February 2015

Recommendations for Accelerating the Development of Ebola Vaccines

REPORT & ANALYSIS

wellcome trust

CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

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The Center for Infectious Disease Research and Policy (CIDRAP), founded in 2001, is a global leader in addressing public health preparedness and emerging infectious disease response. Part of the Academic Health Center at the University of Minnesota, CIDRAP works to prevent illness and death from targeted infectious disease threats through research and the translation of scientific information into real-world, practical applications, policies, and solutions. For more information, visit www.cidrap.umn.edu.

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Foreword

As the world has battled the unprecedented morbidity and mortality from the 2013-2015 Ebola virus disease (EVD) epidemic in West Africa, it has become clear that Zaire Ebola virus transmission can be reduced by employing traditional public health measures such as contact tracing and infection control practices aimed at barrier protection. Nonetheless, the potential for EVD to become endemic—whereby ongoing virus transmission in the region occurs into the foreseeable future—is a real and very concerning possibility.

The availability of an effective and safe Ebola virus vaccine will be a crucial component of an integrated control approach that includes classic public health measures, medical treatment, and community interventions based on the social determinants of virus transmission. To accomplish this requires an unprecedented and well-coordinated public-private effort to develop vaccines that could be used in various possible scenarios.

We applaud the extraordinary efforts to date of the national and international communities to address the emergence of Ebola virus. To support the ongoing international effort, the Wellcome Trust and the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota established an Ebola Vaccine Team B in November 2014. Team B was created to put fresh eyes on the same issues being addressed by vaccine manufacturers, government regulatory authorities, government public health agencies, non-governmental organizations, and global, national, and local leaders. Our purpose is to provide a complementary and creative review of all aspects of developing and delivering effective and safe Ebola vaccines, from funding, research, development, vaccine efficacy and effectiveness determination, licensure, manufacturing, and vaccination strategy (distribution and administration).

The Wellcome Trust–CIDRAP Team B includes 26 international subject matter experts involved in one or more areas of vaccine work. On Jan 12, we published an interim report, "Fast-Track Development of Ebola Vaccines: Principles and Target Product Criteria." We provide here the comprehensive report, "Recommendations for Accelerating the Development of Ebola Vaccines." We intend this information to serve as a "living document" and assist the global community by providing an additional expert framework for immediate consideration as part of global efforts to accelerate the availability of effective and safe Ebola vaccines to help bring an end to this epidemic and better prepare the world for inevitable future Ebola epidemics. The Team B report offers solutions to the great scientific, social, logistical and financial challenges of urgently delivering an Ebola vaccine.

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February 2015

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Executive Summary

The ongoing Ebola epidemic in West Africa has galvanized the will and resources of the international community toward an unprecedented goal: to make and deliver safe, effective vaccines that protect against EVD and do so *in record time*. This report analyzes the issues and challenges that such an endeavor faces and sets forth recommendations to address them. It synthesizes expertise shared by a panel of 26 distinguished leaders in public health, medicine, bioethics, pharmaceutical manufacturing, and humanitarian relief, and information from the scientific literature and other sources on vaccine development and delivery.

The goal of the project was to assist the vaccine development effort by providing a fresh perspective (a Team B analysis) of the same issues and challenges being addressed by the international collaborators.

The panel of work group members that formed the Ebola Vaccine Team B provided critical analyses collectively and in focus area work groups during a series of teleconferences held from November 2014 to January 2015. Discussions covered research and development; manufacturing; safety and efficacy/effectiveness determination; regulatory pathways; ethics; vaccination strategies; and community engagement. Results of the Ebola Vaccine Team B initiative are captured in the following documents:

- *Fast-Track Development of Ebola Vaccines: Principles and Target Product Criteria* is a 14-point framework that emerged early in the project as a guide for the accelerated effort to make vaccines available. It was released Jan 12, 2015.
    - *A Target Product Profile* was included in the framework and compares immediate and longer-term needs for an Ebola vaccine. The Research and Development Work Group identified optimal and minimal criteria. The profile has been revised since it appeared in the Jan 12 framework.
- *Recommendations for Accelerating the Development of Ebola Vaccines* (this report) presents the complete set of Ebola Vaccine Team B findings. The document is divided into focus-area sections that detail issues and challenges as well as recommendations specific to the topic.

Key Recommendations

A compilation of all recommendations can be found in Appendix B on page 63. Key points from the recommendations include:

- *Continued assessment of vaccine attributes is needed* to inform long-term use and future outbreaks. First-generation Ebola vaccines may or may not reflect the same

attributes needed for different scenarios. Ongoing assessment would be useful in guiding multiple pathways in Ebola vaccine research and development.

- *Ebola vaccine manufacturing could be accelerated* by streamlining the production process using existing vaccine technologies, thereby enhancing specific aspects (such as yield of bulk product) that improve cost-effectiveness, and focusing on monovalent formulations in the near term to address the current epidemic in West Africa.
- *Phase 2/3 clinical trials of Ebola vaccines should be conducted* even if efficacy cannot be determined, because substantial safety data will be needed for licensing and decision-making regarding its evaluation and further development.
- *The WHO should continue to coordinate international efforts* to identify appropriate options for accelerated regulatory approval of Ebola vaccines and provide expert oversight and guidance. In preparation for a future public health emergency, the World Health Organization (WHO) should consider creating a permanent capability within the organization to coordinate accelerated regulatory review processes.
- *The clinical trial process needs to be innovative and flexible* to provide opportunities to continue evaluating efficacy of new product candidates when disease-prevention impact cannot reliably be assessed because of low disease incidence. In addition, all promising vaccines should be evaluated in clinical trials, even if one vaccine shows early efficacy, since it is not clear which vaccines may ultimately prove to be most efficacious.
- *Post-marketing surveillance should be in place* once vaccines are approved or authorized for use. Consideration should be given to determining if any applicable baseline data are available from any in-country epidemiologic sources for anticipated potential adverse events. In addition, a community engagement strategy should be developed for addressing adverse events (that are either causal or coincidental).
- *African stakeholders should be at the forefront of ethical decisions* that affect the safety, wellbeing, and resilience of the populations hardest hit by the Ebola epidemic. This includes clinical trial work and oversight of vaccination strategies.
- *The key framework for developing vaccination strategies* should be based on initial targeting of those at highest risk of exposure. The strategy can be phased in, according to vaccine availability, and may evolve. Leaders in the affected countries need to be involved in the decision-making and in determining priority groups for vaccination.
- *Community engagement efforts should be under way* to address any perceived barriers to vaccine acceptance, to build trust, to promote awareness, and provide any needed education. Inclusivity is a priority.
- *Once the West Africa epidemic is controlled, stockpiling vaccines* to be used for future outbreaks should be considered if additional analyses determine that this approach is feasible and cost-effective.
- *Ensure transparency in financial transactions* that affect pricing as well as decisions regarding who receives limited doses.

- *Examine creating an integrated funding strategy* that prioritizes public health as the driver over commercial considerations. Public-private partnerships aimed at vaccine development could prove helpful.

Team B Project Limitations

Every effort was made to secure similar information for comparison from pharmaceutical firms advancing vaccine candidates. Given the tight timeframe of the project, gaps are likely. Furthermore, Team B members did not have access to all relevant details. The project benefited from inclusion of a broad range of experts, but missing data and points of view are always a risk. Additionally, 26 leaders in their fields do not always agree on finer points. Every effort was made to address comments and suggestions that panel members offered when they reviewed final drafts. When conflicting positions emerged, the project team exercised its best judgment to find a compromise solution and preserve the point of view that reflected the majority of the work group.

The Ebola epidemic shifted dramatically in the timespan the project occurred. A welcome and promising trend was a dramatic falling off of cases. Ironically, the progress introduced new challenges in developing vaccines, particularly with regards to clinical trials for efficacy and effectiveness that rely on the strength of numbers. Additionally, a drop in media coverage took the epidemic off the public radar, and it is unclear how this will ultimately affect vaccine development.

Broader Implications

Taken as a whole, the Ebola Vaccine Team B findings have intriguing implications. Discussion in work groups consistently reflected tensions between conflicting viewpoints—for example:

- The catalytic power of intense public interest and the vacuum left when it disappears
- The fundamental conflict between public health and profit as a driver for developing new vaccines

The discussions and research that shaped the findings in this report also showcased strengths that could lead to new opportunities. Although the hardest-hit countries may experience repercussions from the current outbreak for some time, neighboring countries are willing to share expertise in medicine, science, ethics, and community engagement. The WHO's ability to coalesce, coordinate, and steer a diverse mix of assets toward a unified goal suggests possibilities for an expanded role in developing vaccines for populations whose needs are great and resources are limited. Within the limited body of literature on vaccines for neglected and emerging diseases in under-resourced countries lies a repository of lessons learned that can be showcased and applied. And a cadre of public-private partnerships has built a track record of success fostering vaccine discovery, presentation

and delivery innovations, and funding from which new approaches for rapidly producing vaccines may emerge.

The Ebola Vaccine Team B initiative serves as a call to answer the question: How can public health ensure that safe and effective vaccines for emerging diseases are created and delivered rapidly and affordably? The need for a vaccine development paradigm shift became evident, grounded in the following points:

- The current Ebola epidemic is not a "one-off" event.
- Future Ebola (and other emerging disease) epidemics are inevitable.
- The commercial vaccine manufacturing model is not a good fit for meeting needs to rapidly develop and deploy new vaccines.

Introduction

Beginning in December 2013 with the probable index case—in a 2-year-old boy in a remote village in southern Guinea—an outbreak of Zaire Ebola virus quickly surged, surpassing the number of cases that occurred in all previous outbreaks of EVD in Africa. It reached epidemic proportions by early summer 2014 in Guinea and neighboring Sierra Leone and Liberia. By August, when the WHO declared the Ebola epidemic in West Africa a public health emergency of international concern, reported cases of new EVD and deaths were increasing rapidly, far outpacing traditional public health and medical measures mobilized to contain the epidemic.

In early September, the WHO convened an international meeting to review available Ebola therapies and preventive options that highlighted the need for Ebola vaccine as an urgent international priority. What followed was a collaborative effort, coordinated by the WHO, among global public health organizations, pharmaceutical companies, regulatory agencies, and nongovernmental organizations to accelerate the development of Ebola vaccine from preclinical research to clinical trials.

Delivering an effective, safe vaccine to West African populations in time to help extinguish the current epidemic presented a global challenge that required not only considerable resources and expertise, but also an unprecedented degree of determination, transparency, trust, and cooperation. Multinational pharmaceutical firms stepped up, with support from public and private entities, to test their most promising vaccine candidates, with no assurances of profit. And before the end of the year the largest purchaser of vaccines for impoverished children committed to spend nearly US$400 million to procure and deliver vaccines, and clinical trials were under way or about to begin.

Goals

Wellcome Trust and CIDRAP established the Ebola Vaccine Team B initiative in November 2014. In a proactive, science-based approach, the Ebola Vaccine Team B was formed to critically examine the vaccine development process, challenge assumptions, and identify potentially overlooked aspects of all phases of developing and delivering Ebola vaccines, including funding, research and development, manufacturing, efficacy and effectiveness determination, regulatory approval, and vaccination strategy.

Methods

Team B members include 26 internationally recognized subject-matter experts (SMEs) with specific expertise in one or more areas of vaccine development. The group was co-chaired by Jeremy Farrar, MD, PhD (Wellcome Trust) and Michael Osterholm, PhD, MPH

(CIDRAP). From November 2014 to January 2015, the group convened a series of discussions by teleconference in a large-group format. In addition, nine smaller working groups were formed to enable more in-depth discussion in specific focus areas.

The groups and their co-chairs include:

Research and Development: Arthur Elliott, PhD, and Joan Fusco, PhD

Manufacturing: Thomas Fuerst, PhD, and George Poste, DVM, PhD, DSc

Safety: Jon Andrus, MD, and Tumani Corrah, MD, PhD, CBE, MRG

Efficacy/Effectiveness Determination: Patricia Fast, MD, PhD, and Marc Lipsitch, DPhil

Regulatory Pathways: Norman Baylor, PhD, and Regina Rabinovich, MD, MPH

Ethics: Clement Adebamowo, BM, ChB, ScD, and Ross Upshur, MD, MSc

Vaccination Strategy: Fred Binka, PhD, MPH, and Walter Orenstein, MD

Community Engagement: Christian Happi, PhD, and Faisal Shuaib, MD, DrPH

Funding: R. Gordon Douglas, Jr, MD, and Adel Mahmoud, MD, PhD

Early in the process, Ana Maria Henao-Restrepo, MD, (WHO) provided the Ebola Vaccine Team B with a comprehensive update on vaccine candidates under development; current plans for clinical trials, scaling up development, and delivery of the vaccines; and potential target populations for vaccination. Following working group discussions, CIDRAP's development and policy team reviewed relevant literature, followed up on requests for additional documentation, and drafted initial reports on each of the focus areas. Working group members reviewed the drafts and provided additional feedback by conference call and in writing. A final draft of the full report and recommendations was sent to the entire group for review and feedback.

Interim Report

On Jan 12, 2015, the Ebola Vaccine Team B released an interim report, "Fast-Track Development of Ebola Vaccines: Principles and Target Product Criteria," to provide timely input into the rapidly evolving process while continuing to develop this document, its more comprehensive report. The interim report's target product profile (optimal and minimal criteria for Ebola vaccines used in epidemic or endemic settings) has been revised and included in this report (Appendix C, page 72). This full report is intended to be revised and updated as events move forward and new information becomes available.

How This Report Is Structured

The primary categories of discussion among Team B's working groups are reflected in the following sections: manufacturing (page 11); safety and efficacy/effectiveness determination (page 18); regulatory pathways (page 28); ethics (page 34); community engagement (page

40); vaccination strategies (page 46); and funding (page 55). Two different Team B working groups addressed key issues regarding vaccine safety and vaccine efficacy/effectiveness determination; as a result of the overlap between the two topics, their summaries were integrated into a single section.

Appendices include:

A. List of abbreviations used (page 62)
B. Complete list of Team B recommendations (page 63)
C. Target product profile (page 72), which reflects the main outcome from Team B's research and development working group
D. Public-private partnership involved in vaccine development in low-income nations (page 78)

Additional Investigation Needed

This report focuses primarily on expedient Ebola vaccine development and delivery. A number of longer-term issues are touched on in the report, such as strategies for using Ebola vaccines in future disease control efforts. Other relevant broader issues will be important to address in the future, such as developing sustainable funding models for Ebola vaccines and assessing the potential for future technology transfer for in-region vaccine manufacturing capability.

Manufacturing

Accelerating the delivery of Ebola vaccines hinges on the pharmaceutical industry's capacity to produce sufficient quantities of affordable, high-quality Ebola vaccines in compliance with standards defined by the International Conference on Harmonization Good Manufacturing Practices (GMP). Managing the complexities of high-quality Ebola vaccine manufacturing with unprecedented speed during a public health emergency requires an extraordinary degree of innovation, flexibility, and collaboration. Manufacturers can play a central role in securing and sustaining commitments for an effective strategy to ensure a sufficient supply of Ebola vaccine, not only for the current epidemic but also for future epidemics. In the current accelerated pathway, where manufacturing overlaps with R&D, clinical trials, and regulatory review,[1,2] several different Ebola vaccine candidates are now being produced for investigational use in phase 1/2 clinical trials while simultaneously scaling up for pivotal phase 3 clinical trials[3] and subsequent public health deployment, if needed. At present, manufacturers are focusing on production of the following three vaccine candidates, which are the furthest along in planning for phase 2 or 3 clinical trials:

- cAd3-EBO: a live-virus replication-defective monovalent (Zaire) or bivalent (Zaire and Sudan) recombinant chimpanzee-derived adenoviral vaccine, manufactured by GlaxoSmithKline Pharmaceuticals (GSK). The cAd3-EBO vaccine was co-developed by the US National Institute of Allergy and Infectious Diseases (NIAID) and Okairos, a biotechnology company acquired by GSK in 2013. It uses a chimpanzee adenovirus type 3 as a carrier to deliver the glycoprotein (GP) gene from the Zaire Ebola virus or the GP genes from both the Zaire Ebola virus and Sudan virus.[4] The cAd3-EBO vaccine may also be used in a heterologous prime-boost strategy with a recombinant modified vaccinia Ankara (MVA) GP booster vaccine (MVA-BN-Filo) manufactured by Bavarian Nordic (see bulleted item below).

- rVSV-ZEBOV: a single-dose, live-virus replication-competent monovalent recombinant vaccine based on an attenuated vesicular stomatitis virus (VSV) platform.[5,6] The rVSV-ZEBOV vaccine was developed by the Public Health Agency of Canada. rVSV-ZEBOV and the underlying technology were licensed to BioProtection Systems (BPS), a wholly owned subsidiary of NewLink Genetics (NLG). In November 2014, Merck Vaccines established an exclusive licensing and collaboration agreement with BPS-NLG for the research, development, manufacture, and distribution of the vaccine.

