March 2016 *Ebola Vaccine Team B*

Plotting the Course of Ebola Vaccines

CHALLENGES AND UNANSWERED QUESTIONS

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CIDRAP
Center for Infectious Disease Research and Policy
University of Minnesota

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Foreword

Since the Ebola outbreak began in West Africa in 2014, the global community has made great strides in moving Ebola vaccine development forward. First, numerous clinical trials have been initiated or completed over the past 2 years, and a phase 3 trial has demonstrated clinical efficacy for one candidate Ebola vaccine, rVSV-ZEBOV. Second, Gavi, the Vaccine Alliance, has agreed to purchase 300,000 doses of pre-licensed rVSV-ZEBOV vaccine to be stockpiled for use during future Ebola outbreaks. Third, Merck, the manufacturer of rVSV-ZEBOV, has submitted an application to the World Health Organization for an Emergency Use Assessment and Listing (EUAL) for rVSV-ZEBOV and plans to move forward with an application for full licensure of the vaccine sometime during the next year. Finally, other vaccine manufactures, notably Johnson & Johnson and GlaxoSmithKline, have advanced their respective Ebola candidate vaccines well into the clinical trial process. These activities, among others, represent remarkable progress over a very short period, and we applaud these successes.

While many in the international public health community believe these efforts have solved "the problem of Ebola," the path forward is not quite so simple, and many unresolved challenges and questions remain. In this report, the Ebola Vaccine Team B identifies four key areas in which critical additional work and effort are needed to (1) enhance Ebola preparedness for future outbreaks (particularly in the megacities of equatorial Africa) and (2) address the ongoing concern that Ebola virus disease may become endemic in West Africa. These issues involve: (1) gaps in data on the safety and efficacy of Ebola vaccines, (2) regulatory pathways for Ebola vaccines, (3) direct input from African public health leaders to clarify how Ebola vaccines will be used or evaluated in respond to future Ebola outbreaks, and (4) the business case for ongoing Ebola vaccine development and deployment.

We urge members of the international community not to shift all of their attention to other pressing public health issues but instead strive to complete the work on Ebola vaccines that began so diligently in 2014 as a result of the West Africa Ebola outbreak. Our vision is that collaboratively we can address these issues and ensure that Africa never again is confronted with an Ebola outbreak as devastating as the one we witnessed during these past 2 years.

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(The Wellcome Trust–CIDRAP Ebola Vaccine Team B includes 25 international subject matter experts involved in one or more areas of vaccine work. The Ebola Vaccine Team was formed in fall 2014 to explore and address issues related to Ebola vaccine development and deployment.)

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Introduction

The dramatic rise of Ebola virus disease (EVD) in three West African countries, which began in 2014, galvanized the international community around the need to develop vaccines and treatments aimed at curtailing the epidemic. Collaborative efforts among government officials, scientists, philanthropic organizations, and pharmaceutical companies enabled the extraordinarily rapid initiation of clinical trials of candidate Ebola vaccines in 2015. During the 2014-15 epidemic, 13 Ebola vaccine candidates (which include different combinations of vaccines) were evaluated in phase 1 and/or phase 2 clinical trials, and three phase 3 efficacy trials were initiated in Africa—one each in Guinea, Liberia, and Sierra Leone.[1] The phase 3 trial in Guinea advanced far enough during the epidemic to demonstrate preliminary efficacy for the recombinant vesicular stomatitis virus-based vaccine (rVSV-ZEBOV). As the incidence of EVD declined throughout 2015, the efficacy components of the other phase 3 trials in Africa had to be suspended. Phase 2 components have continued to evaluate safety, immunogenicity, and duration of protection for the vaccines under study. Phase 1 and 2 trials of other vaccine candidates are ongoing.[1]

Based on the preliminary results of the completed phase 3 trial in Guinea, Gavi, the Vaccine Alliance, entered into an agreement in January 2016 with Merck to support rVSV-ZEBOV development through the regulatory review process and into the procurement phase. As part of this agreement, Gavi agreed to purchase 300,000 doses of the rVSV-ZEBOV vaccine as a stockpile for use during future Ebola outbreaks (in West Africa or in other at-risk countries). This remarkable progress over a short period represents the culmination of tremendous effort by diverse organizations on regional and global levels forming unprecedented alliances, as well as effective use of incentives to attract researchers and manufacturers.[2] To date, however, no vaccine has been submitted for regulatory review and many questions regarding Ebola vaccines remain unresolved. Furthermore, we have not yet reached a point of ensuring safe and effective Ebola vaccines for a range of populations and for use under the various circumstances that may be encountered during future Ebola outbreaks across Africa.

