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The Market Shaping Goal

Shape vaccine markets to ensure adequate supply of appropriate, quality vaccines at low and sustainable prices for developing countries.

Supply and Procurement Roadmap

Licenced Ebola Vaccine

Public Summary

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Infectious disease epidemics, including Ebola, pose a clear and ongoing risk to global health, security, and economic prospects.

Ebola virus disease (EVD) is caused by the transmission of Ebola virus to people from contact with infected animals and spreads in the human population through human-to-human transmission. Once the human population has been infected, health workers; family members or others in close contact with infected people; and mourners who have direct contact with bodies during burial rituals are most at risk. The average EVD case fatality rate is around 50%.

The virus is prevalent in the Ebola belt, which extends from West to Central Africa. Historically, outbreaks have been in localised rural jungle areas and while there was a high mortality rate relatively few people died. In the 2014-2016 West African outbreak the number of cases and deaths exceeded those from all past outbreaks combined.[1]

The 2014-2016 outbreak was unusual in its scope and detrimental impact and we should not assume that future epidemics will have similar trajectory or impact. The World Bank estimated that Sierra Leone, Liberia and Guinea lost at least US$2.2 billion in forgone economic growth in 2015 alone as a result of the epidemic.[2]

Ebola outbreaks can be controlled through well-defined interventions: 1. early isolation of patients to prevent transmission at home and in the community; 2. early detection of new Ebola cases through close monitoring of contacts and isolation of contacts when they show symptoms and; 3. safe burial of the deceased to reduce transmission through contact with dead bodies. Vaccines can also play a role in Ebola emergency response and control either reactively in response to an outbreak or prophylactically.

Gavi Engagement

In 2014, the Board approved a funding envelope not exceeding $390 million which includes about $300 million earmarked for the procurement through UNICEF of licensed, prequalified Ebola vaccines and the establishment of a stockpile for 2016-2020.

In 2015, Gavi offered an Advanced Purchase Commitment (APC) to several manufacturers of candidate Ebola vaccines and in late 2015 the Gavi Executive Committee approved an APC, including a prepayment of $5 million to Merck. The value of the prepayment will be used as a credit against the first procurement of licensed vaccine for a stockpile. A requirement of the APC is that a quantity of investigational vaccine be made available for outbreak response under

[1] WHO. 2016 *Ebola situation reports: archive*. See http://www.who.int/csr/disease/ebola/situation-reports/archive/en/ and Colthart, CEM et al. 2017. The Ebola outbreak, 2013–2016: old lessons for new epidemics Philosophical Transactions of the Royal Society B: 372 (1721).

[2] World Bank. 2016. World Bank Group Ebola Response Fact Sheet April 6 2016. See http://www.worldbank.org/en/topic/health/brief/world-bank-group-ebola-fact-sheet

guidance from WHO. A principle across all vaccine investments is that Gavi only supports the procurement of licenced, WHO prequalified vaccines.

Looking forward, the Vaccine Investment Strategy (VIS) for 2019-2024 will review the feasibility and desirability of extending Gavi support for the funding of a licenced second-generation vaccine with enhanced properties or stockpile use.

Market Overview

A key reason for the market failure in Ebola vaccines is the unpredictable and small market: historically sporadic Ebola outbreaks have been relatively contained and impacted small, rural communities in developing countries. However, post 2014-2016 outbreak, Ebola was made a priority. There remains considerable unknowns about the future demand for Ebola vaccines. Due to these uncertainties, it is likely that there will be a limited commercial market that is segmented by prophylactic and reactive vaccines. Governments and non-governmental organizations will be the only likely buyers.

The recommendation for use presented at SAGE in April 2017[3] suggests that localised Ebola outbreaks can be contained with ring vaccination of rVSVΔG-ZEBOV-GP. This assumes a localised, rural outbreak and classic control measures.

Annual demand for a licensed vaccine will be a factor in Ebola stockpile sizing with the need to replenish doses in the stockpile either because of use in an outbreak or the need to refresh expired doses. It may also be useful to consider the implications of a prophylactic use indication for health care and frontline workers on stockpile size and market shaping.