- Ad26.ZEBOV/MVA-BN-Filo: a monovalent, live-virus replication-defective adenovirus-vector vaccine expressing GP from the Zaire Ebola virus (Ad26.ZEBOV) applied in a heterologous prime-boost strategy with MVA-BN-Filo, a booster vaccine. Ad26.ZEBOV is manufactured by Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson (J&J).[7] MVA-BN-Filo is a recombinant multivalent replication-defective MVA booster vaccine containing the GP from Zaire Ebola virus, Sudan virus, and Marburg virus. MVA-BN-Filo is manufactured by Bavarian Nordic.[8] Crucell Holland BV, one of the Janssen Pharmaceutical Companies of J&J, licensed the MVA-BN-Filo booster from Bavarian Nordic for use with the Ad26.ZEBOV vaccine.

In addition, a monovalent (Zaire subtype) recombinant adenoviral Ebola vaccine (Ad5 EBOV), formulated as a freeze-dried product, is being developed in China by the Jiangsu Provincial Center for Disease Control and Prevention and Tianjin CanSino Biotechnology and is entering phase 1 trials.[9] Other Ebola vaccine candidates in the development pipeline include a baculovirus-derived Ebola GP nanoparticle vaccine made by Novavax; a GP-expressing protein-based vaccine based on a baculovirus platform, made by Protein Sciences; and a Russian vaccine based on an attenuated influenza virus developed by researchers at the Influenza Research Institute in St. Petersburg with support from the Russian Ministry of Public Health.[1,10-12]

Given the unusually fast timeline for developing these vaccine candidates, important limitations may occur in the overall robustness of their manufacturing processes that could require process improvements for continued production in the future. One or more of the newer candidates could serve as potential next-generation vaccines if they are more productive or cost-effective or fulfill unmet needs, such as greater suitability for use in a strategic stockpile for deployment in future public health Ebola emergencies, particularly in areas with limited cold-chain and healthcare infrastructure.

Issues and Challenges

Comprehensive assessment of Ebola vaccine development from a manufacturing perspective could benefit from the use of tools such as critical path analysis and integrated product development planning, which help identify and evaluate critical decision points, essential technology requirements, development gaps and barriers, and interdependencies throughout the product development process.[13] In addition, this approach could specifically facilitate decisions that would affect the immediate need to manufacture sufficient doses of Ebola vaccine to deploy in West Africa and for broader decisions regarding cost-effective platforms to produce Ebola vaccines in response to future outbreaks.

The number of Ebola vaccine regimens needed in the near term depends on the course of the epidemic, the number of doses required for protection, vaccination strategies, clinical

trial requirements, and other factors. The projected number of Ebola vaccine regimens needed may range from fewer than 100,000 to 12 million.[14] Sufficient manufacturing capacity reportedly exists to produce enough doses of Ebola vaccine within this broad range by the end of 2015, particularly if at least two of the three candidate vaccines can be used.[7,15,16] The WHO reported that Merck and J&J can each produce up to 5 million doses, if needed, in 2015 and that GSK can scale up to produce about 1 million per month by the end of 2015.[1]

To ensure the quality of final products, commercial vaccine production requires strict adherence to current GMP requirements, which require time-consuming advanced development such as equipment validation and process validation. Key aspects of the manufacturing process for Ebola vaccines also include the following:

- Dose. Higher doses of live-virus vaccines, as measured by the concentration of infectious virus particles (plaque-forming units [pfu]) required for immunogenicity, correspond with lower quantities of final vaccine produced in a given time. A 4- to 5-log difference in dose between different vaccines could become a significant factor in a rapid-response situation, given that relatively high doses, such as 10^{10} to 10^{11} pfu, could take longer to manufacture in a given facility than those in the 10^{3} to 10^{7} pfu range.

- Yield. Assessment of the yield of bulk product in vaccine manufacturing helps determine the feasibility of the process (eg, in terms of quantity, yield per lot, manufacturing cycle times, and cost) to meet the projected demand. Renovation or construction of new manufacturing facilities may be needed if scale restrictions exist for a given process or if flexible, mobile capabilities (such as modular manufacturing platform technologies for rapid vaccine production) are not feasible. Scale-up may require the development of alternative technologies and manufacturing platforms to achieve an overall improved yield. In addition, the larger the number of lots needed to meet demand, the greater the costs and risk of manufacturing failure (lot rejection).

- Fill-and-finish. Sterile fill-and-finish requirements and capacity are key elements and potential bottlenecks in vaccine production and output.[13] In an emergency situation requiring millions of units in a short time frame, end-stage manufacture and quality control (QC) testing is rate-limiting and constitutes the critical path to final product availability. In addition, multiproduct commercial fill/finish facilities require cleaning, validation, and changeover controls to prevent contamination from one product to the next. This is of particular concern for products containing live microbes, including some of the current Ebola vaccine candidates; filling these vaccines may be prohibitive for some commercial manufacturers, which will affect capacity availability and potentially existing licenses and may require building new facilities.

- **Supply chain issues.** Other potential bottlenecks in the vaccine manufacturing process may involve the supply of essential raw materials (such as specific pathogen-free eggs for MVA booster vaccine production or fermentation medium supplements), adequate storage facilities (capacity and location), and the transport of supplies and product from the manufacturer to the location of use or to a stockpile. In addition, potential bottlenecks could result from the need for specialized facilities, such as biosafety level (BSL)-2 laboratories, for the manufacture of specific types of vaccines, such as rVSV-ZEBOV.

- **Thermostability/cold-chain storage.** Minimum temperature requirements for cold-chain storage and transportation to prevent degradation of the vaccines need to be assessed in view of the practical limitations of distributing Ebola vaccines in Africa or in other climates of temperature extremes. Maintaining storage of Ebola vaccine at extremely cold temperatures (-80°C on dry ice), or even at freezer temperature (-20°C), may be challenging for vaccination programs in many areas.[17,18] In the longer term, development of freeze-dried formulations, liquid stabilization, and/or transdermal delivery technologies should be considered for use in remote areas of Africa with limited cold-chain infrastructure (see the target product profile [Appendix C] on page 72 for more information).

- **Cost.** Cost projection for the current vaccine candidates is essential for long-term planning. Direct and indirect costs of manufacturing Ebola vaccine reflect volume of production, dose, specific raw materials, and the site of manufacture, among other factors. It is unknown whether lower-cost options for manufacturing exist in countries such as China, Brazil, or India[19,20] or through collaborative manufacturing (using multiple locations for manufacturing different stages of the process). From a broader economic perspective, significant issues regarding intellectual property and commercialization will need to be addressed to avoid financial barriers to the use of processes that have already undergone licensure and the production of Ebola vaccines based on those processes.

- **Liability.** On Dec 3, 2014, the US government issued a declaration under the Public Readiness and Emergency Preparedness (PREP) Act that extends liability protection in the United States for 2 years related to the production and distribution of three currently unapproved Ebola vaccine candidates being evaluated in clinical trials.[21] The PREP Act declaration does not, however, offer protection from liability for claims arising under non-US law or brought in a non-US court. The WHO previously noted that issues of liability and indemnity could "stand in the way of the most strategic and effective vaccine use" and that a group of donors in collaboration with the World Bank

could be formed to pool resources in an international liability fund.[13] Dialog at the international level will be needed to resolve this important issue with regard to near-term Ebola vaccine administration in West Africa.

Recommendations

1. **Streamline process steps.** Technologies for manufacturing Ebola vaccines that enhance yield or leverage processes that have already undergone licensure should be considered, if issues regarding intellectual property and commercialization can be promptly addressed. Streamlining specific process steps using platforms or methods that have already been evaluated and approved could accelerate the development of new products.

2. **Review factors that could improve cost-effectiveness.** Critical factors in manufacturing the current leading candidate vaccines include dose requirements, production yield, process validation, fill-and-finish capacities, cold-chain storage requirements, QC testing capability and capacity, supply chain issues, scale, cost, and liability. Other specific challenges may occur with alternative vaccine platforms or formulations. Process improvements and refinements in the manufacturing process may be needed for cost-effective vaccine delivery. Comprehensive assessments of key factors and critical decision points in manufacturing and commercialization should be shared openly for consideration, in view of the need to coordinate global public health response efforts.

3. **Focus on monovalent vaccines in the near term.** Depending on the production method used, if monovalent vaccine formulations (Zaire Ebola virus) can be manufactured more quickly than multivalent formulations, an initial focus on effective monovalent vaccines is likely to speed up the manufacturing phase of the current response to the epidemic in West Africa. Multivalent formulations may be more suitable for subsequent next-generation vaccines and could contribute to effective long-term solutions. Since the selection of GP as the primary protective antigen has not yet been confirmed in humans, further research is needed to determine the potential protective role of other antigenic proteins, such as the matrix protein or nucleoprotein, from the Zaire Ebola virus and other filoviruses.

4. **Assess potential for future technology transfer.** The development of in-region manufacturing capacity could enhance access to Ebola vaccines in West Africa or elsewhere in Africa in the longer term. Technology transfer to a reliable in-region manufacturer could also provide an alternative source of vaccine if an originator manufacturer cannot commit to continued production. As the specific technologies for effective Ebola vaccines become clearer, the complex issues involved in technology transfer to an in-region manufacturer will need to be fully addressed.

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Efficacy, Effectiveness, and Safety of Ebola Vaccines

The West Africa epidemic has clearly demonstrated the need for efficacious Ebola vaccines. Such vaccines could have been used to abort the current epidemic at an early stage and may play such a role in controlling future Ebola outbreaks as an adjunct to traditional public health measures. Effectiveness end points in clinical trials of Ebola vaccine candidates can range from disease prevention to surrogate end points that are reasonably likely to predict clinical benefit. Regardless of the regulatory pathway taken, any Ebola vaccine candidate will require rigorous demonstration of safety.[1]

Vaccine efficacy is generally defined as the proportionate reduction in the disease attack rate in vaccinated participants compared with unvaccinated participants, demonstrated in an individually randomized controlled trial (RCT).[2] A well-designed efficacy study measures the extent to which the vaccine reduces the occurrence of the target disease, in an acceptably safe fashion, under optimal conditions designed to minimize the bias in measuring the level of protection.[3] Effectiveness studies demonstrate how well a vaccine works when deployed in public health practice.[4] Efficacy studies generally are conducted as part of phase 2/3 (pre-licensure) vaccine research, and effectiveness studies are usually undertaken as part of phase 4 (post-licensure) research.

Research into filovirus vaccines has been ongoing for a number of years. The surface GP is responsible for viral entry into host cells, and therefore GP has been the primary candidate antigen for Ebola vaccines, with some candidate vaccines using alternative virus vectors to carry the GP. Currently, two primary candidate vaccines that follow this approach are undergoing accelerated testing in clinical trials, and trials with a third vaccine started recently. Progress regarding these three vaccines is outlined briefly below. Several additional candidate vaccines also are in pre-clinical or early clinical development.

Leading Candidate Ebola Vaccines

- **cAd3-EBO.** Clinical development of this GSK vaccine began in 2011, and entry into clinical trials was accelerated in response to the West Africa Ebola epidemic. Studies in nonhuman primates (NHPs) have shown that the vaccine is efficacious with challenge and that protection can be extended with a booster dose using a recombinant MVA GP vaccine.[5] A phase 1 clinical trial of a bivalent Ebola virus vaccine (Zaire and Sudan), which involved 20 human subjects, demonstrated antibody responses similar to those considered to be associated with vaccine-induced protective immunity in NHPs.[6] No

significant safety concerns or serious adverse events were reported, although two participants developed transient fever. An additional phase 1 clinical trial of a monovalent cAd3-EBO vaccine, involving 60 participants (59 of whom were followed), was conducted in the United Kingdom in the fall of 2014.[7] No safety concerns were identified at any of the dose levels studied. Of the 59 participants who were evaluated, fever developed in 2 and prolonged activated partial-thromboplastin times and transient hyperbilirubinemia were observed in 4 and 8 participants, respectively. At the vaccine doses tested in that study, both antibody and T-cell responses were detected but at levels lower than those induced in NHPs protected by the same vaccine. Additional phase 1 and phase 2 trials using this platform are under way or will soon be initiated in the United States, Europe, and Africa.[8] Pediatric cohorts will be included in some of them.

- rVSV-ZEBOV. Because this product from BPS-NLG and Merck is a live-virus replication-competent vaccine, some experts have raised concern about viral shedding (which could pose a threat to livestock and possibly some humans). Animal studies, however, have not demonstrated significant VSV shedding post-vaccination.[9] VSV primarily causes disease in livestock and rarely causes illness in humans, although mild influenza-like symptoms have been associated with human infections. Filovirus vaccines using the rVSV platform have been under study for a number of years, and animal models using NHPs have demonstrated efficacy against infection, both pre- and post-exposure.[9] In addition, studies involving NHPs suggest that a single dose confers lasting protection. A recent phase 1 clinical trial in Geneva was temporarily halted when several of the 59 volunteers who received doses of either 1 X 10^7 or 5 X 10^7 pfu per milliliter (mL) developed transient arthritis with grade one pain in small joints, mainly in the fingers. News reports at the time indicated that four patients had joint pains, whereas a WHO teleconference held on December 18, 2014, indicated that approximately 20% of participants had experienced joint symptoms.[11] This pattern has not been observed elsewhere, and regulatory authorities did not consider this a significant issue; the Geneva trial resumed in early January 2015 using a dose-escalation approach.

- Ad26.ZEBOV/MVA-BN-Filo. This vaccine, made by Janssen Pharmaceuticals, is undergoing a phase 1 clinical trial that began in early January 2015 in the United Kingdom, and further studies are planned in Africa. The vaccine involves a prime-boost strategy.

Planned Phase 2/3 Clinical Trials

Phase 2/3 clinical trials of Ebola vaccines are planned for early 2015 in Liberia, Sierra Leone, and Guinea.[11-14] These trials will focus on the two primary candidate vaccines (cAd3-

EBO and rVSV-ZEBOV), although additional trials (with these or other vaccines) may be planned in the future.

- At the time of this writing, the Liberian trial is planned as an individually randomized, double-blind, placebo-controlled trial and will include three arms—cAd3-EBO, rVSV-ZEBOV, and a placebo arm—with at least 9,000 volunteers in each arm.

- The Sierra Leone trial will focus on high-risk groups, including healthcare workers. This study was originally planned as a stepped-wedge design with vaccine being introduced sequentially over 18 weeks; however, the collaborators have updated the design recently in light of the changing epidemiology of EVD in the country. At the time of this report, the vaccine to be used in the trial has not been specified and further details on the study design are not publicly available.

- The trial in Guinea will involve two components: (1) a ring-vaccination approach whereby residents of villages with confirmed EVD cases will be randomized, by village, to be vaccinated either immediately or beginning 6 to 8 weeks after case identification and (2) vaccination of frontline workers, which will assess safety and immunogenicity only. At the time of this writing, the vaccine to be used has not been specified.

Challenges in Demonstrating Vaccine Efficacy in the Current Situation

- **Lack of predictable disease incidence.** One major challenge for conducting efficacy or effectiveness trials of Ebola vaccines in West Africa is the uncertainty over future disease incidence in the countries in which phase 3 trials are being implemented. The disease incidence has dropped markedly recently, and this trend may continue over the next several months. If the incidence declines substantially, the clinical trials may not have enough statistical power to demonstrate vaccine efficacy. A decline in the disease incidence would have the greatest impact on the ability to conduct multi-arm trials, which could limit the opportunity to perform direct comparisons of vaccines under similar field conditions. Spatial heterogeneity in disease incidence further complicates design and implementation of studies. This may occur in different areas or regions for a variety of reasons: variations in the time of viral introduction and transmission, variations in implementation of control measures and behavior changes to limit vial spread, and regional differences in prior incidence of EVD—and thus the level of existing immunologic protection in the population. Such heterogeneity also may increase the required sample size in cluster-randomized trials because of the large between-cluster variations in disease incidence.[15]

- **Logistical challenges.** The logistical challenges of conducting high-quality clinical trials in the affected countries are substantial, given the lack of resources and limitations of

the existing infrastructure, particularly if trials need to be conducted in remote areas. Also, the different vaccines may not be ready for entry into a phase 3 trial at the same time, which could affect whether or not multi-arm trials are conducted. In addition, some candidate vaccines may require storage at -80°C; maintaining this level (or even -20°C) of cold chain will be challenging under field conditions in the affected areas of West Africa. Efforts are under way to develop these vaccines to have more manageable cold-chain requirements, and at least one candidate vaccine already has been reported to have less stringent storage conditions.

- Population perception issues. Another challenge is related to perception of vaccination and mistrust of outsiders or local governments by affected populations, which could decrease enrollment in clinical trials. Factors that contribute to perception issues include miscommunications from scientists, government officials, and healthcare personnel about the "lack of treatment for Ebola" and the high prevalence of infection with associated mortality among healthcare workers. Because of time constraints, it will be challenging to develop and implement robust communication plans and engagement strategies to enhance acceptance of vaccination and participation in clinical trials, and to address any concerns or quell rumors that may arise if cases of EVD or adverse events are detected post-vaccination.

- Lack of serologic correlates of protection. To date, validated serologic correlates of protection in humans have not been identified for any of the vaccine candidates, and such correlates are not available for the currently planned phase 3 clinical trials. Clearly, the best assessment of vaccine efficacy is to actually show protection against acquiring EVD in the field, but having validated correlates of protection would be of great value in developing next-generation Ebola vaccines. This process is complicated by the fact that the vaccines do not have identical mechanisms of action and may have different correlates of protection. Although correlates of protection have potentially been defined from animal studies, it is uncertain whether these correlates will translate to humans. Obtaining blood samples post-vaccination in the planned clinical trials would prove invaluable in identifying and validating an appropriate correlate of protection, but the logistic and biosafety challenges in doing this are formidable.

