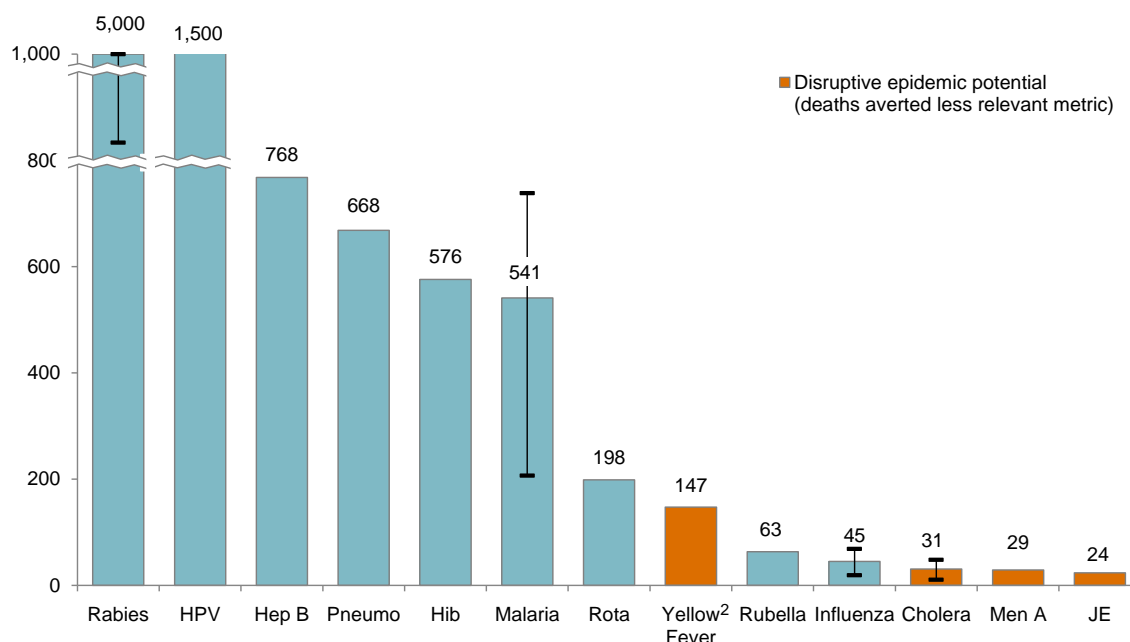
	2014	2015	2016	2017	2018	2019	2020	2014-2020
Cholera stockpile	9	17	26	34	29	-	-	115
Yellow fever campaigns	-	14	14	16	10	24	31	109
Annual totals (programme), recommended investments	9	31	40	50	39	24	31	223
Malaria ^{39,40}	-	-	-	12	49	86	140	287
Annual totals (programme), incl. malaria	9	31	40	63	88	110	171	510
Strategic period totals (programme)	39		471					
Business plan costs	1.5	3.0	2.7	2.7	2.1	0.6	0.6	14
Strategic period totals (business plan)	5		9					

³⁹ Contingent on future board approval per recommendation 2.1 (a)

⁴⁰ For illustrative purposes, assumes a scenario with vaccine administration in children 5-17 months old ('expanded EPI'), with booster