In late 2015 and early 2016, Ebola Vaccine Team B, convened by the Wellcome Trust and the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota, identified four areas in which additional work is needed on key issues: (1) gaps in data on the safety and efficacy of Ebola vaccines, (2) regulatory pathways for Ebola vaccines, (3) direct input from African public health leaders to clarify how Ebola vaccines will be used or evaluated in respond to future Ebola outbreaks, and (4) the business case for ongoing Ebola vaccine development and deployment.

This report, which is a follow-up to the initial Ebola Vaccine Team B report,[3] discusses key issues within these four areas and provides recommendations for addressing them.

Safety and Efficacy of Ebola Vaccines

Issues and Challenges

Safety Data for Ebola Vaccines

A number of clinical trials on the safety and immunogenicity of Ebola vaccines have been published in the past 2 years, and additional clinical trials are ongoing.[1] Four reports have assessed the rVSV-ZEBOV vaccine,[4–7] and four have assessed adenovirus-vectored vaccines, including the chimpanzee adenovirus type 3–vectored vaccine (cAd3-ZEBOV) and a recombinant adenovirus-type 5 vector-based vaccine.[8–11] Key overarching points from these studies include:

- In general, the rVSV-ZEBOV vaccine appears to have an acceptable safety profile, although a study from Switzerland found that 22% of 51 subjects developed reactive arthritis following vaccination.[4] Other reports have not confirmed this finding, but all studies have involved relatively small numbers of subjects.
- Studies involving adenovirus-vectored vaccines have not identified significant safety concerns, but, again, all studies have involved relatively few subjects.
- Studies to date have involved healthy adults; information on vaccine safety is not yet available for children or special populations, including pregnant women or immunosuppressed persons.

In addition to published studies, preliminary unpublished results from a randomized phase 2 clinical trial in Liberia (PREVAIL) involving the rVSV-ZEBOV and cAd3-ZEBOV vaccines demonstrated acceptable safety profiles for both during a 1-month follow-up period. In addition, more than 85% of participants in each vaccine arm had an antibody response to the vaccine 1 month after vaccination.[12]

On the basis of data from published studies, the World Health Organization's (WHO's) Strategic Advisory Group of Experts on Immunizations (SAGE) concluded in October 2015 that "available safety data for both cAd3-ZEBOV and rVSV-ZEBOV vaccines indicate an acceptable safety profile in healthy adults. Data on safety in children, pregnant women, and those with underlying medical conditions are insufficient to draw conclusions."[13]

Efficacy Data for rVSV-ZEBOV Vaccine

Only one study demonstrating clinical efficacy of an Ebola vaccine has been published.[5] Preliminary results from that trial, which used a ring-vaccination approach, reported a vaccine efficacy of 100% (95% confidence interval [CI], 74.7% to 100.0%; $P = 0.0036$), based on evaluation of 90 case clusters. At the cluster level, with the inclusion of all eligible subjects, the authors estimated the vaccine effectiveness as 75.1% (95% CI, –7.1% to 94.2%; $P = 0.1791$). This lower value can be attributed to the fact that six cases of EVD occurred in subjects who were randomized to the immediate vaccination group but did not

receive vaccine (because consent was not obtained or they were not home at the time vaccination was offered). A final report from this trial is expected to be published in 2016.[14]

Considerations for Other Ebola Vaccines

Even though one trial has shown efficacy of the rVSV-ZEBOV vaccine, this vaccine candidate may not meet all of the requirements to ensure protection against EVD for all at-risk populations. Ideal vaccine attributes include rapid and long-lasting induction of immunity and protection against multiple strains of Ebola virus. A vaccine that provides rapid development of immunity following a single administration but has limited duration of protection could be useful for controlling an outbreak, whereas a vaccine that requires more than one dose (eg, a prime-boost strategy) over several months before protective immunity is achieved, but potentially has a longer duration of protection, may be most useful in protecting healthcare workers and community response members in advance of future outbreaks.[15] Multivalent vaccines (or multiple monovalent vaccines) may ultimately be needed to confer protection to other filoviruses (eg, Marburg virus and Sudan ebolavirus). Because these attributes have not been elucidated for the rVSV-ZEBOV vaccine, it would be advisable to continue efforts to study other Ebola candidate vaccines.