- Need for prime-boost strategy. Incorporating booster vaccines into any regimen significantly complicates the process and raises a number of additional logistical challenges for tracking, record keeping, and follow-up. Some data suggest that cAd3-EBO may require administration of a booster vaccine to increase immunogenicity and induce lasting protection (such as with an MVA recombinant vaccine). For disease control purposes, a single-dose vaccine would be preferable, and adding a booster dose

would complicate clinical trials. There is a danger, however, that if a booster dose is not included in the clinical trial protocols, the vaccine may have lower efficacy. The Ad26.ZEBOV/MVA-BN-Filo vaccine involves a prime-boost regimen. A separate booster may not be required for the rVSV-ZEBOV vaccine.

- **Potential for local herd immunity.** In some areas, the past incidence of disease has been relatively high, and researchers have not identified the proportion of the population that has experienced subclinical infections. If this proportion is large and subclinical infection confers immunity against disease, then there may be insufficient cases in clinical trials of vaccines to demonstrate efficacy. This may be of particular concern in cluster-design studies, where herd immunity may vary by the populations being compared. Seroprevalence surveys could help clarify this issue, although criteria for determining seropositivity following natural infection have not been clearly defined.

As a result of these various challenges, clinical trials may be non-conclusive or may show conflicting results. Also, because study designs vary and the efficacy/effectiveness measure is different in each of the planned designs, combining results from different trials involving the same vaccine may be difficult. Furthermore, if one vaccine shows convincing efficacy ahead of the others, it may be difficult to continue other trials if sufficient supplies of the efficacious vaccine are available for widespread use. In this situation, continuing other trials would raise ethical issues that may need to be addressed by in-country ethics committees. A quick rollout of a vaccine that shows early efficacy may be of benefit in the short term. But it could be problematic in the long term, because the leading candidate vaccine ultimately may encounter issues or problems (eg, manufacturing, changed tolerability, early waning immunity), while vaccines that become ready for testing later may offer logistical benefits (eg, single-dose formulations) and/or superior protection (eg, higher efficacy, multivalent formulations). Choosing only one vaccine would lead to a single point of vulnerability and could limit vaccine choices for the future.

Considerations for Vaccine Safety

Significant challenges and issues related to the safety of candidate Ebola vaccines are outlined below.

- **Selecting the proper dose for optimal safety and optimal efficacy.** This may have important implications for the success of clinical trials. If the vaccine dose is too high, the rate of adverse events may be increased. Conversely, if the vaccine dose is too low, an adequate protective response may not be generated. Data from phase 1/2 trials can help inform the choice of dose.

- Use of new technology platforms. The leading candidate vaccines involve relatively new technology platforms, so safety data will be limited. While animal studies and phase 1 trials have not demonstrated significant safety issues with candidate vaccines so far, safety issues could still arise. Thus, careful monitoring for adverse events is essential throughout the clinical trial process and, to the extent possible, through post-marketing surveillance (although this will be challenging in the affected countries because of inadequate healthcare systems).

- Availability of limited data from phase 1/2 trials. To date, few clinical trials to assess vaccine safety have been conducted. Because of the urgency of the situation, investigators and health officials have decided to employ an accelerated approach, in which detailed safety studies are conducted in countries outside of the Ebola epidemic area in parallel with efficacy studies in the affected region.

- Limited pharmacovigilance systems. The health infrastructures for conducting and maintaining pharmacovigilance are limited in the primary impacted countries because of past civil strife, the effects of the current epidemic, and weak healthcare systems. This limitation creates challenges for conducting adequate post-marketing adverse-event surveillance. To the extent possible, surveillance should be established during the clinical trial process and beyond. This could be done through active or passive health center–based targeted surveillance, follow-up of vaccinated cohorts, or canvassing villages several weeks after a vaccination campaign to search for serious adverse events. For example, following a meningococcal A vaccination campaign in Burkina Faso, public health officials implemented heightened passive surveillance countrywide and active surveillance for 12 clinical conditions in one sentinel district.[16] This type of approach may be considered in this situation, with identification of possible adverse events temporally associated with vaccination. Such efforts are costly, however, and resources would be needed to conduct surveillance activities. In addition, a community engagement strategy that targets both healthcare providers and the general public is needed to address any serious adverse events—either causally related or coincidental—that may be detected following vaccination. Serious adverse events include those that result in death, are life-threatening, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or involve congenital anomalies or birth defects.[17]

- Limited epidemiologic baseline data for possible adverse events of interest. The affected countries lack pre-vaccination baseline epidemiologic surveillance data on conditions that may be of interest as possible vaccine-associated adverse events. Again, this is related to limited health and public health infrastructure in affected areas.

Consideration also should be given to determining background rates of serious illnesses to assist in evaluating whether serious adverse events temporally related to vaccination are likely to be causal or coincidental; approaches to obtaining such information have been suggested, including in sub-Saharan Africa.[18,19]

In addition to addressing the issues above, in the setting of an epidemic, the risk-benefit ratio will be important to consider when determining if the vaccine safety profile is acceptable for deployment for disease control. When examining the risk-benefit ratio, public health officials will need to consider the severity of the disease and the likelihood of individuals becoming infected in relation to the types and rates of post-vaccination adverse events. In a number of situations, low levels of serious adverse events have been associated with vaccines, but their occurrence has been accepted because such serious adverse events are rare and the overall risk-benefit ratio for vaccination remains favorable. Examples of rare serious adverse events associated with other vaccines include paralytic polio from oral polio vaccine (OPV), post-vaccination encephalitis from yellow fever vaccination, intussusception associated with rotavirus vaccines, and life-threatening complications from smallpox vaccination, such as eczema vaccinatum, progressive vaccinia, and postvaccinal encephalitis. If an Ebola vaccine is to be used prophylactically in the future in areas at risk of Ebola outbreaks but during non-outbreak periods, public health officials may need to reconsider the risk-benefit ratio.

Recommendations

Applicable to Vaccine Efficacy and Effectiveness

1. **Ensure flexibility in the clinical trial process.** The clinical trial process needs to be innovative and flexible to provide opportunities to continue evaluating efficacy (eg, through measurement of surrogate end points) of new product candidates when disease-prevention impact cannot reliably be assessed because of low incidence of disease. Designs of efficacy trials should, to the extent possible, permit adaptive decisions to add participants or increase follow-up time in response to patterns of incidence that were not anticipated in the original study design, such as declining incidence or occurrence of localized outbreaks.

2. **Evaluate all promising vaccines in clinical trials.** Because it is not clear which vaccine(s) may ultimately prove to be most efficacious, and which may be most effective in the field once approved, all promising vaccines should be evaluated in clinical trials. It should be noted, however, that human efficacy studies may be possible only in the context of the current large epidemic, and even this possibility has become uncertain with declining disease incidence. Alternatives to clinical efficacy trials in the absence of an epidemic should be considered that would allow vaccine candidates a development path to licensure (eg, use of the US Food and Drug Administration [FDA] Animal Rule).

3. **Plan for contingencies.** Investigators and public health officials need to address how ongoing or additional trials will be handled if one vaccine shows efficacy and is available for widespread use or will become available in the near future. Rolling out a vaccine that shows early efficacy must be balanced with the need for mature data.

4. **Obtain post-vaccination blood specimens if possible.** Investigators involved in vaccine efficacy studies should be encouraged to obtain post-vaccination blood specimens if at all possible. Such specimens will be invaluable in determining correlates of protection, which could enhance future work in developing next-generation Ebola vaccines. The challenges and risks of collecting such samples are recognized.

5. **Consider seroprevalence surveys.** Seroprevalence surveys may be of value in determining the degree of herd immunity, particularly in areas where cluster-design trials are being conducted.

Applicable to Vaccine Safety

6. **Continue to obtain safety data.** Phase 2/3 clinical trials for Ebola vaccines should be conducted even if efficacy data cannot be obtained, because such data may contribute importantly to future licensing efforts.

7. **Anticipate the risk-benefit ratio.** To the degree possible, investigators and public health officials should begin considering the anticipated risk-benefit ratio as far in advance as possible and discuss what level of safety risk will be tolerated in the setting of an ongoing epidemic. In addition, they need to discuss how the risk-benefit ratio will be different if and when the vaccines are to be used in a non-outbreak setting. This is potentially challenging, particularly if limited safety data are available.

8. **Plan for adverse events.** Procedures for responding to possible rare but serious adverse events that may occur during clinical studies or post-marketing surveillance should be specified in advance. The procedures need to take into account that, in view of the very high mortality associated with EVD, such events may or may not compromise the risk-benefit ratio of vaccination, depending on their severity and frequency, and the risk of EVD infection in the trial population.

9. **Develop a risk communication plan for adverse events.** A community engagement plan that addresses the risk-benefit concept should be developed in advance for public sharing of information if any of the following are recognized: serious adverse events; coincident events, not necessarily caused by the vaccine; or post-vaccination EVD cases. A risk communications plan will help clarify expectations and mitigate any misperceptions that could substantially lower vaccine acceptability.

10. **Identify baseline data.** Consideration should be given to identifying adverse events that may be likely to occur, developing appropriate case definitions for those events, and determining if any applicable baseline data are available from any in-country epidemiologic sources, particularly in preparation for post-marketing deployment of one or more vaccines.

11. **Develop post-marketing surveillance plans.** Post-marketing surveillance should be in place once vaccines are approved or authorized for use. This could be done through active or passive health center–based targeted surveillance, follow-up of vaccinated cohorts, or canvassing regions several weeks after a vaccination campaign to search for serious adverse events.

12. **Think proactively.** Developers of next-generation Ebola vaccines should consider the need to protect against other filovirus infections in addition to Zaire Ebola virus, which ultimately will require development of multivalent vaccines. Furthermore, antigenic drift may be an issue over time—particularly with ongoing evolutionary pressure through serial passage in humans—and future efforts will need to consider the impact of antigenic drift on vaccine product development.

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Regulatory Pathways

As Ebola vaccine candidates are evaluated for safety and immunogenicity in phase 1/2 clinical trials in North America, Europe, and Africa, and phase 3 efficacy studies are under way or about to begin in West Africa in early 2015, accelerated regulatory pathways are being considered concurrently rather than after completion of the clinical trials.[1-3] The goal is to advance one or more of the vaccines, depending on safety and efficacy determination, to availability in West Africa as quickly and flexibly as possible without compromising the critical safeguards that the regulatory process is designed to ensure.

Risk-benefit analysis of the scientific evidence for safety, efficacy, and value to public health provides the conceptual framework for vaccine regulatory decision-making. A key ongoing priority is to streamline regulatory pathways within the scope of existing pharmaceutical law to facilitate access and remove barriers to safe and effective Ebola vaccines. At the same time, it is critical to examine any potential health risks or tradeoffs resulting from accelerated approval or authorization and implement effective strategies to mitigate them.

Background on Existing Regulatory Options

The delivery of Ebola vaccine in West Africa ultimately depends on regulatory approval or authorization in each of the affected countries, as governed by pharmaceutical law in those countries. Approval by a national regulatory authority (NRA) such as the FDA, the European Medicines Agency (EMA), Health Canada (HC), or Swissmedic could facilitate West African NRAs' regulatory processes.

The EMA recently established a "rolling review" process to accelerate the assessment of Ebola vaccine safety and efficacy data.[4,5] The EMA also offers an alternative regulatory pathway, Conditional Marketing Authorization, which is valid for 1 year and requires demonstration of a positive benefit-risk ratio, based on scientific data, pending confirmation. It also offers a related option, Marketing Authorization Under Exceptional Circumstances, also valid for 1 year, that applies when comprehensive data cannot be provided.[6]

In the United States, regulatory pathways to license vaccines to protect against diseases that are not endemic or do not occur in the United States are the same as those for vaccines to protect against diseases that occur in the United States. In its 2011 guidance for industry on the development of vaccines to protect against global infectious diseases, the FDA highlighted the critical public health importance of safe and effective vaccines against enteric and other neglected diseases of the developing world "for which there is no significant market in developed nations and that disproportionately affects poor and

marginalized populations."[7] The FDA clarified two US licensing options in its 2011 guidance document that may be appropriate for consideration with Ebola vaccines, given that the traditional drug approval process is not suitable for rapid response during an international public health emergency:

- Accelerated approval may be an option for a vaccine that has been studied for safety and efficacy in protecting against serious or life-threatening illness and that provides meaningful therapeutic benefits over existing interventions. Accelerated approval requires: (1) data from adequate and well-controlled clinical trials establishing that the vaccine has an effect on a "surrogate endpoint that is reasonably likely…to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity"; (2) further studies to verify and describe its clinical benefit "where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcome"; and (3) adequate and well-controlled post-marketing studies, usually under way at the time of approval, to verify clinical benefit.[7] Approval can be withdrawn if post-marketing studies fail to verify clinical benefit or if they are not performed with due diligence.

- The Animal Rule provides an alternative regulatory pathway when definitive human efficacy studies are not ethical or feasible to conduct. Aimed at facilitating approval of therapeutic products for treating or preventing highly lethal diseases, the FDA's Animal Rule could become an option for vaccine approval during the Ebola epidemic if vaccine efficacy cannot be determined through clinical trials in West Africa. Approval under the FDA's Animal Rule requires that (1) safety has been established in human studies and (2) adequate and well-controlled studies in animals provide evidence that the product is reasonably likely to produce clinical benefit in humans, according to specific criteria.[8-10] The Animal Rule would not be applicable if a vaccine could be approved through traditional or accelerated approval pathways. Approval of Ebola vaccine by the Animal Rule may require identifying and measuring relevant immune responses that correlate with protection against Ebola in experimental animals and obtaining corresponding evidence in phase 1/2 clinical trials.[11,12]

In addition, a regulatory mechanism exists under US law to allow emergency access to investigational (non-licensed) products under certain circumstances when no acceptable alternatives exist. Under expanded access regulations, the FDA can authorize the use of an unapproved vaccine (or the unapproved use of an approved vaccine) under its **Emergency Use Authorization** (EUA) during a public health emergency for a population not enrolled in clinical trials.[13,14] This option requires a determination by the Secretary of the US Department of Health and Human Services (HHS) of a public health emergency or significant potential for public health emergency and a declaration that circumstances

justify issuing the EUA.[15] Specific criteria applicable to using the EUA to provide access to unapproved Ebola vaccines include demonstration that:

- The disease is serious or immediately life threatening, and no comparable or satisfactory alternative product is available
- The potential benefits justify the potential risks, and the risks are not unreasonable in view of the disease severity
- Provision of the vaccine will not impede clinical trials that could support the vaccine's approval or marketing or otherwise compromise progress toward expanded availability

The EUA requires recipients' informed consent, Institutional Review Board approval, and adverse event reporting.[16] The EUA can allow shipment of a product authorized for use under the EUA from the United States to other countries, provided that the EUA's criteria for issuance, scope, and conditions for emergency use are met.[17] The FDA could authorize one or more Ebola vaccine candidates for use under the EUA; the FDA recently issued EUAs for five Ebola diagnostic tests.[18] Authorization of vaccine use under the EUA option does not preclude the vaccine's eventual approval and licensing, provided all relevant criteria are met.

International Collaboration

In September 2014, the WHO began efforts to coordinate discussions regarding potential regulatory pathways for the developing Ebola vaccines. Representatives of the vaccine manufacturing companies, the African Vaccine Regulators Forum (AVAREF), and the NRAs, including the FDA, the EMA, HC, and Swissmedic, participated in the discussions, which have focused on developing procedures for joint regulatory reviews and harmonizing regulatory requirements.[3,19-21] At the AVAREF's November 2014 meeting, ethicists and regulators agreed to conduct joint ethical and regulatory reviews to expedite approval of phase 3 clinical trials in African countries.[22] In addition, national ethics and regulatory authorities from Cameroon, Ghana, Mali, Nigeria, and Senegal met at the WHO in December to conduct a joint review of the phase 2 clinical trial application for the cAd3-EBO vaccine.[23] The WHO has reportedly begun devising an emergency regulatory pathway for Ebola vaccines, but specific requirements have not yet been determined or announced.[1]

In a related capacity, the WHO will have a central role in Ebola vaccine availability if one or more vaccines are licensed for use in West Africa. Following regulatory approval, the WHO vaccine Prequalification Program (PQP) forms a single point of reference internationally for vaccines that meet the WHO's standards of quality, safety, and efficacy so that organizations such as the United Nations Children's Fund (UNICEF) can purchase and distribute approved vaccines rapidly where needed.[24] The GAVI Alliance currently requires that all vaccines purchased using its funds are WHO/PQP-recommended.[25] Based in part on WHO/PQP recommendations, the affected countries' leadership decides if and

how the approved vaccines will be used within their borders.[26] However, there appears to be no international mechanism, including WHO/PQP, to prequalify *unapproved* vaccines available under emergency authorization (such as the EUA), which may create barriers to importing and distributing such vaccines in the near term in the affected West African countries.[27]

Finally, the Global Health Security Agenda (GHSA), established in February 2014, provides an overall framework for international health organizations and government agencies to collaborate and build legal, regulatory, and logistic capacities for enhancing response to global health emergencies.[28] The GHSA is designed to foster collaboration among domestic and international partners to identify gaps in global preparedness, create expedited regulatory pathways for new medical countermeasures, and accelerate mechanisms for developing, acquiring, stockpiling, and deploying countermeasures to epidemic areas. Reinforced by similar agency-level initiatives (such as the FDA's Medical Countermeasures Initiative) and special mechanisms, such as the FDA's EUA or the EMA's conditional authorization mechanisms, the GHSA could provide an effective mechanism to accelerate regulatory review and deployment of Ebola vaccines in the future.[17,27]

Recommendations

1. **Maintain WHO coordination.** The WHO should continue to coordinate international efforts to determine appropriate regulatory pathways for Ebola vaccines and provide expert oversight and guidance, in collaboration with the NRAs, the AVAREF, pharmaceutical companies, and international health and humanitarian organizations. Key goals include developing consensus recommendations regarding emergency approval or authorization pathways, identifying opportunities for reciprocity to expedite approvals among multiple NRAs, and clarifying the role of potential FDA or EMA approvals in the West African vaccine regulatory process.