Annex C: Impact and cost estimates benchmarked against GAVI vaccines

Figure 1: Future deaths averted per 100k vaccinated¹



1. Based on deaths averted over 2015-2030

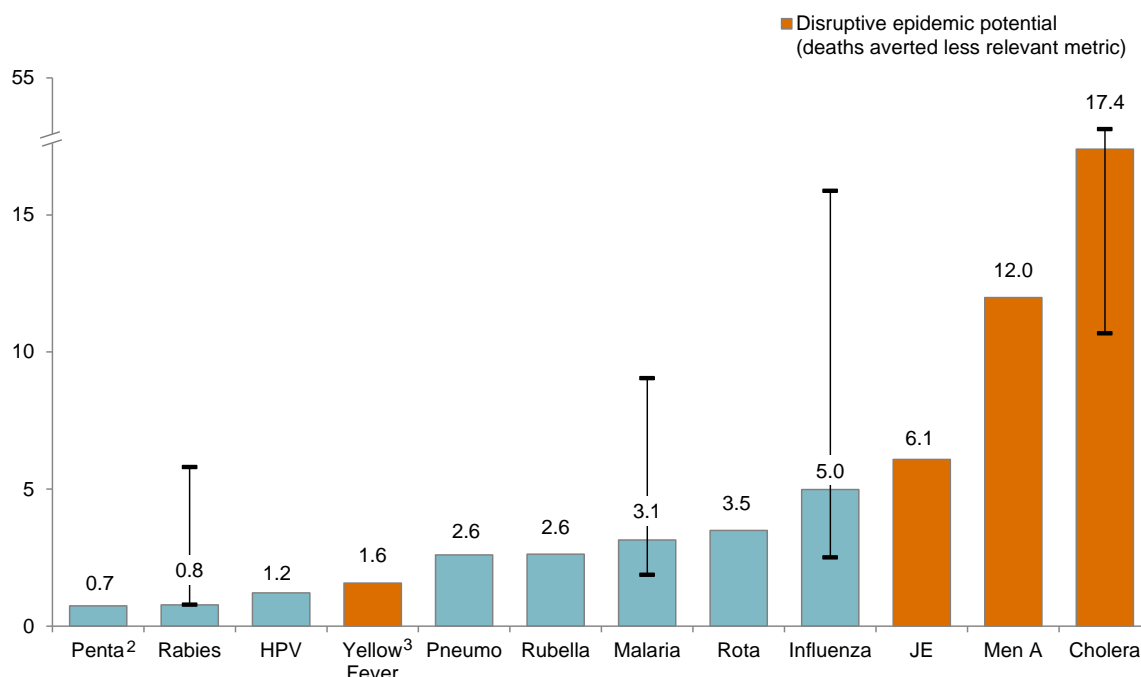
2. VIS only

Source: VIS impact analyses (detailed sources in individual vaccine assessments on MyGAVI)

Notes:

- **Malaria:** model outputs shown for Expanded EPI with booster scenario, for illustrative purposes; error bars show highest and lowest value generated by malaria sensitivity analyses and are driven by decay rate of protection. The lower bound of the error bar corresponds to a decay rate of 1 year to half initial efficacy (vs 3 years in the base case); point estimate represents midpoint of Imperial and STPH models
- **Cholera:** model outputs shown for vaccination of 1-15Y every 3 years for illustrative purposes; error bars show highest and lowest value generated by sensitivity analyses and are driven by sensitivities in CSQUID and IVI models; point estimate represents midpoint of IVI and CSQUID estimates
- **Influenza:** model outputs shown for introductions in 45 GAVI-eligible countries for illustrative purposes; error bars show highest and lowest value generated by influenza sensitivity analyses and are driven by baseline infant mortality
- **Rabies (post-exposure):** model outputs shown for intradermal administration (vaccine only) for illustrative purposes; error bars show highest and lowest value generated by sensitivity analyses and are driven by assumptions on patient treatment seeking behavior; high impact is driven by narrow target population for vaccination, ie treatment-seeking patients at increased risk of rabies infection (as opposed to for example infants in an entire birth cohort) combined with 100% efficacy of vaccine and 100% fatality of the disease.

Figure 2: Total cost¹ per death averted, 2015–2030 (\$'000)