A phase 2/3 trial intending to examine safety and efficacy of rVSV-ZEBOV and cAd3-ZEBOV was initiated in early 2015 in Liberia; however, the phase 3 portion of the trial was suspended in April 2015 owing to a low incidence of EVD. No clinical data are available to show efficacy of the cAd3-EBOV vaccine, but investigators recently demonstrated an acceptable safety profile and showed that a single dose was immunogenic in almost all vaccine recipients, with antibody response still present at 6 months post-vaccination.[8,16] The cAd3-ZEBOV vaccine may also be used in a heterologous prime-boost strategy with a recombinant modified vaccinia Ankara (MVA) booster vaccine manufactured by Bavarian Nordic (MVA-BN-Filo). Vaccines that use a prime-boost strategy theoretically could confer longer lasting immunity than the current rVSV-ZEBOV vaccine. Investigators still need to determine, however, whether a prime-boost regimen induces stronger and more durable immune responses than a single dose of vaccine,[17] and additional work is needed to demonstrate clinical efficacy of such vaccines.

On the basis of results from the Guinea clinical trial results and of promising data from clinical trials involving other vaccines, the WHO SAGE concluded in October 2015 that "vaccination during [Ebola] outbreaks should be part of an integrated strategy and complement other public health measures to interrupt transmission."[13]

Correlates of Protection

In general, vaccine correlate-of-protection studies aim to: (1) characterize immune markers that develop in response to exposure to an antigen, such as glycoprotein (GP), introduced by the vaccine, and (2) assess the degree to which such markers are predictive of protection against occurrence of disease among an exposed population (vaccinated and unvaccinated). To date, one or more validated correlates of protection have not been fully elucidated for

the rVSV-ZEBOV vaccine or other Ebola candidate vaccines, which creates challenges for ongoing clinical and animal studies to assess potential Ebola vaccine efficacy in the absence of EVD outbreaks. Existing data from EVD patients and from animal studies suggest that the following immune markers are important for protection against EVD:[17–20]

- GP binding IgG antibodies. Based on experimental studies with nonhuman primates, immunoglobulin G (IgG) antibody production appears to be an important marker associated with protection against Ebola infection and disease across vaccine platforms that deliver Ebola GP as a structural protein antigen. The magnitude of the IgG antibody response in humans for each applicable vaccine platform may be a clinically significant marker of vaccine efficacy.
- Cell-mediated immunity (CMI) may play an important role in protection against Ebola infection and disease in some vaccine platforms. Measurement of CD8+ T-cell responses may be an important element of Ebola vaccine efficacy determination for vaccines in which CMI appears to play a significant role.

The phase 3 ring vaccination study conducted in Guinea did not include blood sampling, which would have allowed analysis of immune responses after vaccination. Even if blood samples had been obtained, no vaccine "failures" occurred (ie, individuals who developed EVD after vaccination) to compare their immune responses with the immune responses of vaccinated individuals who did not develop disease. In other phase 2/3 clinical trials of Ebola vaccines, investigators have obtained blood samples following vaccination from participating subjects. One project—the VSV-EBOVAC project on "vaccine safety and immunogenicity signatures of human responses to rVSV-ZEBOV"—aims to: (1) use available clinical samples to characterize the innate and adaptive immune responses induced by the vaccine very soon after vaccination and (2) bridge this information with parallel data to be generated from nonhuman primates after rVSV-ZEBOV vaccination and subsequent challenge with Zaire ebolavirus.[21] This ongoing work may provide useful data on correlates of protection, which could provide important information on vaccines that are likely to have clinical benefit.

Ongoing follow-up of clinical trial participants over time may clarify the duration over which potential protective immunologic markers are present, which can help inform the durability of immunity for the vaccines under study. Various study designs can be devised to address this issue. For example, investigators could obtain sera a year (or more) after vaccination from persons who participated in phase 2 trials and passively transfer that to experimental animals to determine if they can be protected against challenge with Ebola virus.

