Report to the Board
10-11 December 2014

SUBJECT:	**ACCELERATING ACCESS TO EBOLA VACCINES AND COUNTRY PERSPECTIVE**
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Agenda item:	05
Category:	For Decision
Strategic goal:	Affects all strategic goals

Section A: Overview

1. Purpose of the report

1.1 The purpose of this report is to respond to the Executive Committee's request to explore a potential role for Gavi, the Vaccine Alliance, in supporting procurement and delivery of licensed Ebola vaccines as soon as they become available.[1]

1.2 This report submits recommendations for Gavi to support the global response to decrease further Ebola-related mortality in the most affected countries, particularly in Guinea, Liberia, and Sierra Leone; to contribute to the recovery of health and immunisation systems in those countries most impacted; to avert further economic disruption in affected areas of West Africa; and to reduce the risks that both the current and potential future Ebola outbreaks pose to human security and the wellbeing of populations worldwide.

2. Recommendations

2.1 The Gavi Board is requested to:

(a) **Approve** a funding envelope (the "Ebola Envelope") from which the Secretariat shall allot, in accordance with the principles of the Gavi Programme Funding Policy and the processes (including delegations to the CEO) and periods set out in Table 1 below, funding for Ebola programmes, to:

i. **Endorse** new amounts for multi-year programme budgets for new and existing programmes referred to in Table 1 for an aggregate amount not exceeding US$ 390 million. (These endorsements

[1] Given the global emergency of Ebola, this report and consultations were done in an 8 week accelerated period.

would constitute acknowledgement of such budget amounts at the time of allotment but would not constitute a funding approval, decision, obligation or commitment of Gavi or its contributors); and

ii. **Approve** near-term liabilities of Gavi in respect of such endorsed programme budgets for periods ending no later than 31 December 2016 for an aggregate amount not exceeding US$ 390 million. (This amount is a sub-component of endorsed programme budgets).

Table 1

Activities	Amount	Post-Board approval process
Funding Vaccine Production and Procurement	**Up to US$ 300m**	
Procurement through UNICEF of up to 12 million courses of first generation Ebola vaccines and related injection safety devices in 2015-2016 under a funding structure potentially including Advance Purchase Commitments to be used for the current outbreak and an estimated 1 million courses for a global stockpile of first generation vaccines for 2016-2020	~US$ 300m	– **Number of courses to be procured** to be approved by Gavi CEO based on advice by WHO or WHO-convened body – **Funding structures** to be approved by the Executive Committee
Funding vaccine roll-out	**Up to US$ 45m**	
Operational costs for planning, management and delivery of vaccines to up to 12 million people to respond to current outbreak in 2015 (and 2016 if necessary)	~US$ 38m	Approval by Gavi CEO based on country-specific needs assessment generated by WHO
Management of first generation vaccine stockpile until second generation vaccines become available (2015-2020)	~US$ 3m	As approved by this decision
Operational costs for use of stockpiled courses in response to future outbreaks (2015-2020)	~US$ 4m	As approved by this decision
Recovery of health systems and immunisation services	**Up to US$ 45m**	
Vaccines and related injection safety devices and programmatic support to restore coverage for immunisation programmes in 2015-2016	~US$ 12.5m	Approval by Gavi CEO based on request endorsed by the country's Interagency Coordination Committee (ICC) or other relevant body and country situation analysis informed by partners

Reprogramming of all remaining, currently approved Health Systems Strengthening (HSS) grants for Guinea, Liberia and Sierra Leone	No additional costs	Approval by Gavi CEO based on High Level Review Panel (HLRP) or Independent Review Committee (IRC) review, as appropriate and timely, of reprogramming proposals (endorsed by ICC or other relevant body)
Doubling of HSS funding ceilings for Guinea, Liberia and Sierra Leone to support recovery activities for the health system towards re-establishing effective immunisation services for the period 2015-2019	~US$ 30.5m	Approval by Gavi CEO based on IRC review of country proposals
Waiving of co-financing requirements for 2014-2015 for Guinea, Liberia and Sierra Leone	~US$ 2m	Approval by Gavi CEO based on request endorsed by ICC or other relevant body
Total Ebola Envelope	**Up to US$ 390m**	

(b) **Note** that to meet the funding requirements of the Ebola Envelope, Gavi could use a combination of existing and new sources of funds and join forces with initiatives which have already pledged funding to address the Ebola crisis. To jumpstart the implementation of the recommendations in this paper, Gavi could make available up to US $100 million from its current resources. The Gavi Board gratefully acknowledged the African Development Bank's spearheading of a regional response and leadership in agreeing to consider a contribution of at least US $50 million subject to the approval of the African Development Bank's Board of Directors and in setting up a funding initiative to fast-track the Gavi support for vaccine development. This will include outreach to other donors already involved in the Ebola response, including other multilateral agencies, to complement their support. For instance, the World Bank Group as part of its overall response to Ebola is looking at how to support the accelerated production and distribution of an effective vaccine against Ebola and in this regard is working closely with Gavi.

(c) **Support** the allocation of funding for a stockpile, designed according to WHO-convened guidance, for second generation Ebola vaccines and related maintenance and operational costs of vaccine use and **request** the Secretariat to revert with related financial implications at an appropriate time.

(d) **Approve** an amount up to US$ 2.5 million to be added to the 2015 business plan budget for Ebola-related Secretariat costs and **note** that the estimate for Ebola-related Secretariat costs for 2016 is an amount of up to US$ 1.0 million.

(e) **Approve** an amount up to US$ 5.0 million to be added to the 2015 business plan budget for Ebola-related WHO and UNICEF costs and **note** that the estimate for Ebola-related WHO and UNICEF costs for 2016 is an amount of up to US$ 2.0 million.

(f) **Approve** an exceptional one-time amount of up to US$ 500,000 to be added to the 2015 business plan in order to support Civil Society Organisation (CSO) activities of the Gavi CSO platform in countries with widespread Ebola outbreaks, including strengthening demand for and confidence in health and immunisation services in Guinea, Liberia, and Sierra Leone, provided the activities are agreed with the respective governments and the government is not in a position to support CSOs through HSS resources.

3. Executive summary

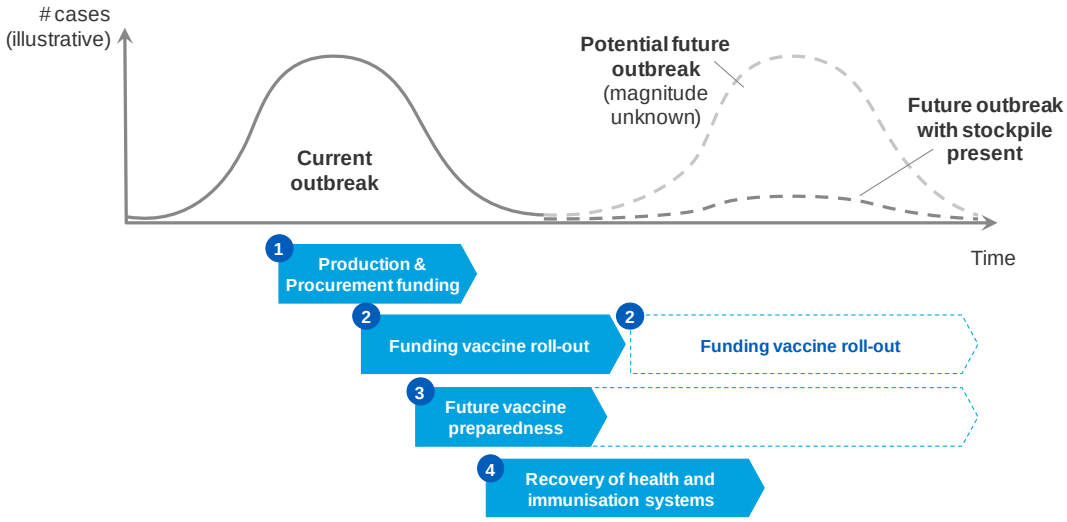
3.1 There is a global mobilisation underway to control and eventually end the present Ebola virus outbreak in West Africa. Many organisations and governments have mobilised quickly to allocate funding and initiate on-the-ground efforts aimed at addressing health issues in the most affected countries. A safe, efficacious Ebola vaccine could be an important addition to the toolkit that these organisations are using in their efforts.

3.2 Therefore, the global community is working with urgency to develop a vaccine to help fight the current Ebola outbreak. Two vaccine candidates are now in Phase I clinical trials, with others expected to enter Phase I clinical trials early next year. This report responds to the request by the Executive Committee at its 23 September 2014 meeting that Gavi's CEO work with Alliance partners to develop options for accelerating the availability of an Ebola vaccine. The approach described below takes advantage of Gavi's core expertise, focusing on areas where Gavi is well-suited to make a distinct contribution and leverage the strengths of Alliance partners (see Figure 1 below).

3.3 This report includes recommendations on actions to combat the current outbreak, support recovery from the current outbreak and prevent future outbreaks. This report makes a recommendation to the Board on the allocation of funds to establish a financing structure for sufficient levels of production and rapid procurement to be achieved, should one or more Ebola vaccine candidates be efficacious and recommended by WHO for use in the current Ebola outbreak in West Africa. This report also makes recommendations to the Board on funding a stockpile to respond to future outbreaks (both in West Africa and other geographies) and to support operational costs associated with the roll-out of vaccines to target populations. It also proposes flexibility and some adjustments to Gavi's HSS support in the affected countries aimed at re-establishing immunisation services as part of recovery efforts. Funding of up to US$ 300 million for vaccine procurement, up to US$ 90 million for in-country support (both vaccine roll out and health systems recovery) and US$11

million for additional Secretariat, WHO, UNICEF and CSO resources are recommended to support these activities.

Figure 1: Proposed areas for Gavi involvement



3.4 The theory of change underpinning this proposal is that the Gavi Board's endorsement will address bottlenecks that would otherwise impede an efficient transition from vaccine development to procurement and deployment of vaccines in current and potential future Ebola-affected countries. Approval for action now would maximise the opportunity for a vaccine to have a significant impact on the current outbreak, and strengthen preparedness for potential future outbreaks. It would also provide clarity on the immediate and longer term support available for reestablishment of immunisation programmes and health systems in the most affected countries.

4. Risk implication and mitigation

4.1 The full magnitude of the current outbreak, the time required to bring it under control, the risks of potential future outbreaks, and even the risk of Ebola becoming an endemic disease are unknown. While there are many risks associated with making decisions in such a highly uncertain environment with imperfect information, rapid action must be taken to maximise the impact on the current outbreak.

4.2 By embracing a higher level of risk than normal, Gavi can potentially play a valuable role in addressing urgent unmet needs. Specific risks that the recommendations in this proposal carry include:

(a) There is a risk associated with the fact that the safety and acceptability of the Ebola vaccine will not be as fully evaluated as usual due to the accelerated timeframe and regulatory pathways, and likely smaller study sizes. This risk will be mitigated by regulatory agency advice and relying on WHO to make a recommendation for use based on review by the Strategic Advisory Group of Experts (SAGE). In addition, decisions by countries to utilise the vaccine will be made with comprehensive information on what is known and not known of the vaccine's safety profile.

(b) There is a risk that Gavi makes investments that have no impact on the current outbreak because the epidemic is soon brought under control, or that the development of the vaccine candidates is not successful, or is not successful in time to have an impact on the current outbreak. Therefore, the recommended Gavi actions may no longer be required. This risk can be mitigated by making Gavi investments contingent on a WHO recommendation for use.

(c) There are risks, both financial and reputational, of negotiating agreements with manufacturers that are later revealed to be sub-optimal as new information becomes available. For example, negotiations could be for a supply level or price that turns out to be much higher than needed if contracts with guaranteed demand are undertaken. In addition, there is a risk that knowledge of a funding envelope by manufacturers could influence the funding they demand for these vaccines. These risks can be mitigated to a certain extent, but not fully, by the establishment of short-term agreements, guided by WHO recommendations, with clauses that allow for adjustment as the situation evolves. These risks can also be mitigated through continued robust analysis of supply and demand considerations and commitments of transparency from manufacturers on their costs.

(d) There is a risk that Gavi-funded vaccines are not able to reach the target population. This could be due to a number of factors, including insufficient infrastructure and high distrust leading to social unrest. This risk can be mitigated through Gavi's support to health systems recovery efforts, careful planning for vaccine implementation with partners and high coverage of funding needs for critical activities such as social mobilisation, communication and cold chain capacity.

(e) There is a risk that Gavi's existing processes may not meet the needs of an emergency situation. While Gavi is already involved in funding stockpiles of vaccines for other diseases with epidemic potential, it is not set up as an emergency response organisation. This risk can be mitigated by utilising existing mechanisms in the Secretariat related to supporting the financing of stockpile vaccine purchase and delivery working through partners such as WHO and UNICEF. This risk can further be mitigated by considering modifications or exemptions to standard Gavi processes, as well as establishing clear guidance for any future Gavi engagement in emergency situations.

(f) There is a risk, already being realised, that Secretariat, WHO and UNICEF human resources are diverted away from current Gavi programmes, thereby hindering current programme performance. This risk can be mitigated by some reprioritisation of current workloads to free up existing staff, together with hiring dedicated staff to manage Ebola-related activities following Board approval.

(g) There is a risk that financial resources are diverted away from current and planned future Gavi programmes, thereby hindering current and future programme performance. This risk will be mitigated by seeking any new funding required (i.e. funding beyond the amounts already committed from existing Gavi resources) from other donors who have already pledged resources for the response to Ebola.