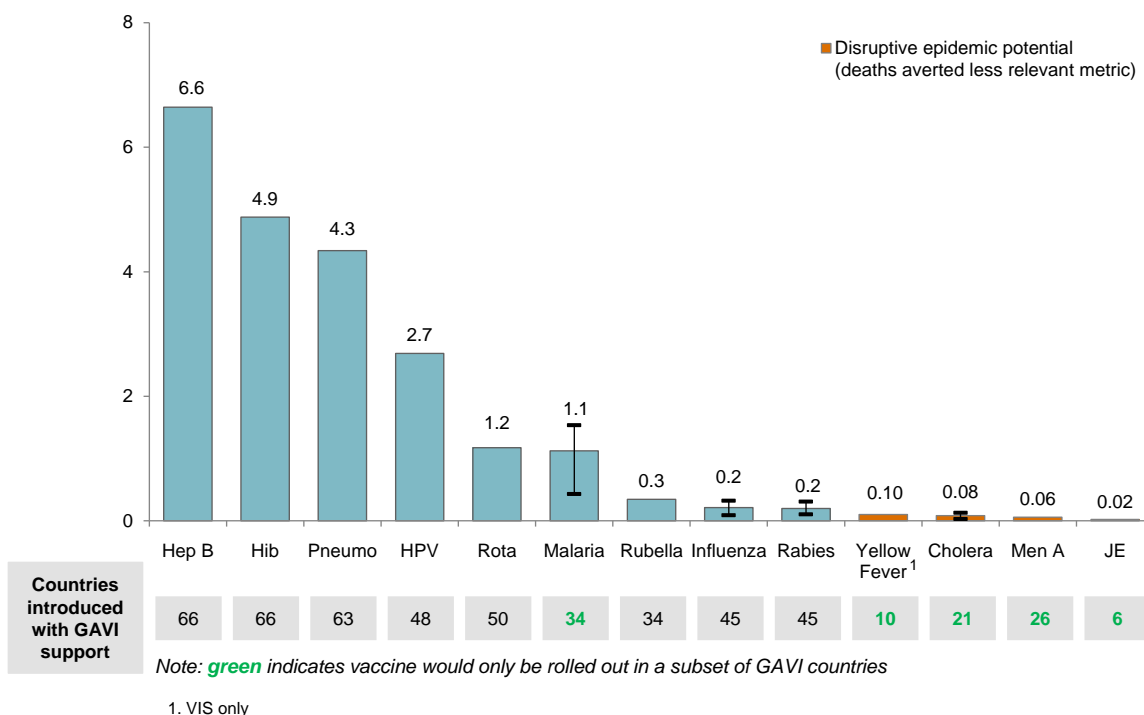
1. Includes operational + procurement cost to GAVI and country
2. Includes deaths averted for Hep B and Hib
3. VIS only

Source: GAVI Strategic Demand Forecast v7.0; VIS analyses (detailed sources in individual vaccine assessments on MyGAVI)

Notes:

- **Malaria:** model outputs shown for Expanded EPI with booster scenario, for illustrative purposes; error bars based on highest cost / lowest impact and lowest cost / highest impact as generated in sensitivity analyses; point estimate represents midpoint of Imperial and STPH models
- **Cholera:** model outputs shown for vaccination of 1-15Y every 3 years for illustrative purposes; error bars based on highest cost / lowest impact and lowest cost / highest impact as generated by sensitivity analyses; point estimate represents midpoint of IVI and CSQUID estimates
- **Influenza:** model outputs shown for introductions in 45 GAVI-eligible countries for illustrative purposes; error bars based on highest cost / lowest impact and lowest cost / highest impact as generated in sensitivity analyses
- **Rabies (post-exposure):** model outputs shown for intradermal administration (vaccine only) for illustrative purposes; error bars based on highest cost / lowest impact and lowest cost / highest impact as generated by sensitivity analyses. High impact relative to cost is driven by narrow target population for vaccination, ie treatment-seeking patients at increased risk of rabies infection (as opposed to for example infants in an entire birth cohort) combined with 100% efficacy of vaccine and 100% fatality of the disease.

Figure 3: Future deaths averted, 2015–2030 (M)



Source: VIS impact analyses (detailed sources in individual vaccine assessments on MyGAVI)

Notes:

- **Malaria:** model outputs shown for Expanded EPI with booster scenario, for illustrative purposes; error bars show highest and lowest value generated by malaria sensitivity analyses and are driven by decay rate of protection; point estimate represents midpoint of Imperial and STPH models
- **Cholera:** model outputs shown for vaccination of 1-15Y every 3 years for illustrative purposes; error bars show highest and lowest value generated by sensitivity analyses and are driven by sensitivities in CSQUID and IVI models; point estimate represents midpoint of IVI and CSQUID estimates
- **Influenza:** model outputs shown for introductions in 45 GAVI-eligible countries for illustrative purposes; error bars show highest and lowest value generated by influenza sensitivity analyses and are driven by baseline infant mortality
- **Rabies (post-exposure):** model outputs shown for intradermal administration (vaccine only) for illustrative purposes; error bars show highest and lowest value generated by sensitivity analyses and are driven by assumptions on patient treatment seeking behavior