Vaccination Strategies

According to the WHO SAGE, "The vaccination delivery strategy for the next outbreak will depend on the extent of the spread of disease, disease incidence at the time when vaccination is initiated, status of implementation of other control measures, effectiveness of contact tracing, and available supply of vaccine….Potential strategies include ring

vaccination [targeting those at higher risk of exposure, eg, based on social contacts with infected individuals], geographic targeting of an area (mass vaccination), and vaccination of front-line workers. When more data are available, more precise recommendations on the choice of vaccination strategy will be considered."[13]

Key Unresolved Issues

Information Gaps Regarding rVSV-ZEBOV

Although one phase 3 clinical trial supports efficacy of the rVSV-ZEBOV vaccine and several phase 1/2 studies addressing other issues with the vaccine currently are in progress, a number of important questions remain. These include the following:

- Will the vaccine be effective if used other than for ring vaccination in an outbreak setting?
- Could post-exposure protection have been a contributing factor to the high efficacy demonstrated in the Guinea ring vaccination trial (by decreasing infectiousness and clinical illness in exposed persons who already had acquired infection)?
- Do existing safety data accurately portray the risk of adverse reactions associated with vaccination, or will adverse events be a bigger consideration if the vaccine is used more widely?
- Is the vaccine safe and effective for a wide range of ages and special populations (including children, pregnant and lactating women, and immunocompromised persons)?
- Does viral shedding of the replication-competent rVSV-ZEBOV occur?
- Are there any interactions or interferences between rVSV-ZEBOV and potential antiviral medications for Ebola (such as favipiravir and ZMapp) or between rVSV-ZEBOV and medications for other conditions, such as for malaria or HIV infection?
- Is there a role for rVSV-ZEBOV in post-exposure prophylaxis, and, if so, what are the indications for its use compared with antiviral treatment?
- What are the guidelines for monitoring for and management of adverse events following immunization with rVSV-ZEBOV?
- What is the overall risk-benefit profile for the rVSV-ZEBOV vaccine?
- What is the duration of immunity for the vaccine?
- Will the vaccine be effective against other strains of Ebola virus, or will multivalent vaccines be needed?
- Can the rVSV-ZEBOV vaccine be formulated to be stable for long-term storage at 2° to 8°C or at least at -20°C?
- What are the appropriate vaccination strategies for using the rVSV-ZEBOV vaccine in at-risk countries (in epidemic or inter-epidemic periods)?

Information Gaps Regarding Ebola Vaccines in General

Similar issues to those noted above also are applicable to other Ebola vaccines, in addition to the need to demonstrate clinical efficacy. Other questions include the following:

- Is there a consensus that future phase 3 trials involving other vaccines will use rVSV-ZEBOV, rather than a placebo, as a comparator?
- Will it be logistically and economically possible to conduct phase 3 trials using other vaccines during future Ebola outbreaks, given that available data suggest the rVSV-ZEBOV vaccine is efficacious?
- What steps can be taken to identify definitive correlates of protection for Ebola vaccines, particularly in the absence of ongoing disease incidence? For example, can data from the phase 3 clinical trial in Guinea shed any light on this issue?

Regulatory Pathways for Ebola Vaccines

Current Status

National Regulatory Authority (NRA) officials in any country affected by Ebola are ultimately responsible for determining whether an Ebola vaccine is approved for use within that nation's borders. Approval from a stringent regulatory authority such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or Health Canada, however, can expedite another country's NRA review, given that such approval signifies to international medical and regulatory communities that the data have been thoroughly examined and the vaccine meets performance and manufacturing standards.[22,23] Noting its commitment to a flexible and rapid regulatory response to the global public health need to develop safe and effective Ebola vaccines, the FDA has actively sought to coordinate and facilitate the research and development (R&D) process for regulatory approval.[18,24,25] Furthermore, the FDA will likely play a major role in reviewing at least one of the current Ebola vaccine candidates.[26]

The FDA's regulatory approval options for a vaccine to protect against an infectious disease that is not endemic in the United States are the same as the options for a vaccine to protect against a disease that exists in the US population.[22] The FDA's **traditional regulatory approval** for vaccines relies on the demonstration of vaccine efficacy based on clinical disease end point studies. Accordingly, efficacy data needed to approve Ebola vaccines via the FDA's traditional approval pathway can be obtained only in situations in which ongoing active disease transmission is occurring. As noted, the phase 3 trial in Guinea produced preliminary efficacy data on rVSV-ZEBOV, but it is not yet clear if the data will be sufficient for licensure or whether additional data and approval options will also be needed.

When direct efficacy studies are not feasible, pathways other than traditional approval may be applicable to Ebola vaccine licensure, not only for those vaccines currently in development but also for next-generation Ebola vaccines.[26,27] For example, the EMA's accelerated approval pathways include "conditional marketing authorization" and "marketing authorization under exceptional circumstances."[23] The FDA offers two nontraditional approval options:

1. **Accelerated approval**, which relies on the demonstration that a vaccine induces an immune response "reasonably likely" to predict clinical benefit, using a surrogate end point (eg, an immune marker or correlate of protection) or a clinical end point other than survival or irreversible morbidity.