5. Risk of inaction

5.1 Inaction by Gavi at this time carries important risks, both for Gavi and for the global Ebola response in affected countries:

(a) *Fragmentation of response:* Gavi is one of a multitude of actors involved in the Ebola response. Current efforts are being coordinated by the United Nations Mission for Emergency Ebola Response (UNMEER) and undertaken within the affected countries and globally by a number of Alliance partners, including specialised UN agencies such as the World Health Organization (WHO) and UNICEF, the World Bank, the African Development Bank, bilateral and multilateral development partners, foundations, civil society organisations, manufacturers, and research and technical institutes. The magnitude of mobilisation is encouraging in the face of the crisis, but it also carries a risk that vaccine procurement and delivery efforts will be fragmented, leading to coordination challenges that further slow down response times. This risk can be partially mitigated by integrating into overall UNMEER efforts and through the use of Gavi's partnership model, which has proven effective in coordinating other actors and donors in aggregating and channelling individual donor funding and drive financial coordination.

(b) *Lack of preparedness for a future outbreak*: There is a risk that another large-scale outbreak of Ebola will occur, either concurrent with this outbreak or at a later date, and the world will again be unprepared, especially if the next outbreak is caused by an Ebola strain not covered by the current monovalent vaccine candidates that are only targeted to the Zaire species of Ebola virus. The recommendations in this paper are designed to mitigate these risks. A failure to take action ahead of time could result in further lives lost as well as criticism for Gavi.

(c) *Further deterioration of Gavi's ability to perform its primary mission in the affected countries.* Ebola has had a profound effect on the health systems in the affected countries, with impact on routine immunisation programmes, including those supported by Gavi, as detailed in Section 14.1. In the absence of other activities to rebuild these systems, a lack of action by Gavi could further impede Gavi's primary mission in the affected countries.

6. Financial implications: Business plan and budgets

6.1 Financial resources will be required for Ebola vaccine production and procurement to respond to this outbreak; operational costs of vaccine roll-out; recovery of health and immunisation systems; and future outbreak preparedness. Estimated financial resource requirements of this "Ebola Envelope" are summarised in the Table 2 below.

Table 2: Summary of Ebola Envelope requirements by proposed Gavi activity area

Activity	Amount
Funding Vaccine Production, Procurement and Preparedness	Up to US$ 300 million
Funding vaccine roll-out	Up to US$ 45 million
Recovery of health systems and immunisation services	Up to US$ 45 million

6.2 These estimates are believed to be in the right order of magnitude based on the current available information, but actual amounts could be significantly different if key parameters related to supply and demand change. For instance, under current assumptions related to where gaps exist in current funding, anywhere from US$ 100 million to US$ 600 million could be required for the vaccine production and procurement element (see Section 11.8). Hence, the Secretariat recommends that the Board approve funding envelopes or in principle increases rather than set amounts to allow the Secretariat the ability to determine the precise values and timing of expenditures as more information becomes available, subject to governance reviews for specific items as highlighted in Sections 11-14 below. Regular progress updates will be brought back to the Board.

6.3 To meet these funding requirements, Gavi could use a combination of existing and new sources of funds and join forces with initiatives that have already pledged funding to address the Ebola crisis. The African Development Bank, which is already spearheading a regional response is willing to consider a contribution of at least US$ 50 million and to provide leadership in setting up a funding initiative to fast-track the Gavi support for vaccine development. This will include outreach to other donors already involved in the Ebola response, including other multilateral agencies, to complement their support. For instance, the World Bank Group as part of its overall response to Ebola is looking at how to support

the accelerated production and distribution of an effective vaccine against Ebola and in this regard is also working closely with Gavi. To jumpstart the implementation of the recommendations in this paper, Gavi could make available US$ 100 million from its current resources.

6.4 Disbursement of funds is anticipated to take place at a time after manufacturers have supplied vaccines for pivotal clinical trials, when additional courses are available and recommended for use by WHO (mid-2015 by current estimates). In this context, the International Finance Facility for Immunisation (IFFIm) could be used to support this effort directly or support existing vaccine programmes by enabling timely replenishment of temporarily diverted funds, in order to ensure no disruption to liquidities required for existing Gavi programmes.

6.5 Additional human resources at the Secretariat, WHO and UNICEF will also be required. For 2015, to support response to the current outbreak, the Secretariat requests US$ 1.95 million for additional Secretariat headcount and consulting support, particularly for market shaping, country support, programme management, policy and scientific engagement, monitoring and evaluation, legal and finance support, as well as a contingency budget of up to US$ 500,000 for additional support as required. The Secretariat requests up to US$ 5 million in 2015 for support to WHO and UNICEF, based on further discussion and needs analysis. Resource needs for 2016, currently estimated at US$ 1 million for Secretariat costs and US$ 2 million for partner cost, will depend on the evolution of the epidemic and will be reviewed next year as part of the budget process for 2016-2017.

6.6 The CSO constituency has submitted a proposal for financial support to support activities in response to the outbreak in the most affected countries. While further work and discussion as well as consultation with governments are required on the specifics of the proposal, it is recommended that up to US$ 500,000 be exceptionally approved through the business plan to support CSO activities in 2015 if the governments of affected countries are not in a position to support CSOs through HSS resources, whether due to timing or HSS resources being otherwise programmed. Such activities should be agreed with the respective governments and coordinated with partners and other on-going Ebola-related activities.

6.7 Approval of the foregoing expenditures is sought through the decisions recommended in paragraph 2.1, the financial implications of which are summarised in Table 3 below.

Table 3: Financial implications of recommendations

Ref.	Recommendation per Board Paper:			US$ million
	Ebola Programme Funding Envelope			
	Ebola vaccine production and procurement			300.0
	Ebola vaccine roll-out			45.0
	Additional HSS investments	30.5		45.0
	Restore immunisation coverage levels & co-financing waiver	14.5		
2.1 (a)	Sub-total: **Ebola Programme Funding Envelope**			**390.0**
	Addition to Business Plan budget	2015	2016	
2.1 (e)	Secretariat costs	2.5	1.0	3.5
2.1 (f)	Support to WHO & UNICEF	5.0	2.0	7.0
2.1 (g)	Support to Civil Society Organisations	0.5		0.5
	Sub-total: **Addition to Business Plan budget**			**11.0**
A	**Total cost of funding the recommendations**			**401**
B	less: **Already provided** in Gavi expenditure forecast for 2014-2015			**(100)**
(A-B=) **C**	**Additional resources required**			**301**
D	Deduct: **Resources from other funding agencies / donors**			TBD
(C-D=) **E**	**Balance to be funded through Gavi**			TBD

6.8 Funding the Ebola recommendations amounts to a total cost of US$ 401 million (per row A in Table 3).

6.9 Of that cost, US$ 100 million is already provided for within the Gavi expenditure forecast for 2014-2015.[2] Provided that Gavi's regular (as distinct from Ebola-specific) resource needs, as reflected in the Gavi financial forecast, are fully funded by donors completing their pledging through 2015, this portion of the Ebola resource needs can be met (per row B in Table 3).

6.10 That would leave a further US$ 301 million to be raised in order to fund the recommendations (per row C in Table 3). Some or all of this need could be met by funding for Ebola that may be made available for that purpose by donors and funding agencies (such as the African Development Bank). To the extent that, after such funding, a balance still remains to be funded through Gavi, this remaining amount would need to be raised through additional contributions to Gavi (per row E in Table 3). The requirements for Gavi Replenishment for 2016-2020, formulated in May 2014, did not include a provision for Ebola. Further Ebola specific donations could be

[2] This US$ 100 million amount available for Ebola-related expenditure forms part of the US$ 150 million mentioned in the Financial Forecast paper (Doc 05), at paragraph 5.2: " The forecast now includes an additional US$ 150 million provision for additional HSS support in 2015, including towards re-strengthening health systems degraded by the Ebola outbreak."

sought primarily from funds that have already been committed to supporting the Ebola response.

6.11 Given the urgency in responding to the needs for Ebola, the Secretariat recommends that the Ebola expenditures should proceed in advance of Gavi receiving commitments to fully cover that remaining amount. If ultimately the Ebola expenditures (within the amounts of the recommendations) were not fully funded, then other forecast Gavi expenditures would need to be curtailed in the years through 2020, in the absence of any other changes.

Section B: Content

7. Background: Epidemiology and Ebola response to date

7.1 According to WHO estimates, as of 18 November , the Ebola outbreak in West Africa has infected over 15,000 people, primarily in three affected countries (Guinea, Liberia, and Sierra Leone), claiming more than 5,000 lives. These are likely to be significant underestimates of the real burden due to suspected underreporting of cases and deaths. There are also new cases occurring in Mali, highlighting the risk that the outbreak could spread. Recent data suggest a drop in the number of new infections in Liberia and Guinea, potentially indicating that active control measures are having an impact.

7.2 A number of public and private organisations are coordinating to implement control measures and treat victims of the outbreak, under the leadership of the UN Mission on Emergency Ebola Response (UNMEER). UNMEER is working urgently to implement a programme focusing on isolation and treatment of infected persons, promoting safe burial practices, building of treatment centres, and increasing logistics capacities. Under the coordination of UNMEER, a number of UN agencies and partners such as Médecins Sans Frontières are conducting activities such as contact tracing, epidemiological surveillance, alert and referral systems, training of staff, community education and mobilisation to reduce disease transmission in the affected countries. An estimated US$ 1.33 billion has been committed to the response effort to date.[3]

7.3 The evolution of the current outbreak remains highly uncertain. WHO, together with the US Centers for Disease Control and Prevention (CDC) and the London School of Hygiene and Tropical Medicine (LSHTM) are considering three potential trajectories for the epidemic in the affected countries through 2015: 1) continuing widespread epidemic, 2) epidemic under partial control, and 3) epidemic under control (see WHO discussion papers on myGavi).

7.4 Research and development on Ebola vaccines is proceeding at an unprecedented pace. Manufacturers have rapidly accelerated their Ebola vaccine development programmes in response to the current crisis. Two

[3] As of 23 November 2014; http://fts.unocha.org/pageloader.aspx?page=emerg-emergencyDetails&appealID=1060

vaccine candidates are now in Phase I clinical trials, with others expected to enter Phase I clinical trials early next year. In early November, WHO projected that if clinical trials were to establish safety and efficacy, nearly 2 million courses of first generation Ebola vaccines could become available by July 2015.[4] At that point, the global community will turn its attention to assuring that the vaccines are procured and deployed rapidly and without delay if they are proved to be efficacious. Modelling undertaken by LSHTM to advise WHO indicates that even if a vaccine were to become available late in the course of the current outbreak, it could still have an important role to play in averting new infections and deaths and helping to bring the epidemic under control. Based on this modelling, and consultations with WHO, an estimated maximum of 12-20M courses will be required if the epidemic is widespread in the three most affected countries (low end of range assumes vaccination is carried out for adults only, as this is the most susceptible population; high end of range assumes vaccination of both adults and children in these countries), and a minimum of 100,000 courses (to vaccinate health care and frontline workers, in the event that the epidemic is under control but still present).

Background: Ebola vaccine candidates

7.5 Two vaccine candidates are currently in Phase I clinical trials to evaluate safety in humans: ChAd3-ZEBOV (GlaxoSmithKline/US National Institute of Allergy and Infectious Diseases (NIAID) and rVSV-ZEBOV (NewLink/Public Health Agency of Canada), each targeting the Zaire species of Ebola virus present in the current epidemic. NewLink and Merck have entered into a licensing and collaboration agreement regarding the rVSV-ZEBOV candidate. An additional number of candidates are in preclinical development. The most advanced of these is Ad26/Ad35/MVA (Janssen/Bavarian Nordic), which is expected to enter Phase I clinical trials in January 2015.

7.6 For the two candidates currently in Phase I clinical trials, accelerated pivotal Phase IIb/III clinical trials are expected to begin in affected countries by Q1 2015, with initial efficacy data potentially available from mid-2015. Multilateral meetings among relevant regulatory agencies have been held (including the African Vaccine Regulators Forum, AVAREF) to discuss product-specific issues and to streamline and harmonise regulatory processes where possible. It is anticipated that recommendations for use would be issued by WHO, likely in conjunction with a recommendation for use, or licensure, by a stringent regulatory authority (e.g. in the US or Europe) prior to Gavi support. This would provide an assurance of the efficacy, quality and safety of the vaccines.

7.7 Through at least mid-2015, the magnitude of vaccine impact on outbreak evolution is likely to be constrained by vaccine supply, as manufacturers work to complete phase I and II trials and increase production for candidates. At present, GSK has plans to add up to 4 production lines,

[4] Includes WHO estimate of $5x10^7$ plaque-forming units (pfu) per mL dosing for NewLink rVSV vaccine. Efficacy at a lower dosage (currently being evaluated in clinical trials) could result in substantially higher dose availability.

generating a capacity of up to 230,000 – 310,000 courses per month by April 2015. Moving to a commercial scale facility by September 2015 would increase GSK's capacity to approximately 1M courses per month. NewLink plans to produce between 50,000 and 5M courses by Q1 2015 through the use of a contract manufacturing organisation (CMO), and 250,000 - 25M by end of Q2 2015, either through a CMO or through their collaboration with Merck. The wide range of NewLink's production volume is due to uncertainty in final dosing levels,[5] which are being evaluated in the current Phase I trials. Janssen plans to produce up to 1 to 2M courses by the end of 2015, then additional 2 to 4M courses by 2016, and expansion to a commercial scale of more than 1M courses per month beyond 2016.

7.8 If development of all three candidates is successful (i.e., each proves efficacious and receives a WHO recommendation for use), this translates to availability of 5-60M courses by the end of 2015. Applying WHO's working assumption of an intermediate dosing level for NewLink's product[6] to this situation means approximately 6.2M total courses (across all three manufacturers) could be available by the end of 2015.[7] This production estimate is contingent upon multiple factors, including successful completion of clinical trials, meeting of regulatory timelines, availability of formulation and filling capacity, optimised quality control release protocols for faster release, and on-time validation of equipment, production lines and facilities.

7.9 Additional background information on the demand and supply context can be found in the WHO discussion papers made available on the Board myGavi site.