2. **Obtain safety data.** Phase 2/3 clinical trials for Ebola vaccines should be conducted even if efficacy data cannot be obtained. Substantial safety and immunogenicity data derived from these trials will be essential for determining whether to use the vaccines in future Ebola outbreaks and for eventual licensure of the vaccines.

3. **Identify options for accelerated approval.** The NRAs, with support from the WHO, should continue to harmonize approval requirements and identify flexible options within their current regulatory requirements for accelerated approval and licensing processes, including the FDA's Animal Rule, when appropriate.

4. Evaluate and monitor use of EUA internationally. The NRAs should consider reciprocity for the FDA's EUA, which may be unique among regulatory options for providing emergency access to new Ebola vaccines. Priorities also include mitigating potential risks involved in using EUA pathways to provide access to unapproved vaccines, such as promoting post-marketing surveillance studies to identify adverse events and enhance trust and confidence in vaccination.

5. Extend PQP. The WHO should assess whether its PQP could be extended to include guidance concerning the distribution of unapproved vaccines in the affected countries under an emergency use paradigm, such as the FDA's EUA.

6. Establish ongoing WHO capability for facilitating fast-track regulatory review. The WHO should consider creating a permanent international forum within the WHO to coordinate and expedite regulatory review processes, in collaboration with the NRAs (including the FDA and EMA), AVAREF, and public/private stakeholders, to enable a streamlined approach to accelerated regulatory review for new vaccines during public health emergencies of international significance. Priorities include coordinating agreements on harmonized regulatory pathways and single sets of data for review.

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Ethics

Ethical review and oversight is a crucial component of Ebola vaccine development and delivery. Investigators are responsible for drafting ethical protocols, national ethics committees and national ministries of health are charged with setting and safeguarding the highest ethical standards, and local research ethics committees attend to the ethical implications for their communities. Rigorous and timely ethical review requires a shared understanding of roles that each organization plays as well as relevant expectations, adequate training, commitment to work expeditiously in reviewing proposals for research, sufficient human resources and administrative capacity (including standard operating procedures), and timely communication of decisions.[1] Once trials are authorized, particular attention is needed to ensure participants can and do give appropriate informed consent, taking into account variations in cultural context, literacy, and languages. When licensed vaccines are ready to use, especially when early supplies for eligible populations are limited, an ethical framework may be necessary to prioritize groups who will be vaccinated first as part of the vaccination strategy.

Ebola vaccine trials

To date, high-level discussions regarding ethical issues in the evaluation of Ebola vaccines, such as informed consent and whom priority recipients might be, have been held and reported by the WHO.[2] In November 2014, ethicists and regulators attending an AVAREF meeting agreed to conduct joint ethical and regulatory reviews to expedite approval of phase 3 clinical trials in African countries.[3] Ethical review was required before investigators could recruit participants into any of the clinical trials.

Ebola vaccination strategies

How, when, and where West African populations are vaccinated with Ebola vaccines will depend on the vaccination strategy (following licensure), which will be informed by characteristics of the vaccines that become available, including the number of doses needed for protection, duration of immunity, cold-chain requirements, safety, and efficacy. Until manufacturing reaches full capacity, early supplies will be limited, and decisions will need to be made regarding who has priority access.

The advisory panel of experts convened by the WHO in August 2014 to discuss ethical issues regarding use of unregistered and experimental interventions for EVD urged transparency and use of traditional ethical principles for making prioritization decisions.[4] Among the principles were **distributive justice** (fairness between countries and among populations within countries), **reciprocity** (placing priority on people who put their lives at

risk to care for others) and **social usefulness** (targeting people who are instrumental to controlling the outbreak, those who perform burial services, and relatives who provide care to patients).

The issue of whether healthcare workers should have priority access to new therapies and vaccines—despite a heightened risk of exposure and mortality rate in the Ebola epidemic—is unresolved and presents ethical questions. The WHO panel did not reach a consensus on this issue and recommended ongoing discussions. Writing in *The Lancet*, two ethicists[5] argued that because healthcare workers are likely to be financially secure and have ties to the healthcare system, they may enjoy a privilege not afforded people who provide care but are not trained as health professionals. The issue underscores the need to engage communities in decisions about prioritization that include an ethical framework.

Issues and Challenges

The following challenges may impede prospects for optimal ethics review and oversight of Ebola vaccine clinical trials, vaccination strategies, and adverse events monitoring:

- **Inadequate African representation in clinical trial decisions.** Concerns have been raised that Liberia, Sierra Leone, and Guinea may not have been adequately represented in decisions regarding clinical trials to date, even though these countries have borne the brunt of the epidemic.[6] The WHO has been facilitating technical support for joint review of vaccine protocols; however, anecdotal evidence collected by the Wellcome Trust–CIDRAP Team B Ethics Work Group indicates that some African scientists from the affected regions are concerned that their input has not been sufficiently considered in decisions regarding the trial designs, enrollees, and individuals used for control subjects. The perspectives, opinions, and preferences of the African scientists need to be properly weighed among opinions expressed by others.

- **Misinformation and suspicions.** The imperative to ensure that Ebola vaccine ethics review is rigorous, inclusive, and transparent is heightened by in-country suspicions about the origins of the Ebola virus, the outbreak's rapid shift into an epidemic, spread of misinformation about the disease, negative perceptions associated with polio eradication efforts in some parts of West Africa, and a chaotic early-response environment in which national ministries of health might not have been adequately engaged. Intense community engagement (CE) efforts have been needed to address beliefs that EVD is neither treatable nor curable and that seeking treatment in a hospital may mean certain death.[7] Lessons learned from past vaccine campaigns in Africa indicate that success pivots on authentic CE that instills and maintains trust.[8] Not all stakeholders will let go of suspicions and mistrust of government authorities, but early, attentive CE and social mobilization can turn the tide in difficult times.[9]

Ensuring that ethically sound and transparent procedures for handling and storing tissue and blood samples collected during clinical trials and monitoring for adverse events is another measure that can contribute to community trust. The policy used by Médecins Sans Frontières (MSF)[10] offers a strong model: Permission and intent are addressed when informed consent is obtained, memoranda of understanding with laboratories that use or store tissue clarify expectations for future use and destruction of samples, annual reports are used to document disposition of samples, and consultation with relevant communities is required before anonymous tissue or blood samples can be used.

- Accelerated processes toward regulation. The fast-track effort to develop Ebola vaccines involves multiple manufacturers, investigators, regulatory/licensing agencies, review bodies, and trial locations that are on three different continents. Such complexity and the accelerated pace may encumber the prospects for consistent, transparent, and rigorous ethical review. Nomenclature and processes across African countries and elsewhere are not consistent. The size and sophistication of protocols add yet another measure of complexity: Protocols may call for clear understanding of the complexities of randomized controlled studies, use of multiple arms to assess different vaccines, and stepped-wedge design. For example, if one vaccine shows early efficacy in clinical trials, ethicists need to be involved in determining the appropriate strategy for dealing with other ongoing clinical trials. A 2009 WHO report addressing ethical considerations during an international epidemic suggests strategies for ensuring rigor and speed of ethical review in outbreak settings, including greater reliance on e-mail and temporarily postponing non-crucial administrative tasks until after the emergency, when higher-priority tasks have been addressed.[11]

- Infrastructure weaknesses in the affected countries. Capacity for ethical review varies across Africa. Among nations in which resources are available and institutions have experienced demand for review of clinical trials, there is strong expertise and capacity to conduct ethical review and oversight as well as to train colleagues.[12] The Pan African Bioethics Initiative (PABIN) sought for several years to foster dialogue and sharing of practices among African nations and broached the idea of accreditation for ethics review bodies. Lack of funding, however, has diminished PABIN as a resource.[13]

  In Sierra Leone, Liberia, and Guinea, the combination of struggling economies, civil wars, and the toll of Ebola on the population and basic services has weakened the infrastructure to conduct ethics reviews and to provide routine health services. The three most affected countries may need outside support to bolster their ability to review and oversee a large number of complex protocols. Such help may come from experts and institutions in other African nations, if requested, or from sources chosen by the

most affected countries. Any appearance that assistance is being imposed on the outbreak nations, however, could lead to political problems and resistance. In the absence of a framework of support, bioethicists from African institutions cannot be expected to automatically volunteer their expertise in West Africa.

Members of the Ethics Work Group suggested that a need exists for a kind of "Ethicists Without Borders" organization that would be akin to the well-funded relief organizations that deploy healthcare workers as volunteers. External subject-matter experts (SMEs) may also need assurances that every effort will be made to prevent their exposure to Zaire Ebola virus. Likely contributors to such a fund would include pharmaceutical firms, whose progress depends on well-run research ethics committees delivering timely, thoughtful decisions. To prevent conflicts of interest, such a fund could be administered independently by a well-established and reputable philanthropic or other non-governmental organization. As an example, MSF has streamlined its approach to conducting ethical reviews remotely with board members, which relies on virtual ethical review.[14] Board members receive reviews electronically and discuss them via e-mail. Problematic issues are reviewed every 18 months. (More frequent review may be necessary for Ebola.)

- Balancing immediate and longer-term needs. The possible need to shore up capacity for conducting ethics reviews and oversight for clinical trials now is symptomatic of a larger and more entrenched need to build enduring bioethics capabilities at national and local levels. The need for strong ethics infrastructures is compelling, given the ever-increasing interest in conducting clinical trials in Africa,[15] the strong likelihood that the current epidemic will not be the last outbreak of an Ebola virus or some other equally dangerous infectious disease, and the large burden of infectious diseases that are potentially vaccine-preventable or treatable with new therapies. The international community, including the people of Africa, stands to benefit from standardizing, to the extent possible, the expectations, approaches, procedures, and structures that ensure quality research ethics review while accommodating local needs.

- Vaccine-related adverse events. Presumably, processes are in place for addressing adverse events during clinical trials as required for approval of protocols. It is unclear, however, how potential adverse events related to the post-licensure administration of vaccines will be handled, who is accountable for oversight, and how reparations will be made. One potential model is the National Vaccine Injury Compensation Program, a part of the US HHS Health Resources and Services Administration.[16] A US$0.75 per-dose excise tax is imposed on vaccines to fund compensation for vaccine-related injury or death.

Recommendations

1. **Safeguard broad and equitable stakeholder representation at every stage.** The urgency and speed of vaccine development and delivery must not be allowed to trump the imperative that African stakeholders are positioned at the forefront of decisions that affect the safety, well-being, and resilience of the populations hardest hit by EVD. From participation in clinical trial decisions to deliberations about post-marketing vaccination strategy to prioritizing delivery of vaccine supplies in a scarcity scenario, African stakeholders in the affected countries must have a leading role. This is particularly important if a candidate vaccine demonstrates sufficient safety and potential efficacy to undergo an accelerated approval process or be approved for emergency use.

2. **Bolster local bioethics capacity now and for the long run.** Resources that become available for immediate ethics review should be used in a way that also builds capabilities for the long term. Consideration should be given, for example, to how fast-tracked training for research ethics committees at the local level also lays the framework for a strong lattice of expertise to address future needs for ethical review.

3. **Establish funds for SMEs to assist ethical review and oversight.** A funding mechanism is needed to cover the travel, per diem, and teleconferencing expenses of bringing in external expertise, as required, to the hardest-hit countries. Efforts to provide assistance should be driven by African requests or be sufficiently informed by African stakeholders. As a longer-term solution, revitalizing a collective of bioethicists in Africa (such as PABIN) willing to work toward shoring up and streamlining ethical review would ensure enduring and consistent bioethics review capacity across Africa.

4. **Safeguard respectful handling, storage, and use of tissue and blood samples.** In addition to ensuring biosafety measures, a guiding principle for taking and storing samples should be respecting the rights and privacy of vaccine recipients. Although cross-country shipping may be necessary, no commercialization of tissues or trafficking of human identity related to samples should be permitted.

5. **Address how vaccine-related adverse events will be handled.** Clarify and communicate broadly how and to whom vaccine-related adverse events should be reported, the process for addressing them, and who is accountable for reparations.

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Community Engagement

Assuming licensed vaccines are made available, the likelihood that they will be used in West Africa as a way to halt morbidity and mortality from EVD and possibly to prevent future outbreaks cannot be considered a given. Even if the ambitious global endeavor to bring safe and effective vaccines to licensure succeeds, the *demand* for Ebola vaccines is not a certainty. Factors that influence such demand in West Africa may vary by country, region, village, or population group and may not be obvious to outsiders.[1] Barriers to vaccine uptake could range from poor communication to fears and resistance based on rumors and suspicions to unresolved logistical difficulties. Evidence from other immunization campaigns in or near the region indicates that a critical determinant of success is a concerted CE approach.[2-4]

Defining the term "community engagement" is difficult, in part because the concept of community can be interpreted in so many ways, such as by affinity and location.[5,6] As such, a single CE definition has not been universally adopted.[7] Commonalities among definitions offered by national and international public health organizations, however, can be found. The term *community* typically describes groups affiliated by geography, beliefs, interests, and/or goals; and *engagement* tends to describe various forms of information exchange, agreements, and activities aimed at achieving shared goals for improving the health of communities. In the context of developing and delivering Ebola vaccines, CE can be interpreted broadly to include local traditional, cultural, religious, and community leadership among affected populations; universities, teaching hospitals, and healthcare workers in the field; and ministries of health.

Examples of Community Engagement

Successful CE activities begin early; build and trade on strong relationships and trust; respect and integrate to the degree possible community points of view, social structures, traditions, and customs; are equitable and result in mutual goals; and are revised as needed and sustained over time.[8] A strong body of literature exists detailing successful CE strategies for clinical trials and post-marketing delivery and mistakes to avoid. The following represent useful examples of successful CE:

- Reversing resistance to polio vaccination. A frequently cited case in West Africa illustrates how CE reversed extreme resistance to uptake of polio vaccine in the northern region of Nigeria.[9] Polio eradication efforts stalled in the region when rumors spread that vaccines were being used to sterilize or infect recipients with HIV. A coalition of Muslim scientists, public health agencies, and religious leaders and the Nigerian Northern Traditional Leaders Committee for Primary Health Care and Polio

Eradication mapped out high-risk regions, then enlisted the help of local Jumu'a imams (highly respected Muslim clerics who deliver Friday sermons and lead prayers that day) to turn public opinion around. The coalition provided multi-media training about polio transmission, Islamic rulings (fatwas) on the concept of vaccination, and 13 customizable sermons on disease prevention in Arabic and native languages. Later, participants in a survey and focus groups examining the role of religious leaders in forming community opinion about polio vaccination strongly affirmed their importance.[4]

- **Explaining research protocols.** In Burkina Faso, investigators used a traditional game to demonstrate the concept of random selection of individuals to be screened for clinical trials of iMSP3-LSP malaria vaccine.[10] Before a cheering crowd of community members, 112 players randomly picked from a collection of 52 long and 60 short sticks inside a drum. Those who picked the short sticks represented individuals excluded from the trials, showing how random selection could be transparent and fair.

- **Building engagement through communication.** The Meningitis Vaccine Project in central Africa relied heavily on frequent, widespread, and multilayered communication to engage communities, beginning before clinical trials and continuing through the 10-day vaccination campaign.[11] During vaccine development, activities included formal and informal press briefings to announce findings from clinical trials and reports from international meetings on meningitis as well as conducting crisis communication training workshops. Closer to release of the vaccine, planners enlisted the help of traditional and religious leaders, town criers, and community volunteers called *relais communautaires* and disseminated messages through national, regional, and village outlets. Radio and television spots announced the launch of the campaign in national languages and emphasized that widespread coverage with the new MenAfriVac could bring an end to the annual epidemics.

Community Engagement Strategies and Use of Ebola Vaccine Post-marketing

Specific CE strategies for delivery of Ebola vaccines post-marketing will depend on the characteristics of vaccines that become available and on target populations. Vaccination strategies to deliver two doses, for example, will be different than if only one dose is needed for achieving and maintaining immunity. If early supplies are limited and a priority group is identified, such as community and family caregivers, burial teams, and healthcare providers, then the CE approach will differ considerably from strategies needed for mass vaccination. In the meantime, a look at CE efforts required to unblock access to *treatment* for Ebola-related illness may provide a clue of what's to come for vaccine delivery.