There are many factors that could impact demand:

- The nature of Ebola outbreaks: unpredictable and sporadic with multiple strains.
- Market segmentation and recommendations for use, specifically whether vaccines are developed that will be recommended for:
    - Preventative use across a broad population base or only in high-risk areas or in high-risk populations.
    - Reactive use during an outbreak across a broad population base or only in high-risk populations (current recommendation equivalent).
- Gaining a longer term view of demand: Potential revisions to recommendations for use could change the size of high-risk populations to be vaccinated reactively during an outbreak and thus the size of a stockpile needed to respond. Some work has been done to model this demand and stockpile needs. SAGE (2017) has suggested that these be further refined.

[3] Camacho, Anton. 2017. Observed and forecasted impact of different candidate Ebola vaccines immunization strategies and target populations. Presented at SAGE Working Group, March 2017.

- Evolution of clinical data: Potential revisions of recommendations for use once more clinical data are available on duration of protection, efficacy, safety for pregnant women, HIV-positive individuals and young children.

Supply

There are currently twelve candidate vaccines (including monovalent, bivalent or multivalent candidates) that have undergone or are actively undergoing clinical development. Only one vaccine trial has generated efficacy data. None are licenced.

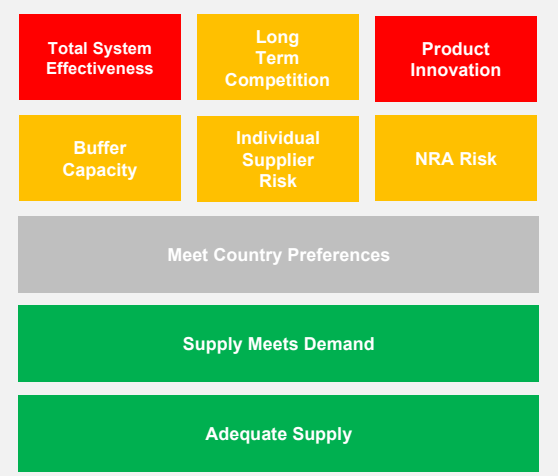
If an outbreak were to occur in the pre-license period, an investigational Ebola vaccine (rVSV vaccine developed by Merck) is ready and available to be accessed in the context of emergency response efforts. Following the SAGE recommendation in April 2017, the rVSV vaccine should be used under an Expanded Access study protocol using a ring vaccination strategy to respond to the outbreak.

In the post licensure period the Gavi APC of a $5 million pre-payment will be used as a credit toward the first doses of licensed and prequalified vaccine to be stockpiled. Several factors could impact the supply of Ebola vaccines:

- Adequate funding and continued political will of international community to create a secure market for Ebola vaccine.
- Effective stockpile sizing and maintenance: low vaccine volumes required for stockpiling may not allow for efficient use of manufacturing plants.
- Regularisation of demand: if an outbreak occurs, additional vaccine doses will likely be needed, either to replenish the stockpile or to control the outbreak. The surge capacity required could create challenges for maintaining manufacturing expertise and capacity, and result in opportunity costs to the manufacturer.
- Stockpile storage capacity requirements of down to -60°C.

Healthy Market Framework

This healthy market analysis (HMA) is different from those found in most Gavi roadmaps. This is because there is currently no licenced Ebola vaccine for Gavi to fund. This HMA assesses the current Ebola pipeline and looks forward to the future Ebola market by drawing on what we currently know and making certain assumptions e.g. the maintenance of current WHO use recommendations.



The HMA suggests that in the medium term, when one vaccine is licensed, the Ebola market will meet 2 of the 9 attributes: adequate supply and supply meets demand. NRA, individual supplier risk, buffer capacity and long term competition are partially met. Product innovation and total systems effectiveness are unmet. These attributes touch upon the appropriateness of vaccines for developing country markets e.g. cold chain requirements, strain coverage and clinical data for diverse populations. There is a risk, given their mandates, that funders of second generation vaccines will prioritise and incentivise the development of products

for developed country markets. The 'meet country preferences' attribute cannot be determined at this time (and is therefore in grey) given there is no currently licenced vaccine on the market.

The affordability of a future Ebola vaccine for developing country markets is an important consideration over the medium and long term and should be monitored as products come closer to licensure. However, at this point we have not focused on affordability because our main short term objective is to secure the availability of appropriate vaccines. It is likely that Ebola vaccines will be expensive relative to others in the Gavi portfolio.
Supply Meets Demand: **Met.** Given current modelling, there is sufficient quantity of investigational vaccine and sufficient production capacity to satisfy future licensed vaccine stockpile requirements. We expect modelling to evolve as use recommendations are updated.