8. Process to develop recommendations to the Board

8.1 The following four-step analytical approach was employed by the Gavi Secretariat, supported by the Boston Consulting Group, to respond to the Executive Committee's request:[8]

(a) Work in close collaboration with WHO to understand the evolution of the outbreak, evidence of vaccine safety and efficacy, potential vaccination scenarios and likely regulatory approval pathway and supply availability of the lead vaccine candidates. Use this understanding to inform estimates of resources required to accelerate vaccine supply in order to meet potential vaccine demand.

[5] The dose to be used for prophylactic vaccination is unknown, and is expected to be within a 1000-fold range currently being evaluated in clinical studies. Such uncertainty makes prediction of number of available courses difficult.
[6] WHO's assumption is $5x10^7$ plaque-forming units (pfu) per mL
[7] If NewLink's product were efficacious at lower doses, as is being tested, even higher volumes would be available
[8] A cross-Secretariat team was created composed of the following staff: Matthew Blakley, Alex de Jonquieres, Zeynep Eroglu, Lauren Franzel, Eliane Furrer, Guillaume Grosso, Judith Kallenberg, Rob Kelly, Melissa Malhame, Stefano Malvolti, Eduard Molnar, Patience Musanhu, Robert Newman, Aurélia Nguyen, Paolo Sison.

(b) Understand current as well as planned partner activity in support of Ebola vaccines, and solicit input from partners as to where they believe Gavi is best positioned to play a role in addressing unmet needs regarding vaccine procurement financing, vaccine roll out, and restoration of immunisation and health systems disrupted by the Ebola crisis. Through this analysis, identify the subset of needs that should be the focus of any Gavi support.

(c) Assess potential financing structures that Gavi could employ to address outstanding needs, considering both traditional and innovative financing structures.

(d) Evaluate each potentially viable option against a set of criteria (initially including unmet need, time to impact, flexibility, Gavi role) and select most suitable options. Make recommendations on most viable options to the Board.

8.2 Consultations were conducted to inform this analysis and validate its results. The consultation process included:

(a) Individual interviews with over 20 Alliance partners, donors, regulators, and other technical experts. Interviewees provided inputs into the analytical approach described above.

(b) Discussions with manufacturers at working and senior levels on technical, regulatory, policy, and financial issues.

(c) A workshop convening 30 external experts on 4 November to validate findings from the preliminary analysis and provide feedback on potential options. See Annex B for the list of participants and meeting report from this workshop.

(d) A review of an initial draft of this Board paper by 12 senior Alliance stakeholders (including a subset of members of Gavi governance mechanisms), country and independent experts.

8.3 The process of generating this Board recommendation was extremely compressed, with only eight weeks from the time of the Executive Committee's request to the submission of the Board report. Consequently, consultations were constrained by interviewee availability and analytics were conducted with limited information.

9. Guiding principles for Gavi involvement

9.1 Six principles guided the identification and assessment of potential options for Gavi involvement in accelerating Ebola vaccine availability:

(a) Plan for high demand: Assume strategies for current outbreak will involve millions of courses of safe and efficacious vaccine for Health Care Workers (HCWs) and large scale vaccination of other target groups among the general population as per guidance from WHO.

(b) Focus on alleviating bottlenecks: Speed is of the essence. Utilise current support to facilitate near-term scale-up as needed, and ensure mass availability as soon as possible, if required. Direct support to ensure processes are streamlined.

(c) Prioritise solutions that are candidate agnostic. Current data do not enable prioritisation among current candidates. Financing should be structured to allow for flexibility in funding multiple manufacturers, provided that the candidates have accrued sufficient evidence to inform WHO recommendations.

(d) Avoid prematurely locking into market that is not fully understood: Design solutions so that they are limited in time or dose volume, to allow flexibility in long-term pricing and vaccine selection.

(e) Ensure that Gavi's actions add clear value. Only enter this effort if Gavi is well-suited to make a critical contribution.

(f) Structure necessary resources to mitigate consequences to existing Gavi programmes. Any financial efforts for Ebola vaccine should not negatively impact Gavi's current or future programmatic efforts and reputation with regard to its existing vaccine portfolio.

10. Proposed areas for Gavi involvement

10.1 Consensus at the workshop and in consultation with partners was that Gavi can add value in four areas: supporting the acceleration of production as well as procurement of vaccines to help combat the current outbreak; funding vaccine rollout; preparing for potential future vaccine use in outbreaks; and supporting the recovery of health systems and restoration of immunisation programmes in the most affected countries. Partner landscaping indicated that current clinical trial efforts were largely funded, but there were significant funding gaps in other areas. There was agreement at the workshop that several of these gaps were outside of Gavi's capabilities or mission, and as a consequence, Gavi is proposing that it will not directly fund the research and development of the vaccines nor will it fund the indemnification of vaccine manufacturers (Figure 2).

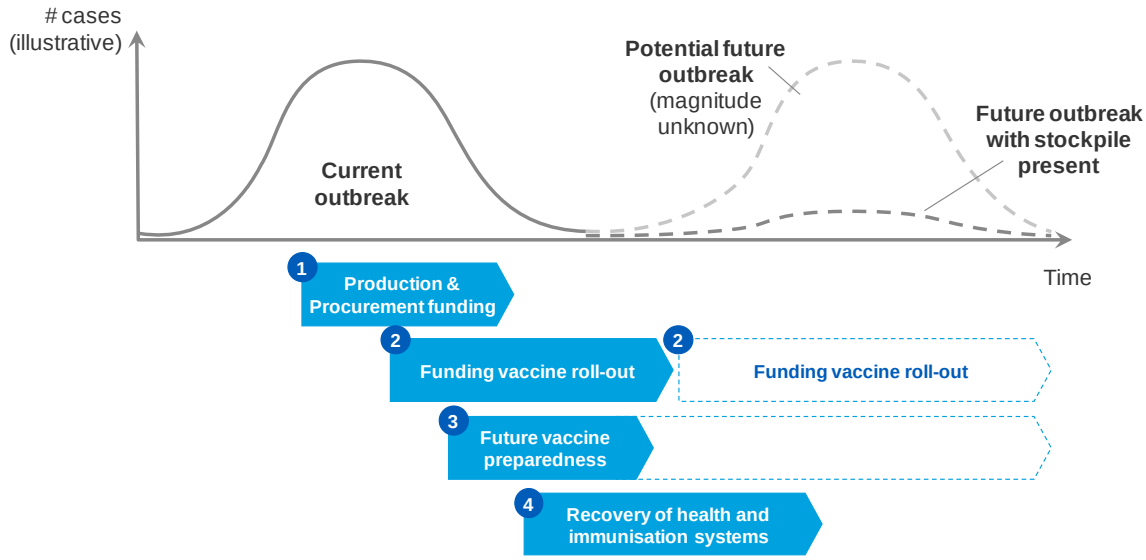
Figure 2: Funding gaps identified through partner landscaping

Cost category		Critical funding area	Est. funding coverage	Fit with Gavi capabilities? (based on past experience, partner input)
Clinical trials		Phase I	High	✗
		Phase II	High	✗
		Phase III	High	✗
Production & procurement	Production scale up	Production at clinical trial scale	High	✗
		Scale up / scale optimization	Medium	✓
		Commercial scale mfg	Low	✓
	Procurement	Vaccine procurement	Medium	✓
	Risk mitigation	Indemnification	Medium	✗
	Diverted manufacturer resources	Diverted manufacturer resources	Low	✓
Vaccine roll-out		Vaccine roll-out	Medium	✓
Future vaccine preparedness		Clinical trials	Low	✗
		Production scale up	Low	✓
		Procurement	Low	✓
		Vaccine roll-out	Low	✓

10.2 Figure 3 below shows that these four areas for Gavi action span different time horizons. As illustrated in the figure, maximizing speed to availability requires that portions of this effort be funded "at risk" by the manufacturers or other partners, meaning before efficacy results are available and before the status of the epidemic at the time of vaccine availability is known. It is our understanding that, for the leading manufacturers, production costs are being supplemented by governmental funding agencies or are being addressed through alternative approaches (see section 11.2), such that Gavi support for these "at-risk" investments may not be required.

10.3 In the immediate term, focus for Gavi will be on accelerating availability of vaccines via facilitating their procurement to combat the current outbreak. In the near term, it is understood that planning for campaign implementation and future outbreak preparedness must begin in parallel, and that the upcoming phase IIb/III clinical trials in the affected countries provide an opportunity to better understand the unique requirements for rolling out Ebola vaccines. Likewise, preparing for future outbreaks must begin now in order to leverage the current donor and manufacturer mobilisation to accelerate research and development activities, including taking advantage of the unique epidemiologic situation for evaluating vaccine efficacy. In the medium term, support for recovery of each affected health system will begin after the current outbreak is under control and emergency responders begin to decrease their support.

Figure 3: Proposed areas for Gavi involvement



10.4 Gavi's contributions would complement the work of other partners contributing to each of these four areas. Sections 11-14 provide additional details on potential funding requirements, current and expected funding coverage, an assessment of what subset of unmet needs Gavi is well positioned to address, and the recommended approach for Gavi to take.

11. Funding production and procurement

11.1 Ebola vaccine development languished prior to the current outbreak because there was no viable market. Ebola outbreaks prior to the current one affected small numbers of people mostly in remote areas of low income countries, and were effectively controlled through containment measures. Consequently, there was no global demand for an Ebola vaccine and manufacturers had little incentive to advance Ebola vaccine candidates into clinical development. In fact, work on current vaccine candidates was not primarily initiated for public health purposes in lower-income countries but rather for biodefense concerns in industrialised countries.

11.2 In response to the current crisis, manufacturers have rapidly accelerated Ebola vaccine development programmes. They are receiving external support to do this but are also committing significant internal resources to their efforts.

Manufacturers have responded in different ways to the challenge of rapid mobilisation of required resources:

(a) Some manufacturers have stated that they are not expecting to make profits from the development and production of Ebola vaccines to respond to the current outbreak. In addition, it should be noted that manufacturers have already indicated that simply understanding that Gavi is exploring financing options has been a contributing factor in their decisions to invest resources, even prior to the Gavi Board decision. However, beyond the current outbreak, these investments may be expected to provide a return that enables manufacturers to justify their continued involvement in Ebola vaccine production to their shareholders.

(b) One manufacturer is pursuing an alternative approach. The manufacturer has also stated that it is not expecting to make profits from the development and production of Ebola vaccines, but wants to take an approach for a longer term view focused on providing an incentive that ensures a sustainable investment in this vaccine supply, as well as to seek to develop a platform for the development and rapid manufacture of other vaccines against emerging pathogens, including those that may trigger biodefense emergencies. In this approach, which would be covered by funding sources other than Gavi, the manufacturer is not seeking a unit price per vaccine course, but is suggesting a contract-based compensation that takes into account the vaccine development costs as well as the opportunity costs associated with the programmes displaced by the emergency.

11.3 Consultations with donors and manufacturers indicate that clinical development costs are likely to be fully subsidised by other funders. Based on conversations with manufacturers and governmental funding agencies, manufacturer costs to establish pilot scale production and then scale up to commercial-scale production are expected to be partially offset by subsidies (with variation by manufacturer). The building of commercial-scale capacity is necessary to ensure availability of millions of courses, if needed, to combat the current outbreak. However, procurement of the vaccine, once available, as well as procurement of related injection supplies remains unaddressed.

11.4 Gavi could add value by establishing a financing structure that helps ensure that production capacity for large scale vaccination exists (in case it is needed) and that vaccine courses are procured for use in affected countries. Gavi offers the advantages of a being multilateral mechanism, enabling coordination and assuring fairness and transparency of funding. Gavi may also be able to leverage its experience in designing and implementing advanced purchase commitments, if required.

11.5 In order to be effective, a funding mechanism would need to be: a) sufficiently robust to give confidence to manufacturers that funding would be available and procurement of initial courses would be rapid; b) flexible enough to allow for the possibility of very different demand scenarios (thousands versus millions of courses needed); c) capable of disbursing funds rapidly so that courses could be available in time to combat the

current outbreak; and d) able to fund the procurement of vaccines as a tool to cover manufacturers' investments. For planning purposes, two vaccine demand scenarios for the current outbreak can be considered:

(a) Scenario 1: Vaccination of health workers in clinical settings and other frontline workers involved in Ebola control (such as burial teams, contact tracers, etc.). Vaccination would likely be delivered by mobile teams at fixed sites with convenient access for staff of Ebola treatment centres and community-based Ebola responders. Potential target population (excluding those receiving vaccines through clinical trials): approximately 100,000.

(b) Scenario 2: Large scale vaccination in affected areas targeting adults and potentially children. Vaccination would likely be delivered through similar mechanisms as other mass campaigns, such as measles or meningococcal A campaigns. Potential target population: approximately 12 million.[9]

(c) Of course, many other scenarios (such as the need for ring vaccination should the outbreak spread to other countries) are possible, and courses would be used in other countries where there is a need. The courses required for these other scenarios are thought to be largely covered by the range included in the two scenarios above.

11.6 To meet the requirements for speed, flexibility and appropriate coverage of manufacturer investments, several structures could be envisaged.

(a) The most simple structure could be long-term arrangements (LTAs) with individual manufacturers, per standard UNICEF procurement processes. These agreements would be effected upon the achievement of WHO recommendation for use.

(b) A second structure could be Advance Purchase Commitments (APCs), which would entail guaranteeing the purchase of, for example, 100,000 courses upon achievement of WHO recommendation for use and up to 12M courses if widespread use is required. This structure would be implemented in response to manufacturer need for guaranteed funding to ensure the availability of vaccine courses.