Annex D: Independent Expert Committee for the VIS – Chair's Summary

GAVI Independent Expert Committee Vaccine Investment Strategy 19-20 August 2013, Geneva

Members attending: Dr. Robert Black (Chair), Dr. Jane Achan, Dr. Raj Bahn, Dr. Fred Binka, Dr. Melinda Moree, Dr. Helen Rees, Dr. Anne Schuchat

Apologies: Kalipso Chalkidou

GAVI Secretariat: Aurelia Nguyen, Judith Kallenberg, Emily Serazin (Boston Consulting Group), Hope Johnson, Melissa Ko, Lauren Franzel

Chair's summary

The IEC commended the GAVI Secretariat for the thorough vaccine assessments and a well-prepared meeting.

General points

The IEC briefly reviewed the original 'long list' of vaccines considered in Phase I of the VIS process and re-confirmed their assessment that there is (currently) no strong case for GAVI investment in those vaccines that were deprioritized.

The IEC supported the Secretariat's proposal not to do further work on a detailed analysis of DALYs averted, based on the strong correlation of DALYs with cases and deaths for this set of diseases, and therefore limited added value of such estimates for decision-making.

With regard to benchmarking vaccine impact and value for money against current GAVI vaccines, the IEC noted that point estimates for current GAVI vaccines can be misleading. Each estimate in reality has a different uncertainty interval depending on the quality of burden and effectiveness data, as well as uncertainty of the models used. In the future, it would be informative to review uncertainty intervals around the impact estimates for all GAVI vaccines.

The IEC noted that impact considerations for vaccines that help prevent epidemics differ from considerations for vaccines with a direct impact on endemic disease. Value for money of vaccines expressed as cost per death averted is inevitably lower for epidemic diseases such as MenA, JE and cholera. The impact of epidemics on health care systems and societies needs to be given consideration for these diseases and the IEC therefore suggested that 'epidemic potential' is highlighted as a separate benefit.

The IEC recommended that the Secretariat present a geographical view of the projected uptake of new vaccines.

Malaria

The IEC reviewed the analyses conducted to assess a malaria vaccine investment. Several technical points were discussed, including model assumptions on co-morbidity, bednet coverage, booster compliance and age-specific impact.

RTS,S is being tested in infants at 6-14 weeks and children between 5-17 months. Pending confirmation by WHO of a recommended schedule, the IEC advised that the Secretariat continue to document cost and impact estimates for four possible scenarios (vaccine administration in the EPI schedule and in an Expanded EPI schedule; both with and without boosting). The IEC noted that preliminary data appear to show that the vaccine is more effective in the older age group.

The IEC also advised that the Secretariat simplify the range of scenarios, impact models and sensitivity analyses for presentation to the PPC and Board.

-

The IEC recognized the strong case for GAVI support of malaria vaccines, which could bring considerable public health benefits. This vaccine was felt to be very clearly "in GAVI's space":

- Malaria is the leading cause of death in young children in the poorest countries in the world
- The vaccine has potential to prevent a significant number of deaths and cases in GAVI-eligible countries
- GAVI-eligible countries have a very strong interest in a malaria vaccine
- GAVI would be best placed to address an important market shaping need

The IEC also recognized there are current gaps in the evidence base. In particular, forthcoming data in 2014 will be instrumental for determining the appropriate vaccination strategy including the need for a booster dose. Other technical advisory committees such as WHO's Joint Technical Evaluation Group (JTEG) are mandated to advise on these issues.

The IEC noted that based on published phase III data it is likely that a partially efficacious vaccine will become available for use in African countries. It felt that current evidence is sufficient for an in-principle decision now. It also noted that such a commitment will send an important signal to industry. The IEC therefore recommended that GAVI prioritize malaria vaccines for inclusion in its portfolio. Implementation of a country support window will be contingent on a positive SAGE recommendation. The IEC also advised that preparatory activities be explored now to ensure efficient implementation if and when a vaccine becomes available. Finally, the IEC suggested exploring ways that the regulatory and policy timings could be accelerated if the vaccine proves to have sufficient efficacy.