A report published on the Ebola Response Anthropology Network Web site[13] details a successful initiative to identify and address resistance to treatment interventions available to 26 villages in a forested area in southeastern Guinea. The unwillingness to seek treatment was rooted in entrenched mistrust of authorities, confusing early outreach efforts and messaging, beliefs that Ebola is untreatable and that funeral rites were now prohibited, and intra-community conflicts.

To address the issues, 150 credible and influential intermediaries from social groups were convened for a 1-day workshop with infectious disease experts from the WHO, Red Cross/Red Crescent, and MSF. Community and opinion leaders represented traditional healers, heads of sacred forests, Muslim and Christian leaders, circumcisers, village birth attendants, youth, returned migrants from cities and other countries, and elders. Concerns were aired, solutions brainstormed, and commitments were reached to facilitate access to treatment. The outcome was a comprehensive, practical, and inclusive initiative that produced culturally appropriate and clear messaging. Families of EVD patients received mobile phones to keep in touch with sick relatives and were invited to see the faces of deceased loved ones and to provide ritual objects and gifts for the burial. The report emphasized the importance of inclusive listening and noted that individuals who tended to be shunned or considered lower class by more powerful community members actually proved better able to mobilize the community than traditional and religious leaders.

Community Engagement Issues and Challenges

To design and implement CE strategies for post-marketing Ebola vaccine campaigns, the following issues and challenges will need to be addressed:

- **Timing.** There is consensus that CE must begin immediately, but without knowing the characteristics of vaccines that will become available, when supplies will arrive, and which populations should be targeted, detailed planning is not realistic. Efficient planning depends on communities receiving information about target populations as soon as possible. CE must also be sustained over time. The likelihood that only limited vaccines supplies will arrive until manufacturing ramps up means vaccine campaigns may occur in stages.

- **A one-size-fits-all approach does not exist for West Africa.** Although there are similar cross-cultural characteristics among populations of the hardest-hit countries, CE strategies will have to be tailored to each country, region, and group.

- **Lack of trust.** Political strife and civil warfare in certain regions have eroded trust in elected or appointed leaders. Rumors of nefarious intentions connected to past vaccine campaigns (eg, polio) continue to smolder. Serious omissions and missteps that reflect poor understanding of the political and cultural context of the region have added to mistrust and now must be addressed for optimal distribution and acceptance of Ebola

vaccines.[13] Additionally, concerns about equitable access to novel therapies emerged when infected Western healthcare workers received unlicensed but promising new therapies that were not made available to other patients.[14] Lack of transparency in the decision-making process raised ethical concerns and prompted a WHO meeting and subsequent recommendations regarding unregistered interventions for EVD treatment.[15]

In light of this controversy and other issues, it would be naïve to expect that people in West Africa assume equitable distribution of Ebola vaccine or have faith in the purity or purpose of the vaccines. The falling incidence of EVD, however, opens an opportunity to showcase the success that teams consisting of local and outside healthcare workers are having in managing the epidemic, and thus to build trust.

- **Misinformation.** Misinterpretation of messaging early in the epidemic about the seriousness of Ebola led to assumptions among some populations that patients with EVD could not be treated or cured.[13] Where these assumptions have not been challenged or corrected, the availability of Ebola vaccines may seem irrelevant, even dangerous, to intended recipients. Anthropological expertise and resources offer a useful framework.[16]

- **Uncertainties about vaccine delivery capabilities.** Early in the epidemic, the failure of external partners to engage national health ministries may have undermined a more coordinated response. On a local level, houses of worship and community-based organizations that constitute part of the response infrastructure have largely been excluded.[17] External partners may be unable to sort out misperceptions from actual weaknesses in the infrastructure, meaning CE strategies should be driven by West Africans and supported as needed by external partners.

- **Cross-cultural miscues.** Healthcare worker assumptions that low demand or rejection of interventions reflects public ignorance or misinformation that needs to be corrected may be unfounded.[18] Instead, reluctance may represent beliefs regarding the strength and the processes that deplete and rebuild strength. In the Gambia, for example, mothers value immunizations as something that strengthens the child's body. If the mothers miss successive clinic appointments, they may be concerned that a backlog of vaccinations administered at one time may overtax the child's body with too much of the strengthening substance.

Recommendations

1. **Begin immediately.** CE activities should be under way specifically to (1) consult with national health ministries and provide any needed educational resources and training and (2) address within communities any general or specific potential perceived barriers

to vaccine acceptance. In addition, communicating vaccine characteristics and target populations to planners needs to happen as soon as possible so they can align vaccination strategies with appropriate CE efforts.

2. **Promote West African leadership.** Trusted leaders from the affected countries should drive CE, with support from external partners as appropriate and requested. Leaders selected by their communities rather than imposed on them by others are essential to CE efforts that are culturally informed, are practical, and build trust.

3. **Promote inclusivity and collaboration.** A broad definition of CE is recommended. Special efforts should be made to identify overlooked stakeholders, including women, who may have untapped strengths to mobilize their communities. To the extent possible, vaccine CE efforts should link to the successful treatment collaborations of local and outside healthcare workers whose management of the epidemic involves building trust.

4. **Employ lessons learned to inform Ebola strategies.** For example, hardest-hit countries should consider creating structures similar to the Nigerian Northern Traditional Leaders Committee for Primary Health Care and Polio Eradication as a way to formally engage with traditional and religious institutions and influential individuals who can reduce misinformation and stigmatization and bring transparency to ethical aspects of Ebola vaccine.

5. **Match strategies to each country.** To be successful, vaccination campaigns should be unique and appropriate to each country affected by the epidemic. As such, embedding vaccine delivery into a multifactorial approach to halting EVD morbidity and mortality may help prevent perceptions of vaccination efforts as invasive or disconnected from traditional and holistic views regarding strength and resilience.

6. **Ensure transparency.** Ultimately, the acceptance of Ebola vaccines depends on whether recipients trust them. Such trust builds when vaccine-related decisions are transparent, when community priorities are considered and built into vaccination strategies, and when ethical principles inform community engagement and are clearly evident. (See previous Ethics section, page 34.)

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Vaccination Strategies

As Ebola vaccines enter phase 2/3 trials and manufacturing is in progress, public health officials need to consider various post-marketing vaccination strategies that can be implemented to end the current epidemic (assuming the epidemic is still ongoing once vaccines become available for noninvestigational use) and to assist with future Ebola prevention and control activities. To rapidly implement campaigns in the affected countries once vaccine becomes available, public health officials need to be planning the most optimal vaccination strategies for vaccine deployment as soon as feasible. Vaccination strategies may require triage of vaccine to those at highest risk of exposure, depending on availability of vaccine doses, with expansion to additional populations over time as more doses arrive. If triage of vaccination is necessary, early engagement of in-country community leaders in shaping the strategy or strategies will be critical to the success of any vaccination campaign (see the previous section on Community Engagement, page 40).

Vaccination Strategies Aimed at the Current Epidemic

In developing a vaccination strategy for responding to the current epidemic, the following options are available; all are considered "reactive," because they are intended to address an ongoing epidemic.

- **Targeted vaccination of population subgroups.** This strategy aims to prevent disease based primarily on the likelihood of exposure. Appropriate risk-based target populations include healthcare workers, community-based Ebola response teams, and funeral workers. Officials in impacted countries may also choose to vaccinate persons involved with maintenance of critical infrastructure (eg, military personnel, police, first responders, high-level government officials). While persons in this latter group may not necessarily be at higher risk of exposure, they are essential for the ongoing functioning and overall well-being of affected communities. Historical examples that have used or supported targeted vaccination of population subgroups include the US smallpox vaccination campaign in 2002-03 and various pandemic influenza response plans.[1,2] During the US smallpox vaccination campaign (a biodefense preparedness effort), approximately 39,500 healthcare workers and first responders were vaccinated against smallpox, along with US military personnel.[1] Public health officials have advocated priority vaccination of critical personnel in the event of a severe influenza pandemic when vaccine is in short supply.[2]

- **Ring-vaccination strategy.** This approach is aimed at preventing disease in potentially exposed persons and serves to disrupt chains of transmission, thereby curtailing and slowing the outbreak. Initial candidates for a ring-vaccination strategy include contacts of EVD patients and home-care providers for EVD patients. In addition, vaccination could also include those whom the initial contacts would expose if they became ill (ie, the secondary contacts). Ring vaccination also may include those in close geographical proximity to cases, regardless of whether they are named as contacts. Ideally, this group should be vaccinated with a single-dose vaccine for two reasons. First, it will be important for persons in this group to achieve protection as soon as possible to maximize the prospects for each of the three benefits outlined below for ring vaccination, which theoretically will be more likely if they are vaccinated with a single-dose vaccine soon after the index case is identified. Second, using a single-dose vaccine simplifies the process and eliminates the need for tracking and revaccination, which may be difficult to achieve in an outbreak setting. Intensive disease surveillance and ring vaccination were key strategies used to locally eliminate smallpox.[3] Ring vaccination also has been employed to contain outbreaks caused by other infectious diseases, such as mumps.[4] In the setting of an Ebola epidemic, ring vaccination may contribute to outbreak control in three distinct ways.
    - *Direct, post-exposure protection*: Persons exposed following contact with an index case may be vaccinated upon identification of the index case, providing them with post-exposure prophylaxis against recent exposure to the index case.
    - *Direct, pre-exposure protection*: Persons who are geographically close to or are contacts of the index case, even if they have not been exposed by the index case, are likely living in a community with ongoing disease transmission, which may continue after they are vaccinated. Vaccine, therefore, may protect them against future exposures occurring after vaccination.
    - *Indirect protection via local herd immunity*: Vaccinating the local community near the index case may induce herd immunity, because many contacts of the index case also will be contacts of each other.[5] This herd immunity may protect those who do not receive timely vaccination.

- **Geographic targeted mass vaccination.** The pattern of disease occurrence in the West Africa Ebola epidemic has demonstrated geographic "hot spots"[6]; therefore, mass vaccination in targeted areas is a potential strategy. The greatest demand for vaccine may be in areas that have already experienced intense transmission; however, the areas that may benefit the most from vaccine may be those where infection recently has been introduced. Effective geographic targeting would rely on surveillance data to indicate where the epidemic is heading and then rapid deployment of vaccination teams to those areas. Reactive mass vaccination targeted to geographic areas is still used to

contain outbreaks of meningococcal type A disease across the "meningitis belt" in central Africa.[7] This strategy also has been considered for cholera epidemics, where vaccine could be provided to residents in the hardest-hit areas as an adjunct to traditional control measures.[8,9]

- **Broad mass vaccination across impacted countries.** If the current epidemic proves difficult to extinguish completely and enough vaccine is available, broad population-based mass vaccination may be an effective strategy in ending the epidemic. This approach may involve prioritization by age-group, since most cases have occurred among adults under the age of 45. Also, clinical trials may show that the vaccine is most effective in the non-elderly adult population, which would also support prioritization by age. The recent risk-based mass vaccination campaigns against meningococcal A disease are an ideal model for this type of approach; all persons aged 1 to 29 were targeted based on likelihood of disease.[10] Meningococcal conjugate vaccine is delivered intramuscularly and not orally as in OPV campaigns, which adds to complexity of the campaign and is comparable to what will be needed for Ebola vaccination, assuming that Ebola vaccines will require use of parenteral injections. Between 2010 and May 2014, meningitis A conjugate vaccine was introduced in 12 countries in the meningitis belt, with more than 150 million people vaccinated.[7] Mass vaccination campaigns are ongoing, with the expectation that all high-risk countries will complete a vaccination program within the next several years.

Factors Influencing Vaccination-Strategy Decisions

Decisions regarding the most appropriate vaccination strategy or strategies will be influenced by certain characteristics of the vaccine, such as the number of doses needed to confer adequate protection, time from vaccination to development of protection, safety and effectiveness of the vaccine in different age-groups and populations (as determined by phase 2/3 trials), overall level of vaccine efficacy/effectiveness, and storage requirements of the vaccine. For example, if a vaccine requires only a single dose to confer protection, it will be easier to use in a range of settings, because tracking and follow-up of vaccinated persons will not be necessary. A single-dose vaccine may be more practical for a ring-vaccination strategy or a mass vaccination campaign than a vaccine that requires more than one dose. If a vaccine requires two doses, it may be more useful in well-defined subsets of the population, such as healthcare workers or community-based Ebola response teams.

Time from vaccination to full protection also is an important factor to consider. If time from vaccination to substantial level of pre-exposure protection exceeds the maximum incubation period of the disease (ie, approximately 21 days), it is unlikely that the vaccine will offer substantial post-exposure protection. The converse is not guaranteed; even if a vaccine provides pre-exposure protection within 21 days, it may not necessarily be effective

post-exposure. Nonetheless, as noted above, post-exposure protection is only one of three ways in which ring vaccination can be of value, so ring-vaccination strategies may retain some effectiveness even if post-exposure protection is not attained.

Also, if a vaccine is not shown to be safe and effective across age-groups, then an initial strategy may be to vaccinate adults only (up to a certain age) until more data are available to support "bridging" to other populations. This type of approach needs to be balanced with the need to protect children and the elderly to ensure those populations are not left in a vulnerable position. If the efficacy/effectiveness of the vaccine is marginal, then larger segments of the population may require vaccination to significantly affect the reproductive number (R_0), which will be necessary to control the outbreak.

Other factors also will influence vaccination strategy. For example, if vaccines are in limited supply, a targeted approach will be necessary. As more vaccine becomes available, the strategy may be broadened to include larger segments of the population. Similarly, logistical issues could affect the strategy. For example, if a vaccine requires freezing at -20°C or -80°C, it will be more difficult to maintain the cold-chain requirements, which could limit use of the vaccine. Again, such a vaccine may be more suitable to small segments of the population that are relatively easy to access, such as healthcare workers.

Finally, the epidemiology of the epidemic will be important to consider when developing the vaccination strategy. Incidence rates have varied substantially by geographic regions within the affected countries, thus supporting geographic targeting. Age distribution also is an important consideration; as of late January 2015, 56.3% of cases had occurred in persons 15 to 44 years of age, with 20.2% of cases in children and 23.5% of cases in persons 45 years of age and older.[11] Also, almost 4% of cases have occurred in healthcare workers, even though healthcare workers make up a very small proportion of the population.[12]

Challenges in Implementation of a Vaccination Strategy

A number of challenges need to be addressed in implementing a vaccination strategy to combat the current epidemic. First, an adequate supply of vaccine needs to be available. The two front-running candidate vaccines (cAd3-EBO and rVSV-ZEBOV) are slated to begin phase 2/3 trials during the first quarter of 2015. A third prime-boost vaccine, Ad26.ZEBOV/MVA-BN-Filo, entered a phase 1 trial in January 2015. Assuming vaccine trials demonstrate adequate efficacy and safety profiles and that the anticipated production schedules can be followed, representatives from the three companies indicated in January 2015 that a million doses or more of each vaccine could be produced before the end of the year. Both BPS-NLG/Merck and J&J have the capacity to produce up to 5 million doses this year if necessary, with GSK able to ramp up production to about 1 million doses a month by the end of 2015.[13]

Another important challenge is the cold-chain requirements of the two front-running candidate vaccines. Both are live-virus vector vaccines that require storage at -80°C. This creates logistical and cost barriers for use in tropical, under-resourced countries. Meningococcal A vaccination in Africa provides valuable insight on this issue. In October 2012, meningococcal A vaccine was granted a label variation to allow use outside the traditional cold chain. At that time, the vaccine, which is a lyophilized product, was approved for use in a controlled temperature chain (CTC) at temperatures of up to 40°C (104°F) for up to 4 days. Subsequent experience demonstrated that decreasing the cold-chain requirements resulted in significant cost savings and improved the success of vaccination efforts.[14,15] In addition to cold-chain considerations, vaccine manufacturers should consider providing the simplest presentation possible to allow for easy administration and limit logistic challenges during a vaccination campaign. These efforts, however, need to balance the ideal situation with what can be achieved urgently to control the current epidemic.

A third key challenge is the need to engage in-country leadership as soon as possible in decision-making around the appropriate vaccination strategies, such as through engagement of national immunization technical advisory groups (NITAGs) and engagement of other community leaders. Again, the importance of community engagement was clearly demonstrated with the meningococcal A vaccination experience. Meningococcal vaccination campaigns were risk based (ie, targeted to persons 1 to 29 years of age because that age-group was at highest risk), and engagement of community leaders to support this strategy was essential in the success of the initiative. The vaccination campaign in Burkina Faso identified a number of key challenges that were successfully managed.[10] One was developing a comprehensive communication plan, and a second was ensuring effective collaboration across all partners, including active engagement of traditional and religious leaders. Community engagement is discussed in greater detail beginning on page 40.

A final challenge is the importance of conducting post-marketing surveillance to identify adverse events, which will be difficult owing to the lack of public health infrastructure in the affected areas. This issue is discussed in greater detail in the section on vaccine efficacy, effectiveness, and safety (page 18).

Vaccination Strategies for Prevention and Control of Future Disease

Future outbreaks of EVD are bound to occur across Central and West Africa; therefore, vaccination strategies beyond the current situation should be considered if EVD is to be controlled. One approach is to use reactive vaccination strategies at the onset of future outbreaks, similar to those outlined above, including reactive mass vaccination in the area of the outbreak, ring vaccination around cases of disease, and reactive vaccination of high-exposure groups such as healthcare workers or Ebola response teams. This would likely

require stockpiling vaccine for future use. While this should be considered, further analyses of the feasibility and cost-benefit of creating vaccine stockpiles are necessary.