(c) A third structure could be the same APC structure described in 11.6.b, implemented in conjunction with prepayments, made after the relevant WHO recommendations for use, but before the courses were delivered. This structure would be implemented in response to manufacturer need for guaranteed funding to ensure the availability of courses and upfront funding, for example, to fund working capital.[10]

(d) In all scenarios, UNICEF, in collaboration with the Secretariat, would

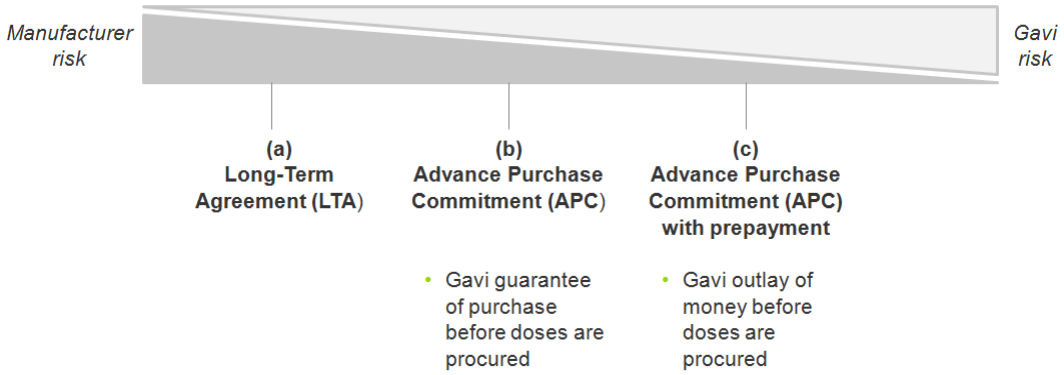
[9] Note that, for modelling purposes, 12M was taken as the target population, reflecting number of adults older than 15 years of age in Guinea, Sierra Leone and Liberia (population ~20M total). Consultations indicated that, due to Ebola transmission characteristics, vaccination of adults was likely to be more effective than that of children.

[10] Prepayments for vaccine purchases ahead of delivery are usually done in exchange for more favourable pricing terms than in the absence of prepayments and/or where there is a strong risk to securing the supply required.

negotiate procurement contracts that are separate and tailored to each manufacturer. Any unused portion of the funding envelope approved for procurement to respond to the current outbreak could be rolled into funding for a stockpile. See Section 13 for further details on the envisioned stockpile.

11.7 This design of these potential structures replicates some elements of the Advance Market Commitment for pneumococcal conjugate vaccines as well as the advanced purchase commitments for rotavirus and pentavalent vaccines and takes into consideration lessons learned. For instance, it allows for the tailoring of negotiations to individual manufacturers and mirrors previous legal agreements undertaken for other vaccine purchases to ensure a more efficient process for implementation.

Figure 4: Relative risk profiles of these three example structures



11.8 Under current assumptions related to where gaps exist in current funding, anywhere from US$ 100 million to US$ 600 million could be required to implement these structures[11]. Some factors driving this wide range are:

(a) Considerable uncertainty surrounding probability of successful development and therefore the likely number of viable vaccines available;

(b) Differences in existing production assets / plants, donor subsidies awarded to manufacturers, contract manufacturing discussions, or donations/grants planned to be awarded;

(c) Differences in technologies employed (VSV versus adenovirus), dosing levels, or dosing regimen (single versus "prime-boost").

11.9 Considering the estimated costs that manufacturers expect to be covering, a cost envelope was established, where for some manufacturers a portion of unsubsidised scale up costs and procurement of courses are covered, and for one manufacturer procurement of courses only is covered. For the latter manufacturer, a contract-based approach not based on a unit price per vaccine course is being considered by funding sources other than Gavi for costs including pre-licensure costs.

[11] See Annex C for modeling assumptions.

11.10 An envelope of US$ 300 million would enable Gavi to ensure multiple strategies could be addressed, resulting in availability of up to 12M courses in 2015-2016. It is important to note that, for the two illustrative examples described below, it is assumed that at least two of the three currently-considered vaccine candidates are successful in development, all successful candidates receive equal WHO recommendations for use, and that current production timelines remain valid.

(a) **Illustrative example 1:** Funds are used to finance vaccine procurement and support unsubsidised scale-up costs of two manufacturers (envelope of US$ 120 million, assuming volume distributed such that maximal numbers of courses are purchased from each manufacturer up to a total of 12M courses for the current outbreak and approximately 1M courses for a stockpile maintained until 2020, or until a second-generation Ebola vaccine(s) is available, with replenishment every two years).

Assessment: Both manufacturers currently in clinical trials are understood to be heavily subsidised, reducing the unsubsidised cost that may otherwise be included in vaccine pricing offered to Gavi. Bringing a third, less-subsidised manufacturer to scale could potentially require a substantial increase to the envelope, depending on the third manufacturer's cost structure.

(b) **Illustrative example 2:** Funds are used solely to procure vaccine from three manufacturers (envelope US$ 200-300 million): Under the assumption that production scale-up is completely subsidised, it would be possible to fund procurement of the maximal available output of three manufacturers in 2015 (over 12M courses) as well as to fund an approximately 1M-course global Ebola stockpile to be maintained through 2020 (or until a second-generation Ebola vaccine(s) is available).

Assessment: This example requires production scale-up support by other funders. Security of supply with three manufacturers able to produce vaccines gives a wide supplier base. As with all scenarios, a number of factors impact this assessment, including successful development and the final determination of vaccine dosing.

11.11 The possible financing structures described in Section 11.6 do not include an alternative and riskier structure including payments made *prior* to a WHO recommendation for use, and therefore current structures assume that funding is enacted only with successful candidates. If the amounts of subsidies received by manufacturers are insufficient for them to be willing or able to trigger investments required for commercial-scale production, the financing structure could be structured for a prepayment to be made in advance of a WHO recommendation for use. This would result in the prepaid amounts being at risk if vaccine development does not succeed, since Gavi would have committed funding for vaccines that do not yet have safety or efficacy data available. The liability risks of committing to purchase vaccines that do not yet have safety or efficacy data would also

need to be carefully explored. This would constitute a risk not taken before by the Alliance.

11.12 To summarise the information above, given current information on manufacturer costs and production support from partners and governmental funding agencies, this US$ 300 million envelope is expected to be sufficient to result in at least two companies being at full-scale production, and for funding procurement of the required courses from these two manufacturers. If production scale up were largely subsidised (i.e., courses could be procured at a price nearer to marginal cost of goods), there may be room within this envelope to procure a portion of courses from a third manufacturer, up to the target of 12M courses.

11.13 The current request for an envelope of funding is based on the understood magnitude of funding required to achieve the goals of vaccine availability. However, the specific details of the financing structures within that envelope have not been determined and will depend on the situation at the time that funding is required. It should be noted that given the combination of the relatively early state of manufacturing of these vaccines, lack of clinical dosing information, and novel technologies being applied, many of the parameters in a standard Cost of Goods Sold (COGS) model are simply not available at the level of certainty that would be typical for a Gavi COGS assessment. Rough magnitudes of numbers provided by manufacturers were checked by interviewing multiple independent sources and by making comparisons to similar products when possible. Nevertheless, there is unavoidable uncertainty around the calculations in this document, and values will need to be updated as the environment evolves.

11.14 Following Board approval of the recommendations, immediate next steps would focus on ensuring that Gavi is in a position to rapidly move forward with procurement, should one of the candidates be recommended for use by WHO. Secretariat and partner actions need to begin immediately, focusing on aligning with procurement partners, opening negotiations with manufacturers, and assembling necessary financing. The negative impact of delayed action, both on the outbreak evolution and on Gavi's reputation, could be substantial.

11.15 Under normal processes (as discussed at the EC meeting on 15 April 2012), the CEO approves manufacturer financing structures and informs the EC. However, given the high uncertainty of the current estimates and the overall cost of the activities envisaged to be funded through the Ebola Envelope mechanism and the resources available for those activities, an alternative process is recommended. It is proposed that in this instance, the CEO would consult with the Board (and EC) Chair to convene the EC, and that the individual manufacturer financing structures, including determination of the adequacy and sources of funds, be subject to EC review and approval.

12. Funding operational costs for vaccine roll out

12.1 If Gavi were to fund the procurement of an Ebola vaccine, it would be beneficial to also consider the funding requirements for effectively rolling out these vaccines to the target populations as recommended by WHO. While the following discussion is based on the three countries most affected currently, it is understood that this support would be extended to any Gavi implementing country for which Ebola vaccine procurement support was provided, assuming additional resources for such procurement were available.

12.2 Currently Gavi provides assistance to countries performing vaccination campaigns in the form of direct financial support to help cover a share of the operational cost for planning, management and delivery of vaccines used in campaigns (currently in place in selected countries for Yellow Fever, Meningococcal A conjugate, Measles, Measles-Rubella, and Japanese Encephalitis vaccines). The aim of such grants is to facilitate the timely and effective delivery of vaccines to the target population by supporting specific campaign requirements not covered by the ongoing investments in health systems. The support is fixed at US$ 0.65 per individual in the country's target population and is expected to cover on average around 80% of estimated total campaign operational costs (US$ 0.80 per person) with the remainder being funded by the government and partners.

12.3 Activities typically covered by this operational support include: programme management; training of health workers; information, education and communication (IEC) and social mobilisation; micro-planning; human resources; transport and logistics; cold chain equipment; immunisation session supplies; waste management; technical assistance; and surveillance and monitoring of adverse events following immunisation.

12.4 The costs of implementing effective vaccination strategies with a potential Ebola vaccine will depend on various factors most of which are currently still unknown: type and size of target population; type of vaccination strategy; number of courses required; characteristics of the vaccine (particularly cold chain requirements); level of trust in healthcare workers and the government health system; and existing local capacities and resources.

12.5 Due to the current situation facing health systems in the most affected countries and the novelty and potential characteristics of Ebola vaccines, operational costs and additional measures for infection control are expected to exceed the cost of campaigns usually supported by Gavi. However, given high levels of uncertainty with respect to key parameters, a precise costing is pre-mature. Hence, the approach described below (and in Annex C) is meant to provide indicative orders of magnitude.

12.6 Based on WHO guidance with respect to potential target populations and vaccination strategies, two scenarios (as listed above in Section 11.5)

were assessed to derive plausible cost estimates for rolling-out Ebola vaccines.

12.7 Cost multipliers were applied to most of the campaign activities listed above to reflect the increased needs due to this specific Ebola situation. For scenario 1 where a smaller but highly dispersed target population has to be reached (healthcare and frontline workers), a distinction was made between categories with a predominantly fixed cost component (e.g. for surveillance, transport, communication) and categories with variable costs mainly driven by volume (e.g. training, human resources and waste management). In addition, the following items were estimated separately using bottom-up costing methods: (1) emergency operations centres expected to be needed at national and possibly regional levels for direction and coordination of vaccination efforts; (2) cold chain and logistic requirements based on potential need to maintain vaccines at storage temperatures of -70ºC; (3) security and crowd control measures to protect vaccinators and stocks under emergency conditions; and (4) equipment to ensure infection control measures are in place for vaccinators and to reassure vaccinees.

12.8 Gavi typically funds approximately 80% of estimated total campaign operational costs. However, given the emergency situation created by the current Ebola outbreak, Gavi would consider funding up to 100% of operational costs as well as the additional cost considerations described above should these costs not yet be covered by other stakeholders. The total costs under scenario 1 for a target population of 100,000 frontline workers are expected to range from US$ 6 to US$ 11 million. The total costs under scenario 2 for large-scale campaigns of up to 12M people in the three most affected countries are estimated to be US$ 17-38 million. A main driver of uncertainty are the cold chain and logistic requirements that will ultimately depend on the storage indications for the candidate vaccines. The current assumption is that vaccines would be transported in dry ice chain from the country's port of entry directly to districts where low temperature freezers would have to be available. Transportation from districts to vaccination sites would either occur in special cold boxes with dry ice or, if distance permitting, in ordinary cold boxes. Given the limited stability of the vaccine at ambient temperature, vaccination sessions would have to be very well timed and efficiently executed.

12.9 In addition to the operational costs of vaccine roll-out during the current Ebola outbreak, there are also operational costs associated with the management and use of the proposed first generation Ebola vaccine stockpile. Gavi will provide funds for management of this stockpile (approximately US$ 500,000/year) as well as provide its typical operational cost support of US$ 0.65 per target person. Together, these funding activities will require up to approximately US$ 7 million for the period 2015-2020.

12.10 In sum, then, a funding envelope of up to US$ 45 million (up to US$ 38 million for operational costs plus US$ 7 million for stockpile

management and operation) will be required to support first-generation Ebola vaccine operational activities.

12.11 Gavi can add value by committing in principle to funding a large share of these operational costs in case they are not yet covered by other stakeholders. Given its multilateral structure and experience synchronising complex vaccine delivery efforts, Gavi can also play an important role in supporting and engaging in collaboration with key implementation stakeholders as well as helping to coordinate their activities.

12.12 More detailed country-level costing will be required to assess specific needs and funding gaps. WHO-led efforts are underway to provide such estimates over the course of the coming months when new evidence (e.g. about the candidate vaccines' characteristics, most appropriate vaccination strategies, and target populations) is expected to become available. Experience from clinical trials of Ebola vaccine candidates in the three affected countries will also inform subsequent assessments of operational needs and potential funding gaps. The level and disbursement channel of potential funding support by Gavi as well as appropriate implementation partners for such activities should be reassessed based on this information.

13. Future outbreak preparedness

13.1 Among epidemiologists, it is widely believed that future Ebola outbreaks will occur, and there is strong expert consensus that if a safe and efficacious vaccine is found, a vaccine stockpile should be established to enable a rapid response. Given the nature of the disease (incidence and transmission dynamics) pre-emptive campaigns and routine immunisation are not currently being considered as appropriate means to control future outbreaks. Maintenance of a stockpile for focused, reactive vaccination is thought to be a potentially effective tool in quickly limiting the spread of a future outbreak.