Influenza

The IEC reviewed the analyses conducted to assess a maternal influenza vaccine investment. It supported the analyses and accompanying limitations linked to limited data availability.

The IEC noted that the SAGE recommends that for any country considering or implementing influenza immunisation, priority should be given to pregnant women. The IEC also noted that the GAVI Board has prioritized women's health in past investment decisions.

However, the projected impact of influenza vaccination on maternal mortality alone is insufficient to justify GAVI support. Influenza is not a leading killer of pregnant women, although of those who are infected, pregnant women are at a higher risk of severe disease and death. The case for GAVI involvement would be significantly strengthened by stronger evidence of impact on infants and the fetus. Data on these effects from trials currently underway is expected in early 2014.

The IEC noted that substantial surveillance data on influenza strains and seasonality exists (including from Africa). However, analogous to the situation with Hib ten years ago, this data is not typically being analyzed or packaged for clinicians or national decision-makers (it is rather used to inform choice of strains for vaccine production). If and when an effect on low birth weight, prematurity and other key causes of neonatal mortality is confirmed and data are disseminated, demand for influenza vaccination of pregnant women is expected to increase, but a substantial investment in evidence-based advocacy and preparatory activities will likely be needed.

In light of weak current evidence base for an effect on the fetus and infants the IEC recommended that GAVI does not open a funding window for maternal influenza vaccination at this time. The IEC proposed that GAVI review the results of the on-going clinical trials which are expected in 2014. If a substantial impact on fetal, neonatal and infant mortality is confirmed, there could be a strong case for future GAVI support. In that case, GAVI may want to consider an initial investment in preparatory activities to facilitate re-evaluation of influenza vaccine support as part of the next VIS process in 2018. Such activities could focus on synthesizing the evidence base for maternal influenza vaccination, addressing regulatory and logistics issues, and understanding programmatic aspects such the optimal delivery route for vaccination (campaigns and/or routine ANC).

The IEC noted that potential future GAVI involvement in maternal immunisation would fit with a shifting focus from infant to 'lifespan' vaccination in line with the objectives of the Decade of Vaccines. There is a global discussion about the development of a vaccination platform for pregnant women and this may further increase when other maternal vaccines (eg RSV) become available.

Yellow Fever

The IEC reviewed Secretariat analyses of an investment in additional yellow fever campaigns and information on GAVI's support for yellow fever vaccines to date (routine vaccination, campaigns and global stockpile).

The IEC acknowledged the public health value of continued GAVI support for planned yellow fever campaigns in areas at high risk of outbreaks. In addition, it noted that such a commitment may contribute towards ensuring more stable global vaccine supply.

The IEC recommended that GAVI fund additional yellow fever campaigns where these are needed to mitigate future outbreaks. It further recommended that the Secretariat reviews the risk assessment mechanism which informs the planning and funding of these campaigns, to ensure that resources are allocated through a robust, evidence-based process.

Cholera

The IEC reviewed the analyses for two possible investment options: a country support window for planned recurring campaigns in high risk areas and support for the global cholera vaccine stockpile.

The IEC noted that cholera is an important, high-visibility disease that affects the most vulnerable in poor settings. Epidemics can be a significant burden on health systems and risks diverting national resources.

The IEC noted that global supply of oral cholera vaccine is very limited and that market-shaping efforts are critical to ensure that this market continues to grow. In addition to boosting capacity, other manufacturers could be stimulated to enter the market and the price of oral cholera vaccines could be further reduced.

The committee felt that periodic cholera vaccine campaigns could play an important role in reducing cholera deaths in endemic countries but acknowledged uncertainties in predicting health impact. The IEC also emphasized that, despite the uncertainty of impact estimates, these metrics should not be viewed in isolation and qualitative consideration should be given to the mitigating effect of vaccination on preventing the devastating consequences of epidemics.

However, the IEC recommended that GAVI do not open a country application window for recurring campaigns at this time. This was considered premature in light of the limited understanding of how to plan and cost-effectively implement recurring cholera vaccine campaigns across GAVI-eligible countries. In addition, the committee expressed concerns about the sustainability of a long-term GAVI investment in recurring cholera campaigns in the absence of a co-financing requirement for countries (per GAVI's current policies). Instead, the committee recommended that GAVI invest in the global cholera vaccine stockpile to help reduce disruptive epidemics in a significant number of GAVI-eligible countries, and in light of an important market-shaping need.