Alternatively, prophylactic vaccination strategies may be considered. This could involve a targeted approach, such as prophylactic vaccination of healthcare workers in high-risk areas, as is conducted more broadly for hepatitis B vaccine. If the epidemiology of EVD or Marburg virus disease evolves and the risk increases, population-based periodic mass vaccination campaigns may be considered every few years. Or filovirus vaccination could be incorporated into routine childhood vaccination schedules, following an approach similar to what is being done for meningococcal A disease across the African meningitis belt. This approach should be pursued only if long-term protection following vaccination can be demonstrated. Moreover, greater certainty regarding the safety profile of the vaccine would be required if mass vaccination of large populations is envisaged, as adverse events that may be tolerable for limited high-exposure groups might not be so for larger segments of the population.

Another approach is a combination of reactive and prophylactic strategies, similar to what has been implemented over the past few years to control yellow fever. As part of the Yellow Fever Initiative, a yellow fever vaccine stockpile is maintained annually for reactive use to control outbreaks and for mass vaccination campaigns for populations in high-risk areas.[16] In addition, the WHO has recommended that high-risk countries reintroduce routine childhood immunization against yellow fever to ensure population-based protection against this disease.[17] Depending on the future epidemiology of filovirus disease in Africa, this could be a cost-effective strategy.

Conceivably, more than one Ebola vaccine may eventually be licensed; such vaccines may be suited to different purposes. For example, a single-dose regimen that offers a relatively short duration of protection may be more suitable to ring vaccination and mass vaccination for outbreak control. Conversely, a prime-boost regimen may be acceptable for vaccination of certain groups such as healthcare workers, or for prophylactic strategies, particularly if more durable immunity can be generated by such vaccines.

Recommendations

Post-marketing Vaccination Strategy for the Current Epidemic

1. Involve in-country leadership. Leaders in the affected countries need to be involved in determining the priority groups for vaccination within their countries and in determining how vaccine will be allocated among the affected countries.

2. Target those at highest risk. The key framework for developing vaccination strategies should be based on initial targeting of those at highest risk of exposure. The strategy can be phased in, according to the number of vaccine doses available, and may evolve

over time with expansion to additional population groups as more vaccine becomes available.

3. **Consider frontline workers as a priority group.** Targeted vaccination of healthcare workers, Ebola response teams, and funeral workers should be considered a priority once vaccine is available. Such frontline workers are essential to the care of the ill and are at relatively high risk of acquiring infection. Vaccination of this group should be feasible with a single-dose or two-dose vaccine.

4. **Consider a ring vaccination approach.** Ring vaccination of case contacts and home-care providers, along with their potential secondary contacts or those in geographic proximity, also should be a priority if vaccine supplies are adequate. For these groups, a single-dose vaccine will be easier to administer.

5. **Consider personnel involved in critical infrastructure as a possible priority group.** A third priority group for consideration includes persons involved in maintaining essential infrastructure (such as police, fire, first responders, and military personnel); persons in this group may not necessarily be at high risk of exposure, but they serve to keep communities functioning.

6. **Develop mass vaccination strategies as necessary if adequate vaccine supplies are available.** Mass vaccination targeted to geographic regions impacted during the current epidemic also should be considered if the epidemic is ongoing when adequate doses of vaccine become available. Use of a single-dose vaccine will greatly simplify this process. Initial efforts should be targeted to adults, since that group has been shown to be at greatest risk of acquiring infection.

Vaccination Strategies for Future Consideration

7. **Resolve cold-chain challenges.** Vaccine companies should make every effort to resolve the cold-chain challenges that require freezing at -20° or -80°C and should strive to produce vaccines that can last several days in the traditional 2° to 8°C range.

8. **Consider stockpiling vaccines for future use.** Once the West Africa epidemic is controlled, stockpiling vaccines to be used for future outbreaks should be considered if further analyses support this approach. Vaccines could be used during outbreaks (eg, by employing the reactive vaccination strategies outlined above) in coordination with traditional public health measures to achieve rapid control.

9. **Consider routine vaccination of healthcare workers in high-risk areas.** Because healthcare workers are at risk of infection, an appropriate strategy may be ongoing routine vaccination of healthcare workers practicing in areas at risk of future Ebola outbreaks, similar to the strategy of vaccinating healthcare workers against hepatitis B. This can also be considered for other types of frontline workers, if they can be identified in advance.

10. **Consider population-based mass vaccination if warranted.** Proactive population-based mass vaccination in at-risk countries should be considered if the epidemiology of filovirus disease changes and officials determine that the risk of disease is high enough to warrant the cost and effort involved and if the safety profile of the vaccine is determined satisfactory. Establishment of such a safety profile may require further, large phase 2 studies in healthy populations with adequate post-vaccination surveillance for adverse events.

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Funding

The development and delivery of safe, effective Ebola vaccines to the people of West Africa and possibly beyond requires sustained funding from an unprecedented mix of public, private, and charitable sources. The decline of EVD morbidity and mortality, though welcomed, is not guaranteed to continue. There remains a compelling need to fund vaccine efforts for the current epidemic as well as to prepare for future Ebola outbreaks in other African countries and to address the potential for Ebola to become endemic in the region. Given the economic realities of the most-affected countries, the magnitude and duration of the current epidemic, and the manufacturing complexities with current vaccine candidates, the funding needs for vaccine efforts are both immediate and long-term.

Funding Vaccine Development and Delivery for Low-Income Nations

Multinational pharmaceutical firms produce most vaccines available today, while a small number of emerging suppliers in China, Brazil, and India (but not in or near West Africa) are increasing regional capacities to produce vaccines.[1] Funding for research and development for new vaccines comes from a mix of public, philanthropic, and other private-sector investments. Presumably, pricing reflects the cost of large-scale manufacturing and an unknown cost that ensures profitability to shareholders and sustains and grows manufacturers' businesses. While public health issues may contribute to the *demand* for new vaccines, forecasted revenue and profit ultimately shape the market for products, effectively making vaccines most affordable to people in high-income countries.

To access these same vaccines, people from low-income countries (LICs) rely on multilateral purchasing collectives, such as GAVI Alliance, a non-governmental organization founded in 2000, which receives and manages donations from public and private sources. GAVI Alliance negotiates with manufacturers for best prices; however, without the benefit of pricing transparency, ascertaining what is the most reasonable lowest price may be unrealistic. GAVI Alliance has tested the use of Advance Purchase Commitments (APCs), a financial tool that in theory can reduce risk to manufacturers by eliminating uncertain revenue forecasting.[2] Evidence exists, however, that manufacturers perceive the APC-related forecasting as hypothetical[3] and that APCs have not as yet delivered expected levels of price reductions.[4] In short, the likelihood that people in LICs will have the right vaccine when and where they need it depends on the (1) availability of vaccine technology and capacity to target emerging diseases, (2) willingness of for-profit manufacturers to risk making vaccines with little profit potential, and (3) enduring

generosity of donors. These funding challenges highlight the need for imaginative thinking about economic considerations and how they shape Ebola vaccine selection and strategies for deployment. They also underscore an imperative to build and fund a *public health*–driven global capacity to immunize against endemic and emerging diseases.

Current Landscape of Ebola Vaccine Funding

To date, sources of funding for accelerated research and development of Ebola vaccine candidates include pharmaceutical companies, philanthropies, and government agencies. GAVI Alliance announced in December 2014 a commitment of US$300 million for 12 million courses of WHO-recommended Ebola vaccines, as well as US$45 million to help affected countries deliver vaccine and another US$45 million to assist recovery of health and immunization services in West Africa.[5] GAVI Alliance made its decision using scenarios that estimated a funding gap of up to US$600 million to ensure manufacture of enough vaccine to address the current epidemic, build a stockpile by 2016, and maintain the stockpile until 2020.[6] Furthermore, GAVI Alliance may use APCs, which can frontload funds, and the International Finance Facility for Immunization (IFFIm) to procure funding for Ebola vaccines and vaccination programs. The funding, however, will not cover indemnity.[7]

Funding Issues and Challenges

In securing sufficient funding to bring vaccine to the fight against Ebola in West Africa, the following issues and challenges have been identified:

- **Waning public interest in the Ebola epidemic.** At the same time that promising vaccine candidates are in clinical trials, the media spotlight is shifting away from West Africa, leaving the impression that the epidemic is over. Concern has been raised that waning media attention may dampen the public and political will necessary to prioritize Ebola vaccine over so many competing interests in government and commerce.

- **The private sector's financial model.** Only the private sector has the capabilities to manufacture Ebola vaccines; however, the market for these vaccines is not likely to be profitable. This is particularly true in the short term, when processes that typically take years must be collapsed into months to rapidly produce a vaccine that can be used during the current epidemic. In the face of opportunity costs, stakeholder profit pressures, and the demand for already licensed vaccines, the private sector's commitment to an Ebola vaccine is not a certainty, nor, some would argue, should it be.

- **Research and development pipeline.** Financial incentives may be needed to continue trials on candidate vaccines that are not the first to show sufficient efficacy, particularly in view of low expectations about return on investment. However, the success of a single vaccine candidate is not a certainty, and the continuation of trials of additional

candidates may be needed to ensure that immediate and long-term needs for Ebola vaccines are met. There is a high possibility that at least two types of vaccine will be needed: (1) a single-dose vaccine that provides immediate immunogenicity and protection for outbreak containment and (2) a vaccine that produces durable protection for use during non-outbreak settings to vaccinate key healthcare workers, for whom a prime-boost strategy may work.

Another consideration in the research and development phase is the need to complete rigorous ethics reviews in locations where vaccine trials are being planned. Owing to civil warfare and disease, the ethics review infrastructure in the three affected countries requires significant bolstering from the international community, which also must be funded. (Along these lines, members of the Ethics Work Group suggested that, in addition to assistance provided by the WHO for ethical reviews, there is a need to create a pool of funding whereby contributions from pharmaceutical companies and/or other sources can be independently administered to deploy ethics SMEs where most needed.)

- Manufacturing trade-offs. No single facility exists that can produce every vaccine; each vaccine requires special engineering targeted to the specific pathogen of interest. Even where a manufacturing plant sits idle, retrofitting it to produce a new vaccine can take months. Pharmaceutical companies have the capabilities to manufacture new vaccines, but they may not have the *capacity* unless they shut down an existing plant that is producing a profitable vaccine and redirect it for Ebola vaccine production. The same challenge exists for fill-finish facilities, which put bulk manufactured vaccine into multi-dose or single-dose vials or single-dose prefilled injection devices. A bottleneck to vaccine delivery is not uncommon at the fill-finish stage, and manufacturers may face a trade-off between bulk supply versus final dosage form. Innovations for safe multi-dose presentations, dose-sparing strategies, product stabilization, and preservation are needed to streamline operations. Additionally, manufacturers must cover the cost of quality control, quality assurance, and meeting stringent safety regulations. These issues can work against the willingness of even the most publicly spirited pharmaceutical executives to risk manufacturing an Ebola vaccine.

- Vaccine pricing and procurement. The price per dose directly affects vaccine affordability and the amount of funding needed to procure enough vaccine to meet immunization objectives. The lack of pricing transparency ultimately hinders efforts to estimate funding needs as well as ensure fair prices for vaccines. In the case of the Meningitis Vaccine Project in central Africa, a target price of US$0.50 per dose was set by the project *before* manufacture.[8] Pharmaceutical companies approached by the Meningitis Vaccine Project team declined to participate. By securing a transfer of

conjugate vaccine technology, the project successfully engaged the Serum Institute of India to build the necessary manufacturing capacity and deliver supplies at the target price.

The technology needed to bring to scale the Ebola vaccine candidates currently in clinical trials is believed to reside primarily in multinational firms. Whether Indian, Chinese, or Brazilian firms can manufacture safe, effective, and more cost-effective Ebola vaccines is not yet known. Ideally, a purchase price for Ebola vaccines should: (1) reflect the direct costs to manufacture sufficient amounts, (2) account for the public and charitable investments in their development, and (3) assume limited ability of affected countries to secure funding for vaccine supplies. Any additional allocation of costs by manufacturers that are factored into the vaccine price should prioritize meeting an urgent public health need while ensuring the sustainability of vaccine production.

- **Rebuilding infrastructure to deliver vaccine.** Ebola's toll on healthcare workers in West Africa and on the fragile healthcare infrastructure in the affected countries requires attention to ensure in-country capacity to provide vaccine services. This will require a long-term funding commitment to rebuild damaged systems. Additionally, capacity is needed to ensure post-marketing surveillance for adverse events.

- **Stockpiling vaccine.** Stockpiling vaccine for future outbreaks or to address the virus becoming endemic is a logical step, if deemed to be feasible and cost-effective, that also requires sufficient funding for vaccine supplies and storage. Even so, all stockpiles expire, and "warm-base" manufacturing capability —whereby a facility maintains readiness to replenish a reasonable stockpile of vaccine in a pre-determined timeframe— may be another strategy that requires funding as well.

Emerging Opportunities

- **New funding paradigms.** In January 2014, GAVI Alliance's CEO described the inability to swiftly and affordably produce vaccines for low-income nations "a market failure."[9] In a November 2014 report on Ebola vaccine development, the Norwegian Institute of Public Health proposed to "establish a sustainable international mechanism for the development of vaccines and medicines for infections such as EVD, where there are insufficient commercial markets."[10] This concept can be applied to the current situation and also could serve as a model for the future in responding to other emerging infectious disease threats.

- **Public-private partnerships (PPPs).** A number of PPPs are demonstrating success stimulating vaccine research and development, encouraging technology transfer, innovating vaccine presentation, and building capacity among "emerging suppliers." An analysis of 11 PPPs (see Appendix D on page 78), whose efforts encompass various

components of vaccine development and delivery for LICs, shows strength in pre-competitive and research and development stages. Manufacturing capacity, however, is lacking among the sample, although three appear able to produce enough vaccine for early clinical work and one facilitated the scaling up of manufacturing capabilities of an emerging supplier. In looking for an innovative solution driven by interests of public health first, PPPs may offer a solid foundation. Details of successful efforts can be found in the literature[11] and include examples such as the following:

- *The Innovative Medicines Initiative (IMI).* Founded in 2008 as a partnership between the European Union (EU) and the European Federation of Pharmaceutical Industries and Associations, IMI fosters collaboration among multinational manufacturers, academic institutions, medium-sized and small biotechnology firms, and regulatory agencies. IMI in November 2012 called for proposals to fast-track "a wide range of challenges in Ebola research, including vaccines development, clinical trials, storage and transport, as well as diagnostics and treatments." IMI has made €240 million available for the work.[12]
- *PATH.* Founded in 1977 with a grant from the Ford Foundation, the international US-based nonprofit is credited with successfully facilitating partnerships to develop and introduce a safe and affordable meningococcal A vaccine across Africa's meningitis belt. Additionally, PATH's public-private ventures have led to widespread adoption of a temperature-monitoring technology on vials to prevent vaccine spoilage and an auto-disable syringe that automatically locks after a single injection, thereby reducing the chances of contamination when needles are reused. In 2013, PATH's revenue was US$315 million, with funding coming from foundations; the US government; other governments, nonprofit organizations, and multilateral agencies such as the WHO; individuals; and interest from investments.[13]

Recommendations

Short Term

1. **Prioritize securing commitments to long-term funding.** The effort to produce and deliver Ebola vaccine could benefit from the stabilizing influence of commitments spanning at least 2 years of funding for all the components needed for this vaccine, including stockpiling doses for future outbreaks.
2. **Actively seek out roles for emerging suppliers.** Because emerging suppliers may be able to provide less costly fill-and-finish services, this option should be explored in the future with the proviso that quality standards cannot be compromised.

3. **Commit to transparency.** It is in the best interest of the people of West Africa (as it is elsewhere) to have access to plentiful and affordable Ebola vaccine that is both safe and effective. To that end, transparency in financial transactions that affect pricing and in decisions regarding who receives limited doses is a priority.

Long Term

4. **Examine creating an integrated global funding strategy.** Although public attention may recede from the current Ebola epidemic in West Africa, the likelihood of disease and death from future Ebola outbreaks will not. Future outbreaks are inevitable, though none should be allowed to reach the scale of the current epidemic, and work must begin to explore a strategy for integrated global funding (and potentially manufacturing), particularly given the WHO's authority to monitor global health and to declare a public health emergency of global importance. Funding should be tied to access provisions to ensure that products supported by such funding are affordable and available to all affected populations.

5. **Explore the possibility of scaling up promising PPPs.** As a next step, a comprehensive assessment of existing PPPs should commence with the goal of identifying strengths that can be leveraged toward establishing comprehensive vaccine capabilities strictly driven by public health priorities, particularly on behalf of populations in areas where resources are most limited.