13.2 There are currently no models that estimate the appropriate size of a vaccine stockpile for Ebola, given uncertainties around the epidemiology of future outbreaks, vaccine characteristics, appropriate vaccination strategy, and future availability of vaccines. In the absence of such data, it is not possible to model stockpile sizes. Consequently, prior vaccine stockpile sizes and understanding of vaccine production capacities were used to estimate the evolution and final size of a potential Ebola vaccine stockpile. Prior vaccine stockpiles intended for reactive use, including those for yellow fever, meningococcal A conjugate, and meningococcal A polysaccharide, averaged approximately ~3.5 M courses (replenished each year) in size. However, dynamics of Ebola detection and transmission (e.g., starting at relatively low scale, spreading slowly) suggest that a lower stockpile volume may be sufficient (e.g., no more than 1 million courses) which at current production capacities, could likely be built starting in 2015-2016. The ideal target product profile for an Ebola stockpile vaccine differs from the characteristics of the candidates

currently in clinical trials. For example, current lead candidates are directed only against the Zaire species of the Ebola virus (responsible for the current outbreak), and require extreme cold chain storage conditions (i.e., current need for storage at -70°C). Vaccines with improved characteristics (e.g., multivalency for other Ebola species and/or Marburg virus) are in preclinical development, and are not expected to be available for at least three years. WHO is expected to develop the target candidate profile for vaccines to be considered under a next-generation stockpile and would advise on the creation and management of such a stockpile, for instance, through convening an International Coordinating Group (ICG). Until these are available, stockpiling monovalent vaccines developed for the current outbreak remains critical for preparation for outbreaks during this interim period.

13.3 Gavi can add value by signalling now its intention to fund the maintenance of a long term stockpile and working together with partners to coordinate and fund implementation, drawing on previous experience working with partners to establish, maintain, and manage stockpiles for yellow fever, meningitis, and cholera vaccines. It should also be noted that strengthening of surveillance systems is an important complementary strategy to maintaining a stockpile.

13.4 A Gavi-supported stockpile of Ebola vaccines would provide a revenue stream for manufacturers, through periodic replenishment as stock expires or is used. However, because of its size and low relatively low revenue potential, such a stockpile is unlikely to provide a sufficient incentive for increased R&D efforts toward a next-generation vaccine. Prompting additional R&D effort will likely require additional contributions from partners and government agencies through direct push funding and other financing mechanisms. The presence of stockpiles maintained by industrialised countries for biodefense purposes may also contribute sufficient commercial interest to spur R&D for next-generation Ebola vaccines. It is envisaged that all countries would have access to a stockpile supported by Gavi for outbreak response, but that Gavi would only fund vaccines for Gavi-eligible and graduating countries.

13.5 As noted above, a second-generation vaccine with enhanced properties would be preferred for stockpiling. Should such a vaccine move forward in development, the Board may be re-approached to discuss the possibility of funding these new vaccines for stockpile use. However, a signal now to manufacturers of intent to purchase multivalent vaccines will be helpful.

14. Recovery of health system and immunisation services

14.1 The current outbreak has crippled already weak health systems in Guinea, Liberia, and Sierra Leone and has disrupted immunisation programmes. Coverage levels of the third dose of Diphtheria, Tetanus and Pertussis (DTP3) in the three affected countries for the 2014 birth cohort is below 50%, relative to 63%, 89%, and 92%, respectively in 2013. In addition, some of the planned new vaccine introductions have been postponed.

Given the current emergency situation resulting in weak health infrastructure and shortage of health care workers, wastage rates in routine immunisation programmes may increase and some vaccines may expire. Gavi's support during the recovery period will aim to support affected countries to re-establish immunisation coverage levels, and strengthen the health systems and their ability to implement immunisation services. While the current focus is on the three currently most affected countries, similar support could be extended to other affected countries should WHO confirm a widespread outbreak, Gavi evaluation deem such support necessary, and sufficient resources be available.

14.2 Gavi's Fragility and Immunisation Policy enables affected countries to request certain time-limited flexibilities from Gavi, such as higher reprogramming of existing Health System Strengthening (HSS) funds, a waiver for co-financing obligations, and procurement of replacement or additional vaccines if needed. A country-tailored approach may be undertaken for the affected countries if required. The recommendation related to reprogramming in this report would increase the reprogrammable HSS amount from 50% of funds remaining in country as stated in the current policy to 100% of unused funds.

14.3 To support the recovery of immunisation programmes, Gavi will draw from the proposed funding envelope to replace vaccines, injection supplies and disposal boxes that have been repurposed. Supplementary immunisation activities may be required to catch up children missed during the Ebola crisis and to increase population immunity to epidemic-prone diseases.

A funding envelope of up to US$ 12.5 million will be required over a 2-3 year period to cover these activities that will be carried out in accordance with the Fragility and Immunisation Policy described above.

14.4 Gavi will coordinate closely with WHO and many other partners working on health system recovery on activities such as rebuilding confidence of local communities in their primary health care services as well as encouraging vaccinators to vaccine and populations to get vaccinated. Existing Gavi-supported CSOs may play a role, for example, in rebuilding trust in health services in affected countries and should be encouraged to participate in the discussions about reprogramming of existing and planning for new HSS support. Training of new health staff as well as refresher trainings for existing staff will also be critical needs. It is noted that the CSO constituency has submitted a proposal for financial support to support activities in response to the outbreak in the most affected countries. While further work and discussion as well as consultation with governments are required on the specifics of the proposal, it is recommended that up to US$ 500,000 be exceptionally approved through the business plan to support CSO activities in 2015 if the governments of affected countries are not in a position to support CSOs through HSS resources, whether due to timing or HSS resources being otherwise programmed. Such activities should be agreed with the respective

governments and coordinated with partners and other on-going Ebola-related activities.

14.5 Flexibility in Gavi's response will be essential to ensure support is provided at the appropriate time and tailored to the specific needs of Guinea, Liberia, and Sierra Leone, and other countries if similarly affected. Accordingly, the Secretariat recommends an increase in HSS funding ceilings. There will be limited absorptive capacity for additional funding in the short term, but over a 3-5 year time horizon an approximate doubling of normal ceilings (from estimated US$ 30.5 million to US$ 61 million for the three countries) is anticipated to be needed and feasible to absorb.

14.6 Reprogramming of all remaining, currently approved HSS grants for Guinea, Liberia, Sierra Leone will be subject to approval by the Gavi CEO based on High Level Review Panel (HLRP) or exceptionally Independent Review Committee (IRC) review of reprogramming proposals (endorsed by ICC or other relevant body). Doubling of HSS funding ceilings for Guinea, Liberia and Sierra Leone to support recovery activities for the health system towards re-establishing effective immunisation services for the period 2015-2019 will be subject to approval by the Gavi CEO based on IRC review of country proposals.

14.7 The current crisis has highlighted the need for strong surveillance systems. Efforts to improve surveillance, not only for Ebola but for the full range of relevant infectious diseases, and monitoring for Adverse Events Following Immunisation (AEFIs) should be part of the broader approach to strengthening health systems and would ideally have to be built into HSS proposals submitted by countries.

14.8 The Secretariat will also consider if assessments could be conducted with partners in 2015 to help guide the tailoring of recovery support. Depending on conditions, these could be in country or part of regional consultations.

14.9 If other Gavi implementing countries have a widespread Ebola outbreak, flexibility will be needed for their HSS funding as well.

Section C: Implications

15. Impact on countries

15.1 Affected countries will not bear the financial costs associated with the recommendations. Nevertheless, roll out of immunisation activities to respond to the current outbreak will place further pressure on overburdened health care systems. A careful balance will need to be established between working primarily through international partners to relieve the burden on countries versus ensuring country ownership. Also, to the extent that existing funds will be used for Ebola efforts, it is not foreseen that funds for vaccine and HSS programmes for other Gavi countries will be reduced.

15.2 It is noted that the discussions in this report are focused primarily on the needs of the three countries currently most affected by the Ebola crisis. It is understood that this is an evolving situation, and that consideration of support needs for other countries may be required as the outbreak evolves.

16. Impact on Gavi stakeholders

16.1 Gavi will work with the international donor community to leverage existing commitments to the Ebola response in order to fund proposed Gavi action if required.

16.2 Gavi's technical partners will be involved in different components recommendation implementation, including but not limited to procurement (UNICEF Supply Division), planning for vaccine roll out (WHO, MSF, others), health systems strengthening activities (CSOs), and stockpile management (WHO/ICG). CSO platforms could potentially play a role in rebuilding confidence in health systems and immunisation services.

16.3 Manufacturers will be engaged in negotiations with Gavi regarding the financing structures to be implemented and will need to incorporate Gavi demand into their planning.

17. Impact on Secretariat

17.1 Subject to Board approval of the recommendations , several Secretariat-led work streams will need to begin immediately, including collaboration with UNICEF for negotiations and contracting with manufacturers, resource mobilisation activities if required, monitoring and evaluation, and planning and coordination with partners and affected countries.

17.2 Additional Secretariat financial and human resources will be required, as described in Section 6.

18. Legal and governance implications

18.1 Subject to Board approval of the recommendations, (i) appropriate legal and grant arrangements will be made with partners such as WHO, UNICEF and countries to implement the recommendations and (ii) appropriate legal arrangements will be negotiated and entered into to implement the agreed financing structures.

19. Consultation

19.1 Every effort was made to consult as widely as possible within the very short timeframe (8 weeks) between the Executive Committee's request and the paper being sent to Gavi Board members. Consultations include over 20 individual discussions with key stakeholders and technical experts, a 30-person workshop, and review of early drafts of the Board paper by senior Alliance member representatives as well as country and independent experts. See also Section 8.2.

20. Gender implications

20.1 The recommended investments are not expected to bring unique benefits for one gender.

Section D: Annexes

Annex A: WHO summary of vaccine characteristics

Annex B: Meeting report and list of participants from 4 November workshop

Annex C: Analyses: Demand and supply; funding gap identification; production and procurement; vaccine roll out

Further documents available on my Gavi site:

WHO discussion papers

ANNEX A: WHO BACKGROUND MATERIALS

1. WHO document on vaccine characteristics

Vaccines summaries (as of 14 November 2014)

A number of candidate EVD vaccines have been tested in animals, but most are not available in formulations suitable for human use.

Two vaccine candidate have entered phase 1 studies: cAd3-EBOV (cAd3) from GlaxoSmithKline (GSK) and the U.S. National Institute of Allergy and Infectious Diseases (NIAID), and rVSVΔG-EBOV-GP (rVSV), from NewLink Genetics and the Public Health Agency of Canada.1,2,3 Both vaccines are recombinant, meaning that a different virus (expected to be safe in humans) causes the expression of just one component of EVD within the vaccinated human in order to stimulate immunity to Ebola virus without risk of causing disease itself.

Both vaccine candidates have been shown to be 100% efficacious in NHP,11,12 and the replicating rVSV vaccine has been shown to convey post-exposure protection.3

The rVSVΔG-EBOV-GP (rVSV) vaccine to be used in the clinical trial will provided by BioProtection Systems (NewLink Genetics, Iowa, U.S). The vaccine product is comprised of a single recombinant VSV isolate (11481 nt) modified to replace the gene encoding the G envelope glycoprotein with the gene encoding the envelope glycoprotein from ZEBOV. The vaccine product contains a replicating virus vector.

Based on challenge studies in non-human primates there are indications that the vaccine may provide post-exposure protection in recently exposed contacts.

The vaccine is administered intramuscularly (i.m.) The dose of the vaccine to be administered in the current trial will be defined based on the results of the ongoing phase 1 studies, of which results are expected in December 2015.

The Chimpanzee adenovirus serotype 3 (ChAd3) vaccine uses a chimpanzee adenovirus that does not grow, containing the gene for EVD surface protein.

A single dose of the vaccine given one month in advance protected 16/16 animals from a lethal dose of EVD.

More than 1 300 people have received similar vaccines for other diseases, including over 1 000 people in Burkina Faso, Gambia, Kenya, and Senegal. These other vaccines seem safe so far, but as yet there is no safety information on an EVD vaccine in humans.

The cAd3 vaccine is being tested in both bivalent (ClinicalTrials.gov number, NCT02231866) and monovalent (NCT02240875) forms; the monovalent form is based on the Zaire strain of Ebola virus, which is the cause of the current West African epidemic, and the bivalent form includes the Sudan strain of the virus as well

The monovalent form will be evaluated in a nonrandomized, open-label study involving 60 adult volunteers who will receive the vaccine at three different doses (1×1010 vp, 2.5×1010 vp, and 5×1010 vp). The bivalent form will be evaluated in a nonrandomized, open-label study involving 20 adult volunteers who will receive the vaccine at two different doses (2x1010PU and 2x1011PU). Both studies will assess safety, side effects, and immunogenicity, including antibody responses as measured by enzyme-linked immunosorbent assay (ELISA) and neutralization assays and T-cell immune responses as measured by intracellular cytokine staining.

Investigators anticipate that preliminary immunogenicity and safety data will be available by December 2015.

IM equipment & supplies for sterile injection & HCW who can administer
Single dose. Storage at -70°C

1. Kanapathipillai R, Restrepo AMH, Fast P, *et al.* Ebola Vaccine - An Urgent International Priority. *N Engl J Med* 2014; published online Oct 7. DOI:10.1056/NEJMp1412166.
2. Geisbert TW, Feldmann H. Recombinant vesicular stomatitis virus-based vaccines against Ebola and Marburg virus infections. *J Infect Dis* 2011; **204 Suppl** : S1075–81.
3. Hoenen T, Groseth A, Feldmann H. Current ebola vaccines. *Expert Opin Biol Ther* 2012; **12**: 859–72.

B

ANNEX B: EBOLA VACCINE ACCELERATION WORKSHOP

1. Meeting summary

2. List of participants

Workshop
4 November 2014

Potential Gavi Roles in Ebola Vaccine Acceleration: Options Development Workshop

1. Meeting Summary

1. Context

As part of the drafting of a recommendation to the Gavi Alliance Board for accelerating availability of an Ebola vaccine as requested by the Executive Committee, the Gavi Secretariat assembled 30 experts with expertise in epidemiology, policy, global funding, financing mechanisms, manufacturing, and in-country implementation for a full-day workshop (see Annex 1 for the list of participants). The goal of the workshop was to share thoughts and evaluate early thinking on different options for potential Gavi support to help accelerate the availability of Ebola vaccines.