2. **Approval via the Animal Rule**, which allows adequate and well-controlled studies in relevant animal models to provide evidence of effectiveness of the vaccine in humans, if specific criteria are met, including evidence of a clear relationship between the animal study end point and the desired end point in humans (ie, prevention of EVD or enhanced survival with EVD).[28,29]

All of the FDA's licensing options involve the same standards for determination of *safety* in humans, but they differ in standards for *efficacy* determination.[18,25,27] In addition, post-marketing (phase 4) studies are required to verify the clinical benefit of a vaccine if either the accelerated pathway or the animal rule is used. Post-marketing studies would likely focus on evaluation of vaccinated at-risk individuals, such as healthcare workers and residents of endemic areas, after an outbreak begins. These efforts also should address special populations (eg, pregnant women, children, and the elderly), long-term vaccine safety, and the possibility of randomizing individuals to receive different vaccines if more than one is licensed.[24]

Although no single, definitive correlate of protection applicable to all Ebola vaccines has been identified, a correlate that appears to be predictive of protection may be adequate for regulatory approval of Ebola vaccines under the FDA's **accelerated approval** pathway. At a meeting in May 2015, the FDA's Vaccines and Related Biological Products Advisory Committee endorsed the concept of using immune markers as a potential tool to predict clinical benefit from Ebola vaccines but recognized that the data on those markers were not sufficiently clear at that time to move forward with an accelerated pathway to Ebola vaccine licensure.[30] Each vaccine construct may involve a different correlate of protection or a different magnitude of response of a common correlate.

For the FDA to apply the **Animal Rule** for Ebola vaccine approval, the agency first has to determine that approval is *not possible* through traditional or accelerated approval. The FDA would have to conclude that an immune marker that is reasonably likely to predict clinical benefit *cannot be identified*—a determination that may be difficult or unlikely, given that the FDA's definition of an "immune marker reasonably likely to predict clinical benefit" is flexible and can focus on various end points. Nevertheless, the FDA can consider opting for the Animal Rule pathway on a product-by-product basis, depending on the time it would take to obtain more definitive data on immune markers and the urgency of the public health need.[30] In a recent development that could help clarify use of the Animal Rule for Ebola vaccine licensure, the FDA approved the BioThrax vaccine for post-exposure prophylaxis against anthrax[31] based on the Animal Rule pathway, which represents the first successful application of the FDA's Animal Rule to license a vaccine.

The FDA's Emergency Use Authorization (EUA) allows for the use of unlicensed Ebola vaccines in limited circumstances outside of clinical trials. In 2014 and 2015, the FDA issued 10 Ebola-related EUAs, all of them for diagnostic testing, in support of the global Ebola response.[32] In July 2015, the WHO announced the availability of a similar interim measure, the Emergency Use Assessment and Listing (EUAL) procedure, a special, time-

limited recommendation intended to respond to severe public health emergencies while further safety and efficacy data are being gathered for formal regulatory review, subject to final approval by in-country regulatory authorities.[33] It is not yet clear if EUAL use will be limited to WHO-designated public health emergencies of international concern or if it will also include response to other severe but more localized epidemics. EUAL-accepted vaccines can be purchased for emergency use by United Nations' procurement agencies and WHO member states. The EUAL approval process includes a risk-benefit analysis of the vaccine in emergency situations and evaluation of available data on the product's safety, immunogenicity, efficacy/effectiveness, and manufacturing quality. Vaccine manufacturers applying for EUAL approval are expected to continue efforts toward licensure and WHO prequalification.[33,34] The WHO is currently assessing Merck's dossier on the rVSV-ZEBOV vaccine under its EUAL procedure.[14]

With the apparent end of the Ebola epidemic in West Africa, public- and private-sector attention is quickly turning to the next public health crisis, leaving Ebola vaccines at the stage of investigational products in clinical trials, which may be inadequate for rapid deployment when the next Ebola outbreak occurs. Based on an advance purchase commitment from Gavi that supports the continued development of Merck's investigational rVSV-ZEBOV vaccine, Merck is aiming to submit a licensing application to a regulatory agency by the end of 2017 and to WHO for prequalification.[35] Until the vaccine is licensed, a stockpile of 300,000 doses of rVSV-ZEBOV will be available starting in May 2016 for investigational use in clinical trials at any time or for emergency use once the vaccine is EUAL-approved.[35] Gavi's prepayment agreement covers three important conditions: (1) ensuring a sufficient supply of investigational vaccine in the short term, (2) continuing to pursue full licensure of the rVSV-ZEBOV vaccine, and (3) stockpiling future licensed and WHO-recommended rVSV-ZEBOV vaccine.[36] It is unclear whether the agreement covers replacement of doses in the stockpile and maintenance of warm-base manufacturing capability over time. The agreement does not prevent Gavi or another funder from purchasing other Ebola vaccines that may be approved for licensure in the future.