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Appendix A: List of Abbreviations

AIDS	acquired immune deficiency syndrome
APC	Advance Purchase Commitment
AVAREF	African Vaccine Regulatory Forum
BPS	BioProtection Systems
BSL-2	biosafety level-2
CE	community engagement
CEO	chief executive officer
CIDRAP	Center for Infectious Disease Research and Policy
CMA	EMA Conditional Marketing Authorization
CTC	controlled temperature chain
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorization
EVD	Ebola virus disease
FDA	US Food and Drug Administration
GHSA	Global Health Security Agenda
GMP	good manufacturing practices
GP	glycoprotein
GSK	GlaxoSmithKline
HC	Health Canada
HHS	US Department of Health and Human Services
HIV	human immunodeficiency virus
ID	intradermal
IM	intramuscular
IMI	Innovative Medicines Initiative
MSF	Médecins Sans Frontières
MVA	Modified Vaccinia Ankara
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NLG	NewLink Genetics
NRA	National Regulatory Authority
OPV	oral polio vaccine
PABIN	Pan African Bioethics Initiative
PQP	WHO Prequalification of Medicines Program
PREP	Public Readiness and Emergency Preparedness
QC	quality control
RCT	randomized controlled trial
SAGE	WHO Strategic Advisory Group of Experts
SQ	subcutaneous
UNICEF	United Nations Children's Fund
VSV	vesicular stomatitis virus
WHO	World Health Organization

Appendix B: Ebola Vaccine Team B Recommendations

MANUFACTURING

Streamline process steps. Technologies for manufacturing Ebola vaccines that enhance yield or leverage processes that have already undergone licensure should be considered, if issues regarding intellectual property and commercialization can be promptly addressed. Streamlining specific process steps using proven platforms or methods, those that have already been evaluated and approved, could accelerate the development of new products.

Review factors that could improve cost-effectiveness. Critical factors in manufacturing the current leading candidate vaccines include dose requirements, production yield, process validation, finish-and-fill capacities, cold-chain storage requirements, QC testing capability and capacity, supply chain issues, scale, cost, and liability. Other specific challenges may occur with alternative vaccine platforms or formulations. Process improvements and refinements in the manufacturing process may be needed for cost-effective vaccine delivery. Comprehensive assessments of key factors and critical decision points in manufacturing and commercialization should be shared openly for consideration, in view of the need to coordinate global public health response efforts.

Focus on monovalent vaccines in the near-term. Depending on the production method used, if monovalent vaccine formulations (Zaire Ebola virus) can be manufactured more quickly than multivalent formulations, an initial focus on effective monovalent vaccines is likely to speed up the manufacturing phase of the current response to the epidemic in West Africa. Multivalent formulations or other panfilovirus vaccine approaches may be more suitable for subsequent next-generation vaccines and could contribute to effective long-term solutions. Since the selection of GP as the primary protective antigen has not yet been confirmed in humans, further research is needed to determine the potential protective role of other antigenic proteins, such as the matrix protein or nucleoprotein, from the Zaire Ebola virus subtype and other subtypes.

Assess potential for future technology transfer. The development of in-region manufacturing capacity could potentially enhance access to Ebola vaccines in West Africa or elsewhere in Africa in the longer term. Technology transfer to a reliable in-region manufacturer could also provide an alternative source of vaccine if an originator manufacturer cannot commit to continued production. As the specific technologies for effective Ebola vaccines become clearer, the complex issues involved in technology transfer to an in-region manufacturer will need to be fully addressed.

EFFICACY, EFFECTIVENESS, AND SAFETY

Applicable to Vaccine Efficacy and Effectiveness

Ensure flexibility in the clinical trial process. The clinical trial process needs to be innovative and flexible to provide opportunities to continue evaluating efficacy (eg, through measurement of surrogate end points) of new product candidates when disease-prevention impact cannot reliably be assessed because of low incidence of disease. Designs of efficacy trials should, to the extent possible, permit adaptive decisions to add participants or increase follow-up time in response to patterns of incidence that were not anticipated in the original study design, such as declining incidence or occurrence of localized outbreaks.

Evaluate all promising vaccines in clinical trials. Because it is not clear which vaccine(s) may ultimately prove to be most efficacious, and which may be most effective in the field once approved, all promising vaccines should be evaluated in clinical trials, although human efficacy studies may be possible only in the context of the current large epidemic, and even this possibility has become uncertain with declining disease incidence. Alternatives to clinical efficacy trials in the absence of an epidemic should be considered that would allow vaccine candidates a development path to licensure (eg, US FDA Animal Rule).

Plan for contingencies. Investigators and public health officials need to address how ongoing or additional trials will be handled if one vaccine shows efficacy and is available for widespread use or will become available in the near future. Rolling out a vaccine that shows early efficacy must be balanced with the need for mature data.

Obtain post-vaccination blood specimens if possible. Investigators involved in vaccine efficacy studies should be encouraged to obtain post-vaccination blood specimens if at all possible. Such specimens will be invaluable in determining correlates of protection, which could enhance future work in developing next-generation Ebola vaccines. The challenges and risks of collecting such samples are recognized.

Consider seroprevalence surveys. Seroprevalence surveys may be of value in determining the degree of herd immunity, particularly in areas where cluster-design trials are being conducted.

Continue to obtain safety data. Phase 2/3 clinical trials for Ebola vaccines should be conducted even if efficacy data cannot be obtained because such data may contribute importantly to future licensing efforts.

Anticipate the risk-benefit ratio. To the degree possible, investigators and public health officials should begin considering the anticipated risk-benefit ratio as far in advance as possible and discussing what level of safety risk will be tolerated in the setting of an ongoing epidemic. In addition, the need to discuss how the risk-benefit ratio will be different if and when the vaccines are to be used in a non-outbreak setting. This is potentially challenging, particularly if limited safety data are available.

Plan for adverse events. Procedures for responding to possible rare but serious adverse events that may occur during clinical studies or post-marketing surveillance should be specified in advance. The procedures need to take into account that, in view of the very high mortality associated with EVD, such events may or may not compromise the risk-benefit ratio of vaccination, depending on their severity and frequency, and the risk of EVD infection in the trial population.

Develop a risk communication plan for adverse events. A community engagement plan that addresses the risk-benefit concept should be developed in advance for public sharing of information if any of the following are recognized: serious adverse events; coincident events, not necessarily caused by the vaccine; or post-vaccination EVD cases. A risk communications plan will help clarify expectations and mitigate any misperceptions that could substantially lower vaccine acceptability.

Identify baseline data. Consideration should be given to identifying adverse events that may be likely to occur, developing appropriate case definitions for those events, and determining if any applicable baseline data are available from any in-country epidemiologic sources, particularly in preparation for post-marketing deployment of one or more vaccines.

Develop post-marketing surveillance plans. Post-marketing surveillance should be in place once vaccines are approved or authorized for use. This could be done through active or passive health center–based targeted surveillance, follow-up of vaccinated cohorts, or canvassing regions several weeks after a vaccination campaign to search for serious adverse events.

Think proactively. Developers of next-generation Ebola vaccines should consider the need to protect against other filovirus infections in addition to Zaire Ebola virus, which ultimately will require development of multivalent vaccines. Furthermore, antigenic drift may be an issue over time—particularly with ongoing evolutionary pressure through serial passage in humans—and future efforts will need to consider the impact of antigenic drift on vaccine product development.

Maintain WHO coordination. The WHO should continue to coordinate international efforts to determine appropriate regulatory pathways for Ebola vaccines and provide expert oversight and guidance, in collaboration with the NRAs, the AVAREF, pharmaceutical companies, and international health and humanitarian organizations. Key goals include developing consensus recommendations regarding emergency approval or authorization pathways, identifying opportunities for reciprocity to expedite approvals among multiple NRAs, and clarifying the role of potential FDA or EMA approvals in the West African vaccine regulatory process.

Obtain safety data. Phase 2/3 clinical trials for Ebola vaccines should be conducted even if efficacy data cannot be obtained. Substantial safety (and immunogenicity) data derived from these trials will be essential for determining whether to use the vaccines in future Ebola outbreaks and for eventual licensure of the vaccines.

Identify options for accelerated approval. The NRAs, with support from the WHO, should continue to harmonize approval requirements and identify flexible options within their current regulatory requirements for accelerated approval and licensing processes, including the FDA's Animal Rule, when appropriate.

Evaluate and monitor use of EUA internationally. The NRAs should consider reciprocity for the FDA's EUA, which may be unique among regulatory options for providing emergency access to new Ebola vaccines. Priorities also include mitigating potential risks from using EUA pathways to provide access to unapproved vaccines, such as promoting post-marketing surveillance studies to identify adverse events and enhance trust and confidence in vaccination.

Extend PQP. The WHO should assess whether its PQP could be extend to guidance concerning the distribution of unapproved vaccines in the affected countries under an emergency use paradigm, such as the FDA's EUA.

Establish ongoing WHO capability for facilitating fast-track regulatory review. The WHO should consider creating a permanent international forum within WHO to coordinate and expedite regulatory review processes, in collaboration with the NRAs (including FDA and EMA) and public/private stakeholders, to enable a streamlined approach to accelerated regulatory review for new vaccines during public health emergencies of international significance; priorities include coordinating agreements on harmonized regulatory pathways and single data packages.

Safeguard broad and equitable stakeholder representation at every stage. The urgency and speed of vaccine development and delivery must not be allowed to trump the imperative that African stakeholders are positioned at the forefront of decisions that affect the safety, well-being, and resilience of the populations hardest hit by EVD. From participation in clinical trial decisions to deliberations about post-marketing vaccination strategy to prioritizing delivery of vaccine supplies in a scarcity scenario, African stakeholders in the affected countries must have a leading role. This is particularly important if a candidate vaccine demonstrates sufficient safety and potential efficacy to undergo an accelerated approval process or be approved for emergency use.

Bolster local bioethics capacity now and for the long run. Resources that become available for immediate ethics review should be used in a way that also builds capabilities for the long term. Consideration should be given, for example, to how fast-tracked training for research ethics committees at the local level also lays the framework for a strong lattice of expertise to address future needs for ethical review.

Establish funds for SMEs to assist ethical review and oversight. A funding mechanism is needed to cover the travel, per diem, and teleconferencing expenses of bringing in external expertise, as required, to the hardest-hit countries. Efforts to provide assistance should be driven by African requests or be sufficiently informed by African stakeholders. As a longer-term solution, revitalizing a collective of bioethicists in Africa (such as PABIN) willing to work toward shoring up and streamlining ethical review would ensure enduring and consistent bioethics review capacity across Africa.

Safeguard respectful handling, storage, and use of tissue and blood samples. In addition to ensuring biosafety measures, a guiding principle for taking and storing samples should be respecting the rights and privacy of vaccine recipients. Although cross-country shipping may be necessary, no commercialization of tissues or trafficking of human identity related to samples should be permitted.

Address how vaccine-related adverse events will be handled. Clarify and communicate broadly how and to whom vaccine-related adverse events should be reported, the process for addressing them, and who is accountable for reparations.

Begin immediately. CE activities should be under way specifically to (1) consult with national health ministries and provide any needed educational resources and training and (2) address within communities any general or specific potential perceived barriers to vaccine acceptance. In addition communicating vaccine characteristics and target populations to planners needs to happen as soon as possible so they can align vaccination strategies with appropriate CE efforts.

Promote West African leadership. Trusted leaders from the affected countries should drive CE, with support from external partners as appropriate and requested. Leaders selected by their communities rather than imposed on them by others are essential to CE efforts that are culturally informed, are practical, and build trust.

Promote inclusivity and collaboration. A broad definition of CE is recommended. Special efforts should be made to identify overlooked stakeholders, including women, who may have untapped strengths to mobilize their communities. To the extent possible, vaccine CE efforts should link to the successful treatment collaborations of local and outside healthcare workers whose management of the epidemic involves building trust.

Employ lessons learned to inform Ebola strategies. For example, hardest-hit countries should consider creating structures similar to the Nigerian Northern Traditional Leaders Committee for Primary Care and Polio Eradication as a way to formally engage with traditional and religious institutions and influential individuals who can reduce misinformation and stigmatization and bring transparency to ethical aspects of Ebola vaccine.

Match strategies to each country. To be successful, vaccination campaigns should be unique and appropriate to each country affected by the epidemic. As such, embedding vaccine delivery into a multifactorial approach to halting Ebola morbidity and mortality may help prevent perceptions of vaccination efforts as invasive or disconnected from traditional and holistic views regarding strength and resilience.

Ensure transparency. Ultimately, the acceptance of Ebola vaccines depends on whether recipients trust them. Such trust builds when vaccine-related decisions are transparent, when community priorities are considered and built into vaccination strategies, and when ethical principles inform community engagement and are clearly evident.

VACCINATION STRATEGIES

For Current Epidemic

Involve in-country leadership. Leaders in the affected countries need to be involved in determining the priority groups for vaccination within their countries and in determining how vaccine will be allocated among the affected countries.

Target those at highest risk. The key framework for developing vaccination strategies should be based on initial targeting of those at highest risk of exposure. The strategy can be phased in, according to the number of vaccine doses available, and may evolve over time with expansion to additional population groups as more vaccine becomes available.

Consider frontline workers as a priority group. Targeted vaccination of healthcare workers, Ebola response teams, and funeral workers should be considered a priority once vaccine is available. Such frontline workers are essential to the care of the ill and are at relatively high risk of acquiring infection. Vaccination of this group should be feasible with a single-dose or two-dose vaccine.

Consider a ring vaccination approach. Ring vaccination of case contacts and home-care providers, along with their potential secondary contacts or those in geographic proximity, also should be a priority if vaccine supplies are adequate. For these groups, a single-dose vaccine will be easier to administer.

Consider personnel involved in critical infrastructure as a possible priority group. A third priority group for consideration includes persons involved in maintaining essential infrastructure (such as police, fire, first responders, and military personnel); persons in this group may not necessarily be at high risk of exposure, but they serve to keep communities functioning.

Develop mass vaccination strategies as necessary if adequate vaccine supplies are available. Mass vaccination targeted to geographic regions impacted during the current epidemic also should be considered if the epidemic is ongoing when adequate doses of vaccine become available. Use of a single-dose vaccine will greatly simplify this process. Initial efforts should be targeted to adults, since that group has been shown to be at greatest risk of acquiring infection.

For Future Consideration

Resolve cold-chain challenges. Vaccine companies should make every effort to resolve the cold-chain challenges that require freezing at -20° or -80°C and should strive to produce vaccines that can last several days in the traditional 2° to 8°C range.

Consider stockpiling vaccines for future use. Once the West Africa epidemic is controlled, stockpiling vaccines to be used for future outbreaks should be considered if further analyses support this approach. Vaccines could be used during outbreaks (eg, by employing the reactive vaccination strategies outlined above) in coordination with traditional public health measures to achieve rapid control.

Consider routine vaccination of healthcare workers in high-risk areas. Because healthcare workers are at risk of infection, an appropriate strategy may be ongoing routine vaccination of healthcare workers practicing in areas at risk of future Ebola outbreaks, similar to the strategy of vaccinating healthcare workers against hepatitis B. This can also be considered for other types of frontline workers, if they can be identified in advance.

Consider population-based mass vaccination if warranted. Proactive population-based mass vaccination in at-risk countries should be considered if the epidemiology of filovirus disease changes and officials determine that the risk of disease is high enough to warrant the cost and effort involved and if the safety profile of the vaccine is determined satisfactory. Establishment of such a safety profile may require further, large phase 2 studies in healthy populations with adequate post-vaccination surveillance for adverse events.

FUNDING

Short Term

Prioritize securing commitments to long-term funding. The effort to produce and deliver Ebola vaccine could benefit from the stabilizing influence of commitments spanning at least 2 years of funding for all the components needed for this vaccine, including stockpiling doses for future outbreaks.

Actively seek out roles for emerging suppliers. Because emerging suppliers may be able to provide less costly fill-and-finish services, this option should be explored in the future with the proviso that quality standards cannot be compromised.

Commit to transparency. It is in the best interest of the people of West Africa (as it is elsewhere) to have access to plentiful and affordable Ebola vaccine that is both safe and effective. To that end, transparency in financial transactions that affect pricing as well as decisions regarding who receives limited doses is a priority.

Long Term

Examine creating an integrated global funding strategy. Although public attention may recede from the 2014 Ebola epidemic in West Africa, the likelihood of disease and death from future Ebola outbreaks will not. Future outbreaks are inevitable, though none should be allowed to reach the scale of the current epidemic, and work must begin to explore a strategy for integrated global funding (and potentially manufacturing), particularly given the WHO's authority to monitor global health and to declare a public health emergency of global importance. Funding should be tied to access provisions to ensure that products supported by such funding are affordable and available to all affected populations.

Explore the possibility of scaling up promising PPPs. As a next step, a comprehensive assessment of existing PPPs should commence with the goal of identifying strengths that can be leveraged toward establishing comprehensive vaccine capabilities strictly driven by public health priorities, particularly on behalf of populations where resources are most limited.

Appendix C: Optimal and Minimal Criteria for Ebola Vaccines* Used in Epidemic or Endemic Settings

This endeavor serves as an initial approach in formulating an abbreviated target product profile (TPP) for Ebola vaccines that addresses vaccine use in controlling the current West Africa outbreak or future outbreaks (ie, reactive use) and vaccine use prophylactically in non-outbreak settings to prevent endemic infections or future outbreaks. While TPPs traditionally have been used in industry or as part of the regulatory process, this section highlights concepts to help drive discussions about optimal and minimal vaccine characteristics and production capabilities, which ultimately can be used to generate products that will maximize EVD prevention and control. This document is intended to be dynamic and will be revised and refined as more information becomes available and additional input is sought and obtained.