2. Ebola outbreak, vaccine demand and supply context

The World Health Organization (WHO) presented the latest information on the evolution of the outbreak, vaccine candidates, potential target populations, supply estimates, potential vaccination strategies, and considerations on operational funding needs. This work was a collaborative effort involving WHO, the US Centers for Disease Control and Prevention (CDC) and the London School of Hygiene and Tropical Medicine (LSHTM). WHO emphasized the high level of uncertainty around the outbreak evolution and outlined three plausible trajectories for the epidemic in the affected countries through 2015: 1) continuing widespread epidemic, 2) epidemic under partial control, and 3) epidemic under control. Modelling undertaken by LSHTM to advise WHO indicates that even if a vaccine were to be available late in the course of the outbreak, it could still have an important role to play in averting deaths and helping to bring the epidemic under control.

The relative effectiveness of vaccinating different target populations was discussed. Modelling data showed vaccine impact to be maximal when targeting adults, given the observed attack rates, especially in areas where disease incidence has not yet peaked. Furthermore, vaccination of health care workers, in particular, was noted as a critical tool to protect those most at risk of infection and allow continued health care delivery in affected areas.

The focus of the vaccine pipeline discussion was on the two vaccines currently in Phase I clinical trials: ChAd3-ZEBOV (GSK/NIAID) and rVSV-ZEBOV (NewLink/Public Health Agency of Canada), each being tested with the current epidemic Ebola-Zaire strain. For each, accelerated pivotal Phase 2b/3 trials are expected to begin in affected countries by Q1 2015, with initial efficacy data potentially available by April. Through at least mid-2015, the magnitude of vaccine impact is likely to be constrained by vaccine supply.

Nevertheless, given the epidemiologic unknowns in the current epidemic and potential risk of further spread, planning for large-scale vaccine use should begin immediately.

3. Funding gap identification

Participants discussed funding gaps, defined by comparing funding requirements to accelerate Ebola vaccine availability with funding support committed by various organizations. As a first step, the group agreed that 12-20 million vaccine doses was a valid estimate for planning purposes, based on the populations (adults only and adults + children) of the currently severely affected countries (Guinea, Liberia, and Sierra Leone). While modelling suggests that herd immunity effects may lead to high impact even if only a sub-set of the total population is vaccinated, and ultimate recommendations may be to target only Health Care Workers (HCWs), carry out ring vaccination, or target only certain geographies, it was agreed that this estimate was prudent, as it is easier to revise downward than upward, if required. If this estimate turns out to be too high, excess vaccine could potentially be stockpiled for later use. A further key uncertainty supporting a higher range in planning is the potential spread of Ebola into other countries with weak public health systems.

Initial assessments of funding gaps showed that near-term clinical trial costs are thought to be well-covered by manufacturers and governmental agencies. Scale-up to commercial production, procurement, large scale use of vaccines in countries, and preparation for future outbreaks were identified as potential gaps addressable by Gavi. The group concurred that compensation for the diversion of manufacturers' resources to Ebola projects is an important factor to take into consideration as part of procurement and production support, although the extent to which the cost for diverted resources should be addressed remains to be determined. Indemnification was also identified potentially as a gap, but not one that Gavi is well positioned to address.

There was consensus that Gavi could play a major role in Ebola vaccine procurement, given prior experience in the area. It is understood that normal procurement by Gavi would require a level of WHO guidance (e.g., emergency use of vaccine authorization or similar and under a WHO Strategic Advisory Group of Experts (SAGE) process, recommendations on target populations, age groups and delivery strategies) before Gavi could purchase the vaccine, though the precise process and required approval status is not yet known, and may require Gavi Board input. Group members agreed that there were advantages to using a multilateral organization like Gavi to provide funding for procurement, particularly for a vaccine that might be supply constrained to assure fairness and transparency of use.

With respect to production, manufacturing experts cited fill/finish, cold chain for processing and filling, and scale-up capacity as specific challenges. For fill/finish (sterile filling of vials with vaccine product), capacity constraints have been identified by the manufacturers, and the experts noted that finding contract manufacturing capacity is made more difficult due to the fact that this is an unlicensed product, contains a live virus, and requires Bio-Safety Level 2 certification for the facility. The current cold chain requirements for these vaccine candidates (reported to be -70ºC or -80ºC), known to be problematic for vaccine storage

and transport in-country, were also cited as an issue, as an end-to-end cold chain would be required for processing and filling the product. Finally, if scaling up production capacity required moving to a new (larger) facility, additional process validation and potentially clinical work would be required to satisfy regulatory requirements, adding time and expense to the production process.

With respect to large scale use (implementation) of vaccines, there was strong belief among the participants that the current Ebola outbreak would require greater support than that usually given in terms of operational costs for delivery of vaccines and planning and coordination, due to the deteriorated health systems and the need for intensified social mobilization, additional cold chain resources, enhanced surveillance and monitoring of adverse events following immunisation (AEFI) and infection control in the affected countries. Beyond the costs of the campaigns themselves, resources will be required before deploying the vaccines for appropriate scoping and planning, as well as after the campaigns to evaluate their impact. While it is difficult to estimate the needed operational resources, clinical trials in the affected countries may provide an opportunity to better understand this need. In the meantime, a costing exercise making use of the best currently available data should be performed to generate an estimate of the operational costs.

With respect to future outbreak preparedness, the group noted that Gavi is well suited for interventions with a longer-term perspective, and that there is a particular need to start to prepare now for potential future Ebola outbreaks. There was understanding that the profile of an optimal vaccine for use in future outbreaks may differ from that of the current candidates (i.e., desire for protection against multiple Ebola strains and Marburg, reduced cold chain requirements, extended shelf life, and potentially higher efficacy/duration of protection), and that development of such a vaccine would require the community to undertake (likely large) investments in research & development, process development, and capacity. There is also uncertainty regarding the delivery strategies and size of target populations in future outbreak response. Many participants noted that it will be important to "build a bridge" between the current and future outbreaks while global attention to Ebola is high. While current vaccine candidates should be included in a stockpile when available, there was consensus that the optimal size and composition of stockpiles for future outbreaks are likely to be different.

4. Potential roles for Gavi

The Secretariat presented an overview of its multilateral approach for increasing access to vaccines, including its funding sources, market shaping mechanisms, and previous support for control of diseases with epidemic potential. Also presented were proposed principles for considering Gavi actions related to Ebola vaccine acceleration: prioritizing speed, remaining vaccine candidate-agnostic, avoiding locking Gavi long-term into poorly understood markets, and ensuring that Gavi's actions add value to the overall vaccine availability effort.

The participants were uniformly positive about Gavi's reputation and track record, which provides a high level of legitimacy to potential funding efforts in support of Ebola vaccines. Many of the funders present expressed interest in channelling funds through Gavi, utilizing

the multilateral mechanism. At the same time, there was strong consensus that financial actions taken with regard to Ebola should not negatively impact Gavi's current or future programmatic efforts with regard to its existing vaccine portfolio. The group indicated that efforts on Ebola would instead require additional resources above what has been requested of donors as part of Gavi replenishment. Some participants noted that this type of emergency response is not thought of as a typical Gavi activity, and that the Alliance must consider the reputational risk associated with activities in this area. Others pointed out that inaction also carries a risk, particularly in light of the global security risk that epidemics of this nature pose.

To address procurement and scale up of commercial production, the favoured mechanism of the group was a form of advance purchase commitment. There was consensus that this type of "pull" mechanism was a more appropriate way for Gavi to intervene than "push" funding, and the donors present indicated that the circumstances justified taking a significant financial risk. A breakout discussion on the design of a financial mechanism concluded that the mechanism should ideally be designed to signal to manufacturers that significant capital will be made available, if needed, and be made flexible enough that funds could be disbursed at various "gates", (e.g. WHO approval for widespread use and WHO recommendations on target populations, age groups and delivery strategies as per a SAGE process). It was also noted that manufacturers are currently scaling up without external funding given the emergency nature of the current outbreak, but that they may nevertheless require near-term support for these investments done at risk. Furthermore, providing support now may increase manufacturers' willingness and ability to consider the longer term work to perfect a stockpile vaccine beyond this current epidemic. The group also supported an approach, if needed, in which agreements with manufacturers could be tailored to each manufacturer's specific needs in order to ensure that all candidates that may have a role to play in responding to the epidemic were supported.

To address large-scale use of vaccines, participants indicated that Gavi's role should be one of catalysing and supporting coordination as well as potentially financing of a larger response by others in this space, given that many other players are already active and skilled in operating in emergency situations.

On the topic of future outbreak prevention, participants were supportive of the notion of a "continuum of support" from responding to the current outbreak to preventing future ones. Given the group's emphasis on the importance of a next-generation vaccine, there was an unresolved question as to whether an advanced purchase commitment mechanism would provide enough of an incentive for the required development activities. Although creation of an appropriate stockpile vaccine — and the incentives to do so — was seen as an important long term priority, the group thought that this work could be tackled in the medium term and should not delay an immediate response.

In conclusion, participants affirmed their support for the work that Gavi is doing and their view that there is an important role for Gavi to play as a multilateral in the Ebola vaccine acceleration effort. Next steps are to use the guidance from the workshop to develop a concrete proposal for what Gavi's role could look like (in terms of an advanced purchase commitment, support for large-scale vaccination and support for a stockpile), estimate the resource requirements and bring a proposal to the 10-11 December Gavi Board meeting.

2. List of Participants

Name	Organisation
Jon Abramson	Wake Forest Baptist Health
Manica Balasegaram	MSF Access Campaign
Jesus Barral-Guerin	UNICEF Supply Division
Seth Berkley	Gavi, the Vaccine Alliance
Julia Blau	Ministry of Foreign Affairs, France
Thomas Cherian	World Health Organization
James Droop	Cross-UK Governmental Ebola Vaccine Response
Christopher Egerton-Warburton	Lion's Head Global Partners
Varatharajan Durairaj *	African Development Bank Group
Don Gerson	PnuVax, Inc.
Dimitrios Gouglas	Norwegian Institute of Public Health
Anuradha Gupta	Gavi, the Vaccine Alliance
Ana Maria Henao Restrepo	World Health Organization
Andrew Jones	Bill & Melinda Gates Foundation
Andrea Holzaepfel	KfW
Samuel Kargbo	Ministry of Health and Sanitation, Sierra Leone
David Kaslow	PATH
Stephen Kennedy	Pacific Institute for Research and Evaluation, Liberia
Marie-Paule Kieny	World Health Organization
Jason Lane	DFID
Eric Mast	US CDC
Neneh Mbye	African Development Bank Group
David Nabarro	Office of the UN Special Envoy on Ebola
Birahim Pierre Ndiaye	Hospital Aristide Le Dantec, Senegal
Michael Kent Ranson	World Bank
Nina Schwalbe *	UNICEF Programme Division
Angela Shen *	USAID
Samuel J Smith	Ministry of Health and Sanitation, Sierra Leone
Brenda Waning	UNITAID
Conall Watson	London School of Hygiene and Tropical Medicine

* Dialed-in by phone

C

ANNEX C:
ANALYSES PERFORMED

1. Demand and supply

- Demand scenarios / target populations, supply estimates

2. Funding gap identification

- Assessment of discrepancies between costs and support

3. Production and procurement

- Key assumptions, envelope sizing, stockpile information

4. Vaccine roll out

- Standard and additional cost categories, scaling for present Ebola environment

ANNEX C1: DEMAND & SUPPLY

Goals

Identify potential demand for an Ebola vaccine in the 3 affected countries

Project potential Ebola vaccine supply through 2015

PLANNING ASSUMPTION: HIGH DEMAND SCENARIO IN 3 MOST AFFECTED COUNTRIES

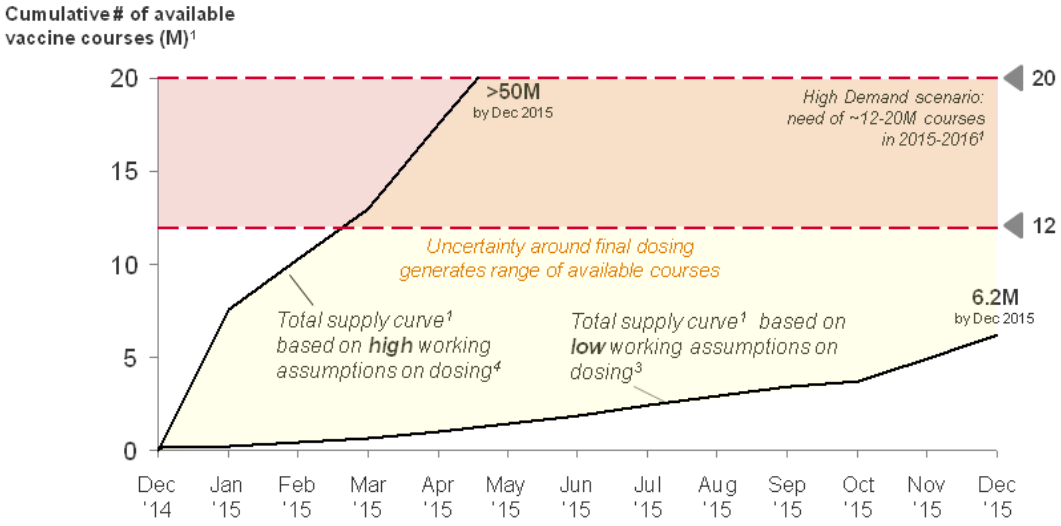
High end of target populations is ~12-20M[1]
– includes adults (~12M) or both adults and children (~20M)