Key Unresolved Issues

With critical support from the 2016 advance purchase agreement, Merck will likely achieve regulatory review of rVSV-ZEBOV. If the efficacy data obtained in the Guinea ring vaccination trial are determined to be sufficient for regulatory approval, rVSV-ZEBOV could become the first licensed Ebola vaccine, although the specific process and outcome may not be known for 2 years or more. In the meantime, Ebola vaccines with better attributes, including those in development and next-generation vaccines, may be needed. The pathway to licensure for those vaccines is even less clear, given the absence of phase 3 clinical efficacy data, and also more tenuous, given the real possibility of rVSV-ZEBOV licensure.[37] Key unresolved issues include the following:

- *Is there a need for more than one licensed Ebola vaccine?* Additional funding or other incentives, such as priority review vouchers to compensate larger companies, may be needed to complete the dossiers on other vaccine candidates. It is unclear whether the end of the epidemic in West Africa or cessation of external funding will change sponsors' commitments to complete the clinical trials and pursue regulatory review.
- *What is the regulatory strategy for licensing Ebola vaccines without clinical efficacy data?* With rVSV-ZEBOV efficacy data as a reference point, it is unclear how other vaccines would be evaluated on the basis of immunologic or preclinical data. The status of research on correlates of protection for Ebola vaccines is uncertain and has not been publicly reviewed since a December 2014 workshop sponsored by the FDA and the US National Institutes of Health (NIH)[24] and a May 2015 FDA meeting.[18] The clinical end points that regulators would use to evaluate efficacy of these vaccines as a basis for licensure have not been identified.
- *How can future collaborative data-sharing be enhanced among vaccine developers and NRAs?* The WHO played a unique role in coordinating information exchange regarding Ebola vaccine development in 2014 and 2015. Potential discontinuation of this central role in 2016 with the end of the West African epidemic could slow the progress toward further vaccine development.
- *If vaccines other than rVSV-ZEBOV are determined to be necessary for effective control and prevention of EVD, should investigational vaccines be manufactured and stockpiled so that phase 3 efficacy studies can begin as soon as the next outbreak occurs?* Heymann[38] noted that if phase 3 trials could not be completed before the incidence of EVD associated with the West Africa epidemic waned, efficacy trials would need to be set to resume as soon as the next Ebola outbreak occurs, requiring prepositioning of several key elements: (1) storing, optimizing, and maintaining sufficient quantities of vaccines to be evaluated; (2) maintaining funding to initiate clinical trial operations when needed; (3) maintaining ethical, regulatory, and other clearances in the inter-epidemic period; and (4) keeping clinical trial protocols available and ready to implement when needed.

Engagement of African Leaders in the Development of Ebola Vaccines

Current Status

In looking at upcoming decisions regarding production, stockpiling, and potential deployment of emergency-authorized and/or licensed Ebola vaccines, African stakeholder engagement at all levels is critical for clarifying optimal characteristics and demand for the vaccine as well as how the vaccine will be deployed in response to the next Ebola outbreak. During the research phase of Ebola vaccine R&D, three factors appear to have hampered optimal engagement with leadership in the affected West African countries. First, the infrastructure for medical research and clinical practice was fragile in Guinea, Liberia, and Sierra Leone from years of civil war and lagging financial investments. As a result, their healthcare systems were quickly overwhelmed.[39] Second, as the epidemic progressed, widespread death and illness further reduced both the availability and number of health experts in these countries. A third, less-well documented, factor was the urgency to conduct clinical trials of vaccines and therapeutic agents before the epidemic waned, which may have limited the potential to optimally engage governments, researchers, and communities in affected areas because of intense time constraints.[40]

On the international level, during the epidemic the WHO involved West African scientists at high-level consultations, meetings, and media briefings regarding Ebola vaccine efforts. These were held via teleconference or in person in Europe and the United States. Generally, however, peers from other countries and continents far outnumbered West African participants at these high-level WHO meetings, during which strategic steps and decisions regarding vaccine issues were discussed. To date, few international meetings on Ebola vaccines have been convened in Africa.