*This assumes vaccine candidates already have met regulatory requirements for phase 1 clinical trials.

CRITERIA	PREVENTION OF EVD IN THE CURRENT OR FUTURE EPIDEMICS (REACTIVE USE)[a]		PROTECTION AGAINST ENDEMIC EVD (PROPHYLACTIC USE)	
	Optimal	*Minimal*	*Optimal*	*Minimal*
Criteria Applicable to Characteristics of Ebola Vaccines				
Indication for Use	▪ For active immunization of at-risk persons residing in the area of the current epidemic or in a future outbreak area; to be used in conjunction with other control measures to curtail or end an outbreak.	▪ For active immunization of at-risk persons residing in the area of the current epidemic or in a future outbreak area; to be used in conjunction with other control measures to curtail or end an outbreak.	▪ For active immunization of persons considered at high-risk of EVD based on specific risk factors (such as occupation) or based on residence in a geographic area at risk for EVD.	▪ For active immunization of persons considered at high-risk of EVD based on specific risk factors (such as occupation) or based on residence in a geographic area at risk for EVD.
Target population	▪ The vaccine can be administered to all age-groups and populations, including special populations (immunocompromised persons, pregnant women, persons with underlying chronic disease, and malnourished persons)[b,c]	▪ The vaccine can be administered to healthy older adolescents and non-pregnant adults[d]	▪ The vaccine can be administered to all age-groups and populations, including special populations (immunocompromised persons, pregnant women, persons with underlying chronic disease, and malnourished persons)[b,c]	▪ The vaccine can be administered to healthy older adolescents and non-pregnant adults[e]

CRITERIA	PREVENTION OF EVD IN THE CURRENT OR FUTURE EPIDEMICS (REACTIVE USE)[a]		PROTECTION AGAINST ENDEMIC EVD (PROPHYLACTIC USE)	
	Optimal	***Minimal***	***Optimal***	***Minimal***
Safety[f]	▪ A safety profile that is consistent with expectations for a licensed vaccine and, if the vaccine is efficacious, will provide a highly favorable risk-benefit ratio, ideally with only mild or transient side effects (ie, grade 1 AEs) and lacks evidence of serious AEs[g] ▪ If fever is an AE, it should be of short duration (preferably resolving within 24 hours)	▪ A safety profile that is consistent with expectations for a licensed vaccine and, if the vaccine is efficacious, will provide a favorable risk-benefit ratio (primarily grade 1 AEs, with grades 2-4 AEs occurring rarely)[g]	▪ Robust safety profile whereby vaccine benefit clearly outweighs any safety concerns ▪ Safety profile demonstrates only mild transient health effects (ie, grade 1 AEs) and lacks evidence of serious AEs[g c]	▪ Robust safety profile whereby vaccine benefit clearly outweighs any safety concerns ▪ Safety profile demonstrates primarily mild transient health effects (ie, grade 1 AEs) and serious AEs (grades 2-4) are rare[g]
Efficacy/ Effectiveness	▪ Interrupts disease transmission ▪ Greater than 90% efficacy in preventing disease in healthy children and adults[d] ▪ Rapid onset of immunity ▪ Evidence for post-exposure efficacy in primate challenge experiments	▪ Greater than 50% efficacy in preventing disease in healthy older adolescents and adults[d] ▪ Rapid onset of immunity	▪ Greater than 90% efficacy or effectiveness in preventing disease in healthy children and adults	▪ Greater than 50% efficacy or effectiveness in preventing disease in healthy older adolescents and adults[d]
Dose Regimen	▪ Single-dose regimen	▪ Prime-boost regimen with booster dose no more than 1 month following initial dose	▪ Single-dose regimen	▪ Single-dose regimen or prime-boost regimen with additional booster doses as needed ▪ Booster dose schedule is designed to achieve optimal long-term protection
Durability of Protection	▪ Confers at least 2 years of protection[h]	▪ Confers at least 3 to 6 months of protection[h]	▪ Confers long-lasting protection of 10 years or more (with booster doses as necessary to maintain durability over time)[h]	▪ Confers protection of at least 2 years of protection after completion of the vaccination regimen[h]
Criteria Applicable for Production and Distribution of Ebola Vaccines				
Route of Administration	▪ Injectable (IM, ID, or SQ) or other formulation, such as ingestible, nasal, or transdermal patch, if available	▪ Injectable (IM, ID, or SQ) or other formulation as available	▪ Injectable (IM, ID, or SQ) or other formulation, such as ingestible, nasal, or transdermal patch, if available	▪ Injectable (IM, ID, or SQ) or other formulation as available

CRITERIA	PREVENTION OF EVD IN THE CURRENT OR FUTURE EPIDEMICS (REACTIVE USE)[a]		PROTECTION AGAINST ENDEMIC EVD (PROPHYLACTIC USE)	
	Optimal	***Minimal***	***Optimal***	***Minimal***
Formulation	▪ Monovalent vaccine effective against Zaire Ebola virus[i] ▪ Does not require an adjuvant	▪ Monovalent vaccine effective against Zaire Ebola virus[i]	▪ Trivalent vaccine effective against Zaire Ebola virus, Sudan virus, and Marburg virus ▪ Does not require an adjuvant	▪ Monovalent vaccines effective against Zaire Ebola virus, Sudan virus, and Marburg virus
Product Stability and Storage	▪ Shelf life of at least 36 months ▪ Does not require storage at -80°C to prevent degradation ▪ The need for a preservative is determined and any issues are addressed ▪ Product is stable at refrigeration temperatures (2°- 8°C) ▪ Heat stability should be maximized to allow product to be used in a CTC (ie, with storage out of cold chain at room temperature for up to several days)	▪ Shelf life of at least 12 months ▪ The need for a preservative is determined and any issues are addressed ▪ Storage conditions comply with cold-chain capabilities; product may be stored at -80°C or at -20°C, if stable for some period of time (hours to a few days) at 2°- 8°C or at room temperature (to allow for shipment and storage in the field)	▪ Shelf life of at least 36 months ▪ Does not require storage at -80°C to prevent degradation ▪ The need for a preservative is determined and any issues are addressed ▪ Product is stable at refrigeration temperatures (2°- 8°C) ▪ Heat stability should be maximized to allow product to be used in a CTC (ie, with storage out of cold chain at room temperature for up to several days)	▪ Shelf life of at least 24 months ▪ The need for a preservative is determined and any issues are addressed ▪ Storage conditions comply with cold-chain capabilities; product may be stored at -80°C or at -20°C, if stable for some period of time (hours to a few days) at 2°- 8°C or at room temperature (to allow for shipment and storage in the field)
Coadministration with Other Vaccines	▪ The vaccine will be given as a stand-alone product not coadministered with other vaccines.	▪ The vaccine will be given as a stand-alone product not coadministered with other vaccines.	▪ The vaccine can be coadministered with other licensed vaccines without clinically significant impact on immunogenicity or safety.	▪ The vaccine will be given as a stand-alone product not coadministered with other vaccines.
Presentation	▪ In an outbreak setting, the simplest presentation is likely best (ie, a mono-dose, liquid product that does not require reconstitution); however, other options noted in the bullets below are acceptable. ▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with	▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent	▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent	▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent

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	Optimal	***Minimal***	***Optimal***	***Minimal***
	multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent			
Production	▪ Can be produced efficiently and as expeditiously as possible after an engendered and validated scale-up that allows for maximum production yields; the dose of antigen required for protection allows for high production yield (which will affect cost and availability) ▪ 5 million doses can be produced by the end of 2015 ▪ Ideally, production involves a single bulk-substance product (without requiring a separate booster product or diluent [needed for lyophilized vaccines]) ▪ If a booster with an alternative product is needed, that product also can be produced quickly and without significant manufacturing barriers or supply-chain issues ▪ If an adjuvant is needed, it can be formulated with the vaccine instead of combined at the time of use	▪ The dose of antigen required for protection allows for high production yield (which will affect cost and availability) ▪ 5 million doses can be produced during the first half of 2016 ▪ If a booster with an alternative product is needed, that product also can be produced quickly and without significant manufacturing barriers or supply-chain issues	▪ Can be produced efficiently and as expeditiously as possible; the dose of antigen required for protection allows for high production yield (which will affect cost and availability) ▪ Can be produced in quantities sufficient for prophylactic use in at-risk regions or populations ▪ If a booster with an alternative product is needed, that product also can be produced quickly and without significant manufacturing barriers or supply-chain issues ▪ If an adjuvant is needed, it can be formulated with the vaccine instead of combined at the time of use	▪ Can be produced in quantities sufficient for prophylactic use in at-risk regions or populations

CRITERIA	PREVENTION OF EVD IN THE CURRENT OR FUTURE EPIDEMICS (REACTIVE USE)[a]		PROTECTION AGAINST ENDEMIC EVD (PROPHYLACTIC USE)	
	Optimal	*Minimal*	*Optimal*	*Minimal*
Licensure	▪ Meets criteria for licensure or accelerated licensure pathway ▪ Recommendation for vaccine use by the WHO	▪ Meets criteria for accelerated licensure pathway or expanded access (such as EUA), with full licensure potentially to follow[l] ▪ Criteria for expanded access or EUA are acceptable to EMA, FDA, and the NRAs of countries affected by the epidemic[l] ▪ Conditional recommendation for vaccine use by the WHO	▪ Meets criteria for licensure ▪ Product is prequalified by the WHO	▪ Meets criteria for licensure

Abbreviations: AE, adverse event; CTC, controlled temperature chain; EMA, European Medicines Agency; EUA, Emergency Use Authorization (applicable to regulations in the US); EVD, Ebola virus disease; FDA, US Food and Drug Administration; ID, intradermal; IM, intramuscular; NRA, National Regulatory Authority; SQ, subcutaneously; WHO, World Health Organization.

[a]Optimal and minimal criteria for vaccines to be used in the current epidemic are similar to considerations for vaccines that may be used in future outbreaks or epidemics if a reactive vaccination strategy is employed. Vaccines developed and produced now or in the future may be stockpiled for reactive use in future situations.
[b]Optimally, a vaccine should be available for all age-groups; however, some vaccines may not be able to be given to the pediatric population because of general reactogenicity or interference with safety or efficacy of co-administered products.
[c]Ideally, a vaccine will be safe and effective in special populations, such as immunocompromised persons or pregnant women; however, obtaining efficacy and safety data for such populations will require special studies that take extensive time to design and conduct; therefore, this feature is not realistic for the current epidemic, but may be a consideration for a future time, if appropriate.
[d]Initial vaccination of older adolescents and adults is a potentially viable strategy because: (1) this will encompass most high-risk persons (eg, healthcare workers, Ebola community workers, funeral workers, and in-home care providers as well as many case contacts); (2) the epidemiology of EVD in West Africa indicates that the largest burden of disease occurs in this age-group, and (3) by targeting this population, enough herd immunity might be achieved to stop the outbreak when combined with other control measures.
[e]A tiered strategy targeted initially to healthcare workers, adults, and adolescents, then later to children and the elderly over time may be considered (depending on the vaccination strategy), with more than one vaccine product being appropriate for different populations and different usages.
[f]Safety profiles for vaccines used in an outbreak/epidemic setting may potentially be lower than the safety profiles for vaccines used on a prophylactic basis to prevent endemic disease or future outbreaks, since the risk/benefits in the two settings may be different.
[g]A system for grading adverse events is as follows. Grade 1 (mild): symptoms cause no or minimal interference with usual social and functional activities; grade 2 (moderate): symptoms cause greater than minimal interference with usual social and functional activities; grade 3 (severe): symptoms cause inability to perform usual social and functional activities; grade 4 (potentially life threatening): symptoms cause inability to perform basic self-care functions, or a medical or operative intervention is indicated to prevent permanent impairment, persistent disability, or death.
[h]Investigators will not be able to determine durability of protection in the current clinical trials; this will require additional observation and follow-up studies.
[i]A monovalent vaccine against Zaire Ebola virus is adequate to control the current West Africa epidemic; however, strategic use of a reactive vaccination strategy aimed at

controlling future filovirus disease outbreaks will likely also require development of monovalent vaccines against Sudan virus and Marburg virus (or a trivalent vaccine against all three pathogens).

[j]Liquid vaccines are easy to administer because they don't need reconstitution. Lyophilized vaccines may be more temperature stable, but require reconstitution with an appropriate diluent. These two different forms of vaccine each have advantages and disadvantages that will need to be weighed based on conditions in the field, including transport and disposal constraints.

[k]Single-dose vials potentially decrease safety risks. Single-dose or low multi-dose vials also decrease vaccine wastage, which is an important factor when considering cost of administration; however, they require increased storage space. The optimal number of doses per vial, therefore, will need to take into consideration field conditions and the vaccination strategy (eg, 50 or more doses per vial may be appropriate for a mass vaccination strategy).

[l]Issues around accelerated licensure and expanded access apply predominantly to this epidemic. Ideally, before any future outbreaks or epidemics occur, time will permit the full licensure process.

Appendix D: Public-Private Partnerships Involved in Vaccine Development for Low-Income Countries

For many reasons, the economic model that sustains for-profit multinational pharmaceutical firms does not lend itself to developing and distributing affordable vaccines for diseases with high morbidity and mortality affecting people in low-income countries (LICs) in Africa. Over the past few decades, public-private partnerships (PPPs)—formal collaborations between large pharmaceutical firms, government agencies, academic teams, and biotechnology companies— have emerged to expand LIC access to vaccines. PPPs have focused on accelerating pre-competitive discovery of vaccine candidates; stimulating cross-sector collaboration among academia, advocacy groups, funders, and pharmaceutical firms; and forging innovative ways to package, procure, and bring vaccines to LIC populations. The massive global collaboration to respond to the 2014 Ebola virus disease (EVD) epidemic in West Africa with suitable vaccines has brought to light the need to prioritize public health as the lead driver in developing and distributing vaccines for LICs.

As such, the Ebola Team B Funding Work Group requested that CIDRAP conduct an environmental scan for examples of PPPs involved in the development and delivery of vaccines for diseases affecting populations in LICs in Africa. Eight PPPs with operations in United States, Europe, and South Africa were identified for this analysis. The following three tables detail:

1. A list of PPPs, year they were founded, geographic region, and vaccine focus
2. A breakdown of the number of PPPs contributing to 10 stages of vaccine development and distribution
3. A matrix of PPPs with stages of vaccine development and distribution

The following tables are designed to identify areas of strength that provide opportunity and significant gaps that will require attention in any effort to create a public health–driven vaccine solution that will protect people of LICs in Africa against morbidity and mortality associated with dangerous emerging infectious diseases like EVD.

Note: Data for this analysis were compiled from publicly available Web sources and should be independently verified and updated. The names of PPPs in Table 2 are hyperlinked to relevant Web pages, which provide details about each organization.

Table 1. Public-Private Partnerships (PPPs) Included **in Analysis**

PPP*	Year	Locale	Area of Focus
PATH	1977	International	Meningitis, malaria, rotavirus
International AIDS Vaccine Initiative	1996	International	AIDS
GAVI Alliance	2000	Multilateral	Purchasing vaccines for children in low-income countries
Vaccine Research Center	2000	USA NIH	HIV, influenza, Ebola, Marburg, chikungunya, SARS, West Nile
AERAS	2003	International	Tuberculosis
NIH Public-Private Partnership	2005	USA NIH	Tuberculosis biomarkers; needle-free, single-dose, & refrigeration-free vaccines
TI Pharma	2005	Netherlands	Proofs of concept; malaria, chikungunya; needle-free vaccine delivery research
Innovative Medicines Initiative	2008	EU	Ebola, filoviral hemorrhagic fevers; vaccine safety & efficacy; risk/benefit; storage, transport

**PPP names are hyperlinked to Web sites that describe vaccine efforts.*

Table 2. **Number of** Public-Private Partnerships (PPPs) per Vaccine Development Stage

Vaccine Stage	Number of PPPs Involved
A. Pre-competition & discovery	8
B. R&D & clinical trials	6
C. Regulatory & licensing	4
D. Manufacturing (prototype)	2
E. Manufacturing to scale	1
F. Fill & finish	3
G. Ethics & community engagement	3
H. Financing technical assistance	3
I. Purchase	1
J. Storage, transport, & delivery	3
K. Post-licensure	0

Among PPPs, capacity appears strongest (based on numbers of PPPs) in the pre-competitive and discovery and research stages and in development and clinical trials stage. Significant gaps (shown in red) appear for manufacturing to scale, purchase, and post-marketing surveillance for adverse events.

Table 3. **Matrix**: PPPs and Vaccine Development and Distribution Stages

	GAVIALLIANCE	AERAS	PATH	INTERNATIONAL AIDS VACCINE INITIATIVE	VACCINE RESEARCH CENTER	INNOVATIVE MEDICINES INITIATIVE	TI PHARMA	NIH PUBLIC-PRIVATE PARTNERSHIP
Pre-competition & discovery		■	■	■	■	■	■	■
R&D & clinical trials		■	■	■	■	■	■	
Regulatory & licensing		■	■		■		■	
Prototype manufacture, fill & finish		■	■		■			
Manufacture to scale*			■					
Ethics & community engagement		■	■	■				
Financing technical assistance	■		■			■		
Purchase*	■							
Storage, transport, & delivery	■	■				■		
Post-licensure*								

** Stages with significant gaps.*