Potential beneficiary populations		Estimated size of potential target population (in thousands)			
		Guinea	Liberia	Sierra Leone	Total
1	Heath workers in clinical settings (e.g. doctors, nurses, cleaners)	1.7	11.7	6.2	**19.8**
2	Community Ebola responders (e.g. burial teams, contact tracers etc)	25.3	40.3	32.2	**97.8**
3	Contacts providing home care of cases and ring vaccination of contacts	2.7	66.9	6.6	**16.0**
4a	Age-based strategy: Vaccinating children in affected areas	4717.4	1740.6	2351.0	**8809.0**
4b	Age-based strategy: Vaccinating adults in affected area	6458.6	2249.1	3261.7	**11969.4**
5	Geographical strategy: affected districts& counties vs unaffected				
6	Pregnant women	251.8	105.1	125.9	**482.8**
7	People with HIV	88.8	16.6	40.3	**145.7**

1. High demand based on trajectory of current outbreak limited to Liberia, Sierra Leone and Guinea. In the case of EVD spread to neighboring countries demand can be as high as 300M based on total population of those countries (which include Nigeria, Senegal, DRC, and Mali).
Source: WHO's background information for Gavi's workshop – Nov 2014

CURRENT SUPPLY PLANS: 2015

BASED ON WHO ESTIMATES AND MANUFACTURER INFORMATION



1. Includes supply estimates from GSK, NewLink and Janssen. 2. 12M adults in Liberia, Sierra Leone, and Guinea; 20M entire population of these countries. 3. Assume dosing of $5x10^7$ pfu for NewLink's candidate (Working assumption of WHO in Gavi workshop report) 4. Assumes NewLink's estimate of 10^6 pfu for final dosing; being tested in clinical trials.
Note: Based on most recent data received as of 25 Nov 2014; Assumes all three candidates successfully complete clinical trials. Landscape evolving rapidly, conclusions are preliminary.
Source: WHO - Vaccine production plans from manufacturers; BCG analysis

ANNEX C2: FUNDING GAP IDENTIFICATION

Goals

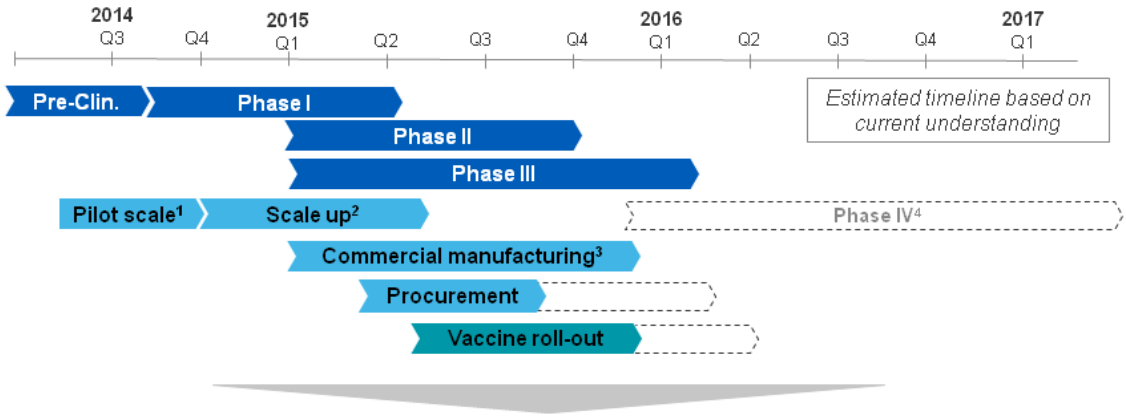
Outline the funding needs for accelerating Ebola vaccine availability

Identify key funding gaps

Highlight subset of unmet funding needs where Gavi could potentially play a value-added role

C2 Funding gap

WHERE COULD ADDITIONAL FUNDING ACCELERATE EBOLA VACCINE AVAILABILITY?



4 major cost categories identified

- **Clinical trials**
- **Production & procurement**
- **Vaccine roll-out**
- **Future vaccine preparedness**

1. Production at levels required to support clinical trials (~10k doses/month), likely done through a CMO; 2. Production in the order of ~100k doses/month, likely scale up via (a) increasing/optimizing current batch size, (b) adding lines to pilot scale, (c) engaging add'l CMO resources; 3. Production of ~1M+ doses/month requiring tech transfer to commercial scale facility, process development, use of larger vessels, establishing additional QC testing, etc. 4. Phase IV trials not included in this analysis; post-licensure trial plans do not exist and cost estimates vary widely based on sample size and length of study. Cost will be incorporated in analysis as companies communicate initial plans/design of study.

OVERVIEW OF COST CATEGORIES

Cost category		Description
Clinical trials		• Execution of Phase I, Phase II, Phase III, and Phase IV[1] clinical trials
Production & procurement	**Production scale up**	• Scale up of vaccine production over time • I.e. clinical trial scale (pilot scale), scale optimization within existing facility, commercial scale up at new purpose built facility and/or substantial increase of bioreactor sizes in existing facilities
	Procurement	• Purchasing of vaccine(s) for current outbreak
	Risk mitigation	• Cover potential vaccine liability costs (i.e. indemnification)
	Diverted manufacturer resources	• Manufacturers' investment threshold may not be met or they may be deprioritizing other vaccine programs with higher market potential
Vaccine roll-out		• Operational costs, including for planning & coordination, social mobilisation, IEC, training, HR, transport /logistics/cold chain, waste management, surveillance and monitoring of AEFI, etc.

Future vaccine preparedness		• Longer-term support for Ebola vaccine development and deployment, including:
		  • Development, including clinical trials
		  • Production scale up
		  • Procurement
		  • Vaccine roll-out

1. Phase IV trials not included in this analysis; post-licensure trial plans do not exist and cost estimates vary widely based on sample size and length of study. Cost will be incorporated in analysis as companies communicate initial plans/design of study.

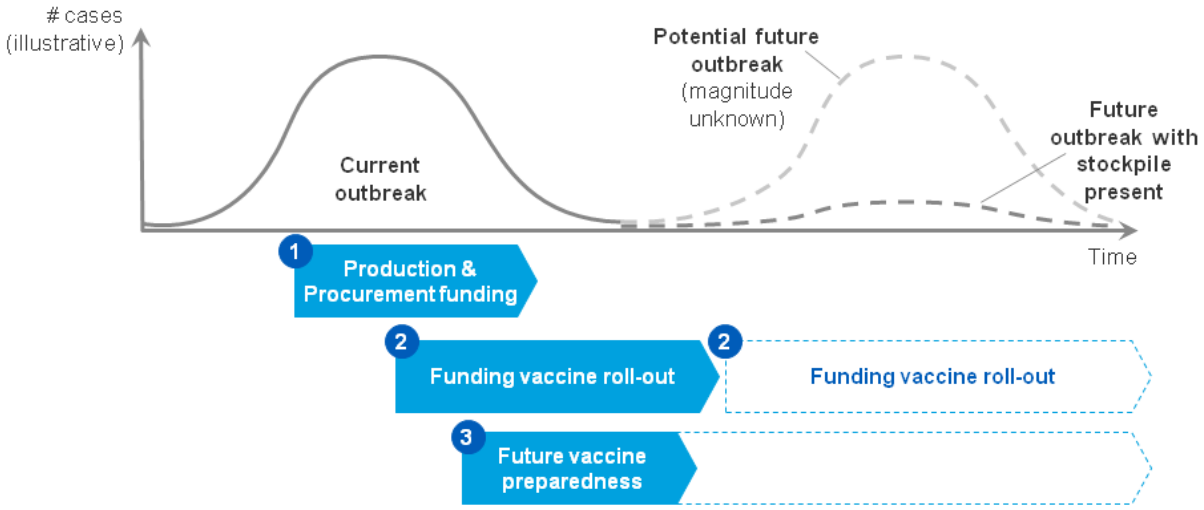
C2 Funding gap

WHERE MIGHT GAVI PLAY A VALUE-ADDED ROLE IN ADDRESSING FUNDING NEEDS?

Cost category		Critical funding area	Est. funding coverage *as of Nov 2014*	Fit with Gavi capabilities? (based on past experience, partner input)
Clinical trials		Phase I	High	✗
		Phase II	High	✗
		Phase III	High	✗
Production & procurement	Production scale up	Production at clinical trial scale	High	✗
		Scale up / scale optimization	Medium	✓
		Commercial scale mfg	Low	✓
	Procurement	Vaccine procurement	Medium	✓
	Risk mitigation	Indemnification	Medium	✗
	Diverted manufacturer resources	Diverted manufacturer resources	Low	✓
Vaccine roll-out		Operational costs	Medium	✓
Future vaccine preparedness		Clinical trials	Low	✗
		Production scale up	Low	✓
		Procurement	Low	✓
		Vaccine roll-out	Low	✓

C2 Funding gap

SUMMARY: PROPOSED AREAS FOR GAVI INVOLVEMENT



Note: Recovery activities added as a result of strong support at Gavi workshop

4 **Recovery of health and immunisation systems**

I.e. strengthen health infrastructure and broader vaccination efforts in relevant countries

ANNEX C3: PRODUCTION & PROCUREMENT

Goals

Describe differences in production cost and revenue structure among three main candidates

- Costs: Fixed costs, marginal costs of production (COGS),
- Revenue: Subsidies, selling to US stockpile, selling to UNICEF with Gavi funding

Share results of modeling

- Calculation of envelope sizes, determined by number of manufacturers and allocation of doses among them

Share the issues around stockpile sizing, and estimates of stockpile size for Ebola

- Assumptions and rationale driving global (procured via Gavi funds) and biodefense stockpile sizes

Understand implications and risk trade-offs in constructing envelopes

CURRENT PLANS FOR CLINICAL & DEVELOPMENT & PRODUCTION SCALE UP (I/III)

C3 Production and procurement

GlaxoSmithKline

Summary of plans: ChAd3-ZEBOV

Clinical trials	**Phase I**	n=~250 patients in US, EU, and Africa (non-affected areas).
	Phase II	n=3,000; Will run in parallel in Africa (not in affected areas);
	Phase III	n = ~30,000 randomised control trial (RCT) in Liberia; n=8,000 step-wedge in Sierra Leone (joint with NewLink product)
Production scale up	**Pilot scale**	One line at Advent (contract manufacturing organization) -- 24k vials (assume vials = doses)
	Scale optimization	Add up to 5 lines, move from contract manufacturer to GSK facility in Italy; ~230-310k doses/month
	Commercial mfg	Move to existing facility in Belgium. Will start process dev on Jan; expect to start Sept '15 ; ~1M doses/mo
Marginal cost of production	**Bulk**	Adenovirus (Ad) based vaccine – costs expected to be comparable to other Ad vaccines
	Fill finish	Potential option to leverage US fill finish network - TBD
	Other reqs	Super cold chain during production – store, handle at -80°C; ship in dry ice

CURRENT PLANS FOR CLINICAL & DEVELOPMENT & PRODUCTION SCALE UP (II/III)

C3 Production and procurement

NewLink GENETICS / MERCK

		Summary of plans: rVSV-ZEBOV
Clinical trials	Phase I	n=~250 patients in US, EU, and Africa (not affected areas)
	Phase II	Phase II – expected to start Jan 2015
	Phase III	Same trial as GSK (RCT n=30,000 in Liberia);
Production scale up	Pilot scale	Pilot scale at IDT – 10L scale
	Scale optimization	Multiple runs at 30L scale. Partnership with Merck.~50k-5M doses in Q1'15 (depending on dosing level).
	Commercial mfg	Process dev. underway to reach to 250L scale -50k vials/lot (assume per month) – 50k-5M doses /month – Unknown by when
Marginal cost of production	Bulk	Adenovirus (Ad) based vaccine – costs expected to be comparable to other Ad vaccines
	Fill finish	Use fill finish network (4 different contractors in the US) made available by BARDA
	Other reqs	N/A

CURRENT PLANS FOR CLINICAL & DEVELOPMENT & PRODUCTION SCALE UP (III/III)

C3 Production and procurement

janssen

		Summary of plans: Ad26 / Ad35 / MVA
Clinical trials	Phase I	Expect to start Q1 2015 in US/EU – expect results by May'15
	Phase II	Phase II in mid Q2 2015 (EU/Africa – outside of affected areas)
	Phase III	Likely in parallel with Ph II in affected areas;
Production scale up	Pilot scale	2x10L reactors. 100-140k courses
	Scale optimization	Scale up to 50L reactor. Up to 1-2M doses 2015
	Commercial mfg	Could scale up to 500L to reach > 1-2M / batch. Not planned yet but facility available late 2016 – early 2017
Marginal cost of production	Bulk	Prime: Adenovirus based vaccine (Ad26) Boost: MVA-based vaccine[1]
	Fill finish	Use fill finish network (4 different contractors in the US) made available by BARDA
	Other reqs	N/A