In September 2014, for example, the WHO convened 145 international scientists, public health officials, pharmaceutical executives, and philanthropists to review potential Ebola therapies and vaccines. Of the participants, only 9 represented the most-affected West African countries: 6 from Guinea, 2 from Sierra Leone, and 1 from Liberia.[41] The WHO's summary report from the meeting acknowledged the contributions of West African scientists, noting: "The presence of West African researchers, scientists, clinicians, and health officials vastly enriched the discussions, especially concerning the practical dimensions of trial design."[41] African panelists on the Wellcome Trust–CIDRAP Team B, however, have noted that West African scientists have expressed concern that input from their African colleagues had not been sufficiently considered.[3] In May 2015, the WHO convened in Geneva an international group of public health experts, researchers, philanthropists, and pharmaceutical industry representatives to discuss future R&D for

infectious diseases, including Ebola vaccine development.[42] Of the 132 participants, 11 were health ministry officials and researchers from Guinea, Liberia, and Sierra Leone, 6 of whom were invited to make brief presentations and join panel discussions during the 2-day event.

The degree to which West African scientists and local communities were actively involved in the planning and conduct of Ebola vaccine clinical trials has varied, depending on the countries involved, the incidence of disease in respective regions, and the strength of the existing research infrastructure. Examples of successful involvement of West African officials in protocol development, implementation of clinical trials, and vaccine deployment in West Africa include the following.

- *Protocol review in Guinea.* Political support for Ebola research and clinical trials was strong in Guinea, and Guinean authorities conducted scientific and ethics review of protocols for vaccines and other therapies simultaneously to help fast-track research efforts. The Ebola Research Commission, composed of 15 Guinean experts from academic and research institutions, met weekly to discuss protocols. The Guinean National Ethics Committee for Health Research had recently received capacity-building funding from the European and Developing Countries Trials Partnership and was functional and able to work in tandem with international researchers.[43]
- *Protocol review and implementation in Liberia.* Under the Partnership for Research on Ebola Virus (PREVAIL), formed late in 2014, US and Liberian agencies each conducted regulatory and ethical reviews. Ethical approvals for PREVAIL were obtained from the National Research Ethics Board in Liberia and the National Cancer Institute in the United States. In addition, protocol approvals came from the Liberia Medicines and Health Products Regulatory Authority in Liberia and the FDA. The PREVAIL partnership paired Liberian and US expertise for key positions to facilitate the vaccine trial. US partners drew from previous trial experiences to share perspectives about implementation feasibility. Liberians worked with US counterparts to build their cultural competence regarding how to communicate with participants. According to Stephen Kennedy, Liberia's coordinator for Ebola research in Liberia, "This buddy system was effective in marshalling the different backgrounds and experiences to address the intricacies of a study that many thought could never happen in resource-limited settings during outbreaks of emerging and re-emerging infectious diseases. Each partner contributed invaluable experiences which led to the successful implementation of the ongoing vaccine clinical trial."[44] During the trials, trained Liberian pharmacists were responsible for preparing the vaccine vials with bar codes for randomized administration.
- *Vaccine deployment in Guinea.* One example of early efforts to inform potential vaccination strategies occurred in Guinea in November 2015. The government of Guinea organized a 3-day workshop in Conakry in collaboration with the WHO

and UNICEF to discuss access to affordable vaccines as a way to prevent emerging diseases with epidemic potential. In its December 2015 situation report, the Interagency Collaboration on Ebola noted, "The workshop brought together scientists, public health experts, biomedical research institutions, pharmaceutical companies, and representatives of international organizations, including WHO. The discussions provided an opportunity to assess current research efforts, constraints in the production and marketing of vaccines, and approval and certification procedures of medicines or vaccines in case of an epidemiological emergency."[45]

- *AVAREF involvement.* Formed in 2006 through the WHO, the African Vaccine Regulatory Forum (AVAREF) is designed to provide expertise and opportunities for capacity building, such as joint regulatory review. The organization remains connected to the WHO and is not yet operating independently. The WHO reported that using expertise from a WHO technical advisory committee, AVAREF conducted reviews of three Ebola vaccines within 60 days.[42]

Key Unresolved Issues

Articulating clear priorities regarding public health within the at-risk countries is central to successful development and deployment of vaccines.[46] Failure to incorporate the African leadership's perspectives could jeopardize any of the critical components of the process, such as obtaining commitments from industry to manufacture the vaccines and identifying appropriate vaccination strategies. While a certain degree of engagement has brought African officials and scientists into the process of Ebola vaccine development and deployment, recent experience also highlights a number of important issues that should be addressed to improve preparedness and ensure an effective response to future Ebola outbreaks.