In addition, the committee emphasized the need to strengthen the evidence base for the feasibility and public health value of planned, recurring campaigns in endemic settings. It recommended that part of GAVI-supported stockpile doses be earmarked for use in such campaigns, accompanied by a robust M&E framework in order to facilitate reconsideration of this strategy in the next VIS process.

The IEC advised that the Secretariat review the extent of historical and current outbreaks in order to better understand the context for a stockpile investment. The IEC noted that, in order to serve all of the objectives, the stockpile would need to be substantially larger e.g. 10 million or more doses than the initial projections presented by the Secretariat. It also recommended that a clear and transparent mechanism would be put in place for stockpile management (requests, release and use) and monitoring of the use of stockpile doses. The IEC further suggested that existing investments in rotavirus surveillance may be leveraged to include cholera.

Rabies

The IEC reviewed the analyses for rabies post-exposure prophylaxis (PEP) vaccine support and validated the methodologies for estimating potential impact and cost, acknowledging several uncertainties as highlighted by the Secretariat.

The IEC questioned the practical feasibility of enforcing intra-dermal administration in certain settings and the use of one vial for multiple vaccinations. It suggested that the Secretariat conduct an additional analysis of value for money based on the assumption of one-time use of a vial of rabies vaccine for intramuscular administration.

IEC members were divided over the fit of rabies post-exposure prophylaxis with GAVI's business model, and the structuring of possible support:

- Treatment versus prevention: rabies PEP vaccine is used in a unique beneficiary group: treatment-seeking bite victims. Some felt that GAVI's operations are tied to population-based preventive vaccination, while the majority of members felt that rabies vaccine (fully effective in preventing a 100% fatal disease) fits within GAVI's programmes.
- Rabies immunoglobulines (RIG): some IEC members felt that if GAVI were to support rabies vaccines, immunoglobulines (for passive immunisation) should also be supported as part of the complete WHO-recommended treatment package. Others felt that GAVI should focus on vaccines only and that support for one component of a recommended treatment package would not imply responsibility for funding other components.

The IEC noted that rabies is a particularly horrific, vaccine-preventable disease and that scaling up the use of rabies vaccine (PEP) could have an important impact on mortality in poor rural areas where the majority of ~55 thousand annual deaths occur.

However, while the vaccine itself is 100% effective, the IEC acknowledged that it is unclear how to programmatically achieve the potential impact, which is therefore to some extent theoretical. Supporting vaccine procurement only would not be enough to increase coverage and additional (health system) investments would likely be required to improve the effectiveness of rabies control. The use of rabies vaccines as part of a routine immunization programmes in high risk populations was not discussed.

The IEC felt that the nature of the disease and the potential impact of scaling up vaccine use post-exposure are compelling reasons for GAVI to intervene. However, because of important questions about effective implementation it recommended that GAVI do not open a country support window at this time.

The IEC noted that similar implementation-related challenges were identified in the previous VIS process five years ago. It recommended then that a learning agenda be advanced in order to catalyze progress in this vaccine-preventable disease area. The IEC reiterates this recommendation to avoid the same uncertainties being raised in the next VIS process. A learning agenda should address questions around treatment seeking behavior, existing levels of rabies vaccine (and rabies immunoglobulin) provision, intradermal vs intramuscular vaccination practices and wastage rates.

The IEC noted there are also broader questions about integrated approaches for rabies control, including dog vaccination, animal control and ensuring the use of RIG in certain bite victims per WHO recommendations.

The IEC did not reach consensus over whether it is GAVI's role to initiate and fund a learning agenda, although the majority of members recommended that GAVI should consider a small investment. If GAVI were to make such an investment, consideration would need to be given to the size of this investment relative to the cost of a potential future support window for rabies, which would probably be relatively modest.

One IEC member noted that rabies is recognized as a neglected tropical disease and suggested that there would be value in presenting the VIS assessment of rabies vaccines at the upcoming Global Immunisation Research Forum 2014.