1. MVA: Modified Vaccinia Ankara

C3 Production and procurement

GAVI ENVELOPE LOOKS TO MAXIMIZE VACCINE AVAILABILITY WHILE MINIMIZING SUPPLY RISKS

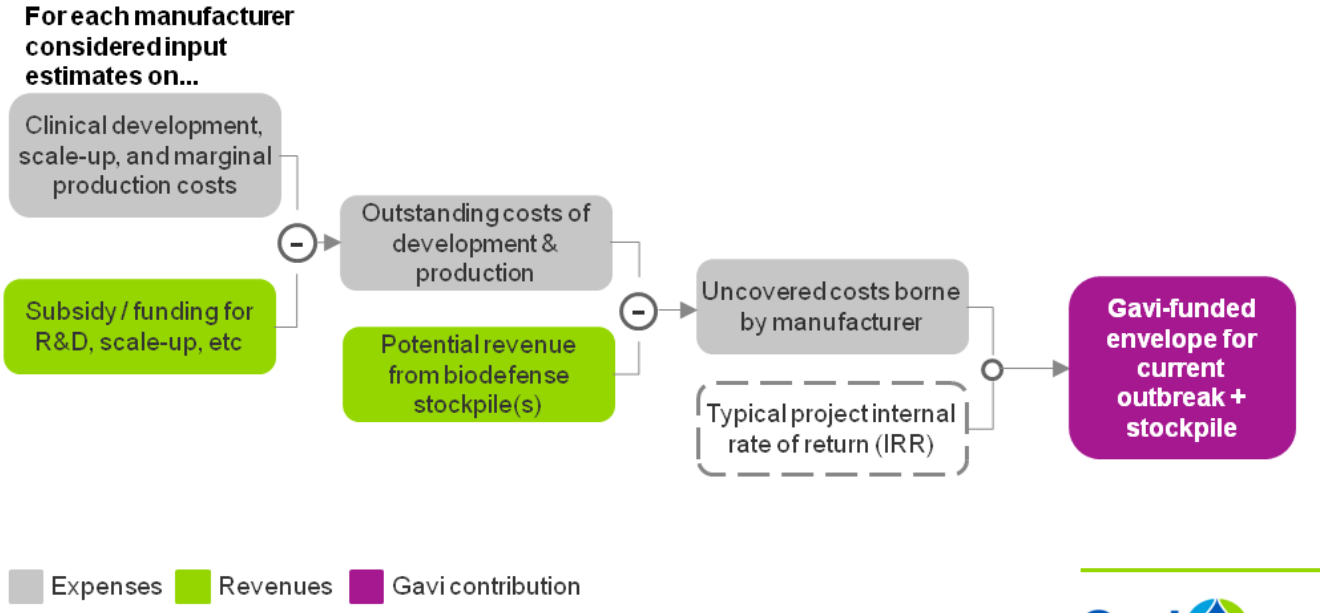
Gavi funding envelope aims to establish financing structure that helps ensure that production capacity of Ebola vaccines for large scale vaccination exists

4 steps process were followed to determine size of Gavi envelope:

1. **Understand cost structure for main vaccine candidates**
   - Focus on clinical development, production scale-up, and vaccine manufacturing
2. **Understand financial needs to ensure rapid scale-up of production capacity**
3. **Understand as much as possible what other partners are doing to address these bottlenecks**
   - e.g. direct funding, procurement of stockpile, etc.
4. **For remaining unsubsidized costs, estimate an envelope that takes into account:**
   - Meeting demand as soon as possible – enough for "high-demand" scenario
   - Assurance of supply security - Preempts potential failure of 1 or more vaccine candidates
   - Cost-effective solutions – funding is limited

MODEL CREATED TO CALCULATE PROCUREMENT AND PRODUCTION ENVELOPE

Underlying question: What is the funding envelope required to support the production and procurement of 12M courses for current outbreak + a global stockpile of 1M course?



C3 Production and procurement

KEY ASSUMPTIONS UNDERLYING MAGNITUDE OF GAP AND ENVELOPE SIZE

A $100-600M gap was estimated...

Underlying assumptions

- Up to 3 manufacturers are being considered for support
  - Those that are closest in development: **GSK, NewLink and Janssen**
- Potential areas of support include production scale-up and vaccine procurement
- Envelope defined by procurement needs related to 'high-demand' scenario – 12M vaccine courses
- Courses for current outbreak are to be rolled out in 2015-2016
  - Vaccines will be recommended for use by WHO in this timeframe
  - Stockpile is to be created in 2015-2016 and maintained until 2020

...from which an envelope of $300M was defined

Underlying assumptions

- Different % of costs are subsidized per manufacturer
  - Based on discussion with them and current donors
- Vaccine course volumes for procurement were largely based on manufacturers' current supply plans – *cannot procure more than they can supply*
- Procurement of a biodefense stockpile offsets part of the total gap
- Does not take into account any residual value of investments to manufacturers
- Limited economies of scale due to replication of small scale processes in some cases and limited process optimization in other cases (due to 'rushed' development)

VARYING # OF MANUFACTURERS AND COURSE ALLOCATIONS RESULTS IN DIFFERENT ENVELOPES

Each of the scenarios below were modeled and the envelope size required was calculated

% subsidised by non-Gavi funders [1]

Gavi support for procurement only — *Gavi support for procurement and scale-up*

Envelope size to produce 12 M courses in 2015-16 [2] ***($USD M)***

1a	Support for 1 manufacturer *(lowest cost to Gavi)*	
1b	Support for 1 manufacturer *(highest cost to Gavi)*[3]	
2a	Support for 2 manufacturers *(lowest cost to Gavi)*	
2b	Support for 2 manufacturers *(highest cost to Gavi)*	
3	Support for all 3 manufacturers	

Gavi envelope size: $100-200M
Gavi envelope size: $100-300M
Gavi envelope size: > $300M

Ultimate envelope size aims at balancing cost, supply security and maximum doses available in 2015

1. These scenarios assume that all manufacturers are subsidised by non-Gavi funders to the same extent (as a % of their costs). More detailed analysis, not shown here, reflects different subsidies by manufacturer, with different outcomes in required envelope size. 2. Timeline shown depends on vaccines receiving WHO recommendation for use within the 2015-16 period. 3. According to current supply plans, the manufacturer in row 1b will only be able to generate ~6M courses in 2015-2016. Envelope sizes are reflective of Gavi procurement of this reduced volume.

KEY IMPLICATIONS OF ENVELOPE SIZING MODEL

Manufacturers each have different economics

Each manufacturer has unique needs around scale-up and production costs

- Emphasises the need for tailored procurement negotiations with each

Several potential scenarios can be addressed with a $300M envelope

Envelope size calculated for high-demand (12M courses) scenarios

- Spend for the lower-demand scenario (100k courses) expected to be $100-200M

High-demand scenarios involve procurement of courses, with either

- Full support of uncovered scale-up costs for the 2 manufacturers with lowest costs
- 3 manufacturers partially-supported for scale-up

$300M envelope balances supply security and cost effectiveness

Envelope structure and size provides flexibility to manage to the evolving situation

- At this envelope size, possible to support 2-3 manufacturers, without "choosing a winner" at this early stage
- Allows for achieving required number of vaccine courses in situation where not all vaccine candidates are recommended by WHO
  - With current information on manufacturer subsidies, envelope could allow procurement of up to 12M doses in 2015-2016[1] with any 2 manufacturers

1. Assumes that relevant vaccines are recommended for use by WHO in the 2015-16 timeframe.

ANNEX C4: FUNDING VACCINE ROLL OUT

Goals

Define approach for estimating operational costs at high level for Ebola vaccine roll out in the current outbreak

Scale regular cost categories as relevant for current Ebola outbreak and account for additional cost categories

Summarize preliminary operational cost estimates for response to current Ebola outbreak

Estimate operational costs associated with first-generation Ebola vaccine stockpile for 2015 - 2020

C4 Vaccine roll out

OVERVIEW: APPROACH FOR ARRIVING AT INDICATIVE OPERATIONAL COST ESTIMATES

	Min / max operational costs based on latest campaign proposals in AFRO countries[1]		Ebola multipliers			Additional cost categories
Scenario 1: 100,000 frontline workers	**Largely fixed cost (absolute amounts)**		Low	High		
	Social mobilisation, IEC and advocacy					
	Surveillance, including AEFI monitoring[2]	x			+	▪ Emergency Operations Centres ▪ Cold chain and logistics ▪ Security and crowd control ▪ Infection control measures
	Vehicles & transportation					
	Evaluation					
	Largely volume-driven cost (per target person amounts)		Low	High		
	Training					
	Human resources	x				
	Waste management					
Scenario 2: 12M people	**Largely volume-driven cost (per target person amounts)**		Low	High		
	Social mobilisation, IEC and advocacy					
	Training					
	Surveillance, including AEFI monitoring[2]					
	Human resources	x			+	▪ Emergency Operations Centres ▪ Cold chain and logistics ▪ Security and crowd control ▪ Infection control measures
	Vehicles & transportation					
	Waste management					
	Evaluation					

Note: the following represent preliminary estimates meant to indicate potential magnitude of implementation costs. More detailed country-level costing will be required to assess specific implementation funding needs and gaps

1. I.e. assessed costs for NVS proposals between 2012-2014 recommended for approval by IRCs from AFRO countries with target population <10M (n=15). Includes 1 Measles SIA proposal, 7 Measles-Rubella proposals, 6 Men A proposals, and 1 Yellow Fever proposal;
2. It is assumed impact monitoring would be implemented/coordinated by Emergency Operations Centres.

C4 Vaccine roll out

EBOLA MULTIPLIERS APPLIED TO REGULAR OPERATIONAL COST CATEGORIES

Regular campaign cost categories	Cost per target person (US$)[1]		Considerations related to Ebola vaccine roll-out	Ebola multiplier	
	Low	High		Low	High
Social mobilisation, IEC and advocacy	0.07	0.1	Higher-than-usual need for mobilisation of special target populations and general public given nature of Ebola outbreak; need for robust crisis management communication	1.5	2
Surveillance, including AEFI monitoring	0.02	0.03	Increased need for and challenges associated with management of vaccine recipients with fever & monitoring of AEFI	1.5	3
Vehicles & transportation	0.08	0.12	Limited in-country resources, challenging infrastructure, higher fuel & rent prices	1.5	3
Evaluation	0.01	0.01	Increased evaluation needed since first time using Ebola vaccine (e.g. lessons learned, coverage survey)	1.5	2
Training	0.09	0.13	Standard training supplemented with increased focus on messaging and personal protection measures	1.5	2
Human resources	0.19	0.29	Very limited national HR capacity, increased supervision needed, daily 'productivity' of vaccinators may be lower	1.5	3
Waste management	0.01	0.02	Special incineration of vaccination equipment to be consistent with Ebola waste management guidelines	1.5	2

1. Based on assessment of costs for NVS proposals between 2012-2014 recommended for approval by IRCs from AFRO countries with target population <10M (n=15). Includes 1 Measles SIA proposal, 7 Measles-Rubella proposals, 6 Men A proposals, and 1 Yellow Fever proposal.

C4 Vaccine roll out

COSTING APPROACH FOR ADDITIONAL COST CATEGORIES

Cost category	Description	Costing approach	Key inputs / assumptions

Planning, management, and coordination	• Emergency Operations Centres (EOCs) at national and possibly regional level to coordinate pre-, intra-, & post-campaign activities, e.g.
	  • High quality micro-planning
	  • Coordination of data managers
	  • Vaccine coverage monitoring and post-campaign assessment
		• Leverage WHO information on the development of EOCs to support polio vaccination in Nigeria	• Potential infrastructure, equipment, and salary costs for small (~15 people) and large (~21 people) EOCs
			• Assumed 1 EOC / country for Scenario 1, 2 EOCs / country for Scenario 2

Cold chain and logistics	• First-generation Ebola vaccine will likely need to be stored at -70°C to -80°C • Existing cold chain infrastructure in affected countries is very limited due to weak health systems	• Leverage Gavi information on potential equipment & transport requirements / costs • Note: high uncertainty due to dependencies on vaccine storage indications, potential distribution plans, etc.	• Estimated cost, capacity, and need for special freezers • Estimated cost, capacity, and need for special vaccine carriers • Estimated cost and needs for dry ice • Estimated transport costs

Security and crowd control	• Need for security personnel to:
	  • Control crowds
	  • Protect limited vaccine stocks
	  • Protect vaccination staff at immunisation sessions
		• Bottom-up costing	• Estimated # of vaccination sites
			• Estimated # security personnel / site
			• Estimated monthly salary for security personnel
			• Estimated # of months security will be needed

Infection control measures	• Personal protective equipment (PPE) for vaccinators to prevent Ebola transmission	• Leveraged WHO data on PPE needs and costs	• Estimated # of vaccinators needed (based on assumptions about # people vaccinated / day in Scenario 1 v. 2

PRELIMINARY OPERATIONAL COSTS ESTIMATES FOR CURRENT EBOLA OUTBREAK

	Cost category	Scenario 1 (100,000 target pop.)		Scenario 2 (12M target pop.)	
		Low ($M)	High ($M)	Low ($M)	High ($M)
Regular cost categories	Social mobilisation, IEC and advocacy	1.37	1.83	1.26	2.39
	Surveillance, including AEFI monitoring	0.42	0.84	0.36	1.08
	Vehicles & transportation	1.70	3.40	1.44	4.31
	Evaluation	0.11	0.15	0.18	0.24
	Training	0.01	0.03	1.62	3.11
	Human resources	0.03	0.09	3.41	10.41
	Waste management	0.00	0.00	0.18	0.48
Additional cost categories	Planning, management, and coordination	1.67	2.67	3.34	5.33
	Cold chain and logistics	0.09	1.32	2.68	5.54
	Security and crowd control	0.03	0.10	1.43	2.86
	Infection control measures	0.11	0.22	1.33	2.65
TOTAL		6	11	17	38

C4 Vaccine roll out

PRELIMINARY OPERATIONAL COSTS FOR FIRST-GENERATION VACCINE STOCKPILE

Cost category	Description	Costing approach	Key inputs / assumptions	Estimated cost
Stockpile management	• Management and coordination of stockpile activities	• Assume typical level of Gavi support	• $500,000 / year • 2015-2020	**$3M**

Operational cost of vaccine roll-out[1]	• Support for key vaccine roll-out activities such as
	  • Social mobilisation
	  • Human resources
	  • Training
	  • Transport
	  • Cold chain
	  • Immunisation session supplies
	  • Waste management
	  • Technical assistance
	  • Surveillance and monitoring
		• Assume typical level of Gavi support
		• Assume 1M course as indicative size of first generation Ebola vaccine stockpile
			• $0.65 / target person to support response to outbreak with up to 1 million courses / year
			• 2015-2020
				$4M

1. Note: assumed roll out of stockpiled vaccines is in response to outbreaks rather than for preventative vaccination before an outbreak occurs