Country presentation preference: **NA.**

Buffer capacity: **Partially met.** Based on current assumptions of vaccine use only in reactive circumstances, buffer capacity will be difficult to maintain and will need to be considered when sizing and constructing a stockpile of licenced vaccines.

Individual supplier risk: **Partially met.** A lead vaccine candidate is under development by an experienced and stable manufacturer with a relatively low risk manufacturing process. The sporadic nature of demand and need for the optimisation of production will create some technical risks.

NRA risk: **Partially met.** The current lead vaccine will be reviewed by a stringent NRA and an Emergency Use Assessment and Listing (EUAL) application is being reviewed by WHO. However, regulatory pathways to licensure, PQ status and criteria for granting of EUAL are currently complex and unclear. New manufacturers are expected to offer further NRA diversity that potentially carry greater risk profiles.

Long-term competition: **Partially met.** Given current information it is anticipated that one vaccine with reactive indication will be licensed. There is a risk manufacturers will exit the market before bringing second generation products to market.

Product innovation: **Not met.** Developing an Ebola vaccine that is appropriate for developing counties and that eventually meet developing country preferences is critical. Current cold chain requirements make the stockpiling and deployment of vaccines difficult. Current vaccines have limited strain coverage. There is a risk that push funding will incentivise the development of vaccines more appropriate for high income markets.

Total systems effectiveness (TSE): **Not met.** Mechanisms and guidelines for country use of investigational and licenced vaccines are unclear. Data on efficacy and safety for pregnant women, HIV-positive individuals and young children are limited. Data on duration of protection conferred by various candidate vaccines, cross protection between virus species and number of doses required, including need for boosting doses, are needed to establish the acceptability of vaccines for use in health-care workers.

Supply and Procurement Objectives

The supply and procurement objectives were analysed and resulted in the following target outcomes:

1. Ensure vaccine related preparations for an outbreak are completed in advance of a licenced vaccine.
2. One (1) manufacturer with sufficient capacity license a first generation vaccine before 2021.
3. Maintain pipeline of two (2) potential second generation vaccines with improved characteristics that are appropriate for developing country markets (e.g. optimisation of supply, thermostability, dosage requirements of vaccines and multi-valent vaccines).
4. Complete collection of on-going clinical data on vaccine efficacy, safety, duration of protection, cross protection between virus species.

Supporting Stakeholder Action Plan

An action plan ensures the coordination between Gavi Alliance stakeholders and is designed to facilitate the achievement of the above target outcomes. The action plan includes the following items:

- Work with stakeholders to finalise practical guidance on the use of both investigational and licensed vaccine in an outbreak response in order to clarify prioritisation, funding, procurement mechanism etc.
- Expedite approval of the expanded access research protocol by local NRAs and an ethics review committee in the event of a future outbreak.
- Update use recommendations and vaccination strategies as additional data and information become available.
- Model and size Ebola demand based on scenarios considering recommendations for use, vaccination strategies and potential new clinical data, risks involved with under sizing the stockpile and ability to manufacture new vaccines rapidly, and publish size requirements for licenced vaccine stockpile in order to allow for optimisation of supply.
- Support stakeholder engagement to close gaps and clarify regulatory pathways to licensure particularly in developing country markets.
- Engage manufacturer on the price of Ebola vaccines (in particular in the context of the APC) as product approach licensure.
- Engage the Gavi Board and support decision making on whether to potentially fund a stockpile of second generation Ebola vaccine after 2020 as part of the VIS process.
- Annually share and discuss Ebola market dynamics with pipeline manufacturers (sharing the public roadmap through the roadshow).
- Support stakeholder engagement to identify and leverage other vaccine technology platforms relevant for the development of Ebola vaccines.
- Work with stakeholders to understand manufacturer funding needs and encourage stakeholders (e.g. CEPI, EU, BARDA, NIH, etc.) to fund the development of second generation vaccines appropriate for Gavi-supported countries.
- Work with relevant stakeholders (e.g. CEPI and WHO) to identify the gaps and coordinate the development of required clinical data.