- *Enhancing engagement of African scientists and public health leadership.* With the West African Ebola epidemic essentially over, a clear path forward has not been defined for ongoing engagement of African scientists and public health officials in furthering future preparedness against Ebola in all at-risk areas of Africa.
    - Is the WHO actively engaging African public health leaders, including ministries of health, in ongoing collaborative efforts? What is the role of the WHO (particularly the Regional Office for Africa [AFRO]) in promoting ongoing engagement of African health officials? What can AFRO do to promote concrete actions by African ministries of health to enhance preparedness for the next Ebola outbreak?
    - Are African public health leaders substantively involved in collaborations with Ebola vaccine manufacturers? If not, are there ways to promote this engagement?

- *Vaccine deployment and vaccination strategies.* At this time, African health officials across Africa have not articulated how Ebola vaccines should be employed in their communities when the next Ebola outbreak occurs, particularly with regard to using rVSV-ZEBOV, since that vaccine will likely be the first to receive regulatory approval or authorization for emergency use from the WHO. While vaccine use will depend to a large degree on the epidemiologic features of the next outbreak, additional work is needed to address the following:
    - What Ebola vaccine attributes are most critical from the perspective of African public health officials, and does rVSV-ZEBOV possess those attributes?
    - Do African public health officials believe that rVSV-ZEBOV is adequate to protect their populations, or do they want to promote continued evaluation of other Ebola vaccines?
    - What steps are necessary to harmonize regulatory approval across Africa for Ebola vaccines, particularly rVSV-ZEBOV?
    - What steps are necessary in at-risk countries to create successful Ebola vaccination campaigns when the need arises?
    - What are the financial and human resources needed to support vaccination campaigns in at-risk countries?

- *Vaccine stockpiling.* Gavi is planning to stockpile 300,000 doses of the rVSV-ZEBOV vaccine, once it is approved, for use during future Ebola outbreaks. African health officials' perspectives will be needed to address key issues regarding vaccine stockpiling, including transparency of decisions, multilateral decision-making, and whether there is support for stockpiling of other candidate vaccines to allow such vaccines to undergo further evaluation in future outbreaks.
- *Coordination of future research efforts.* One of the important lessons learned from research conducted during the West Africa Ebola epidemic is the need for improved coordination between all of the various stakeholders, including African government officials, international government officials, NRAs, pharmaceutical representatives, and academicians.[43,47] The variety of novel government-private-academic-nongovernmental consortia and varying protocols (for vaccines and other therapies) compounded the difficulties faced by decision-makers on local levels.[42] During the next Ebola outbreak, additional research studies will need to be conducted to continue to assess the safety and efficacy of rVSV-ZEBOV and to potentially assess additional Ebola vaccines. An overarching framework or structure—for example, as provided by the WHO—would aid the coordination of research activities during future Ebola outbreaks. Additional efforts may be needed to enhance regional coordination for research during future outbreaks, potentially through AFRO, and to provide technical assistance to national regulatory agencies and coordinate joint regulatory review through AVAREF.

- *Enhancing public health capacity overall in Africa.* As noted in all of the recent assessments of the global public health response to the Ebola epidemic, weaknesses in the West African public health infrastructure, including in research capacity and healthcare workforce training, were clearly important impediments to controlling the epidemic. These also are important issues in other at-risk African countries.
- *Public engagement.* During the epidemic, the interest in being vaccinated, notably among frontline workers, was less than anticipated. Public health officials, in conjunction with African social scientists and health communication experts, should evaluate public perception of Ebola vaccines and develop appropriate communication strategies devised for future vaccine deployment.

Development of a Business Model for Ebola Vaccines

Current Status

Gavi's $5 million advance purchase agreement represents an important step toward ensuring the availability of Merck's rVSV-ZEBOV vaccine at the start of the next Ebola outbreak. The new agreement is part of a series of public and private funding efforts aimed at facilitating the development of Ebola vaccines on an accelerated timeline in response to the epidemic in West Africa.[48] Major financial contributions for Ebola vaccine research were made over the past 2 years by government agencies (particularly Canadian, US, and European), philanthropies, nongovernmental organizations, and the pharmaceutical companies themselves, who redirected considerable internal resources, manufacturing capacity, and expertise to the effort.[1,49–55]

According to the most recent data provided by the independent not-for-profit organization Policy Cures, $69 million was spent globally on Ebola vaccine R&D in 2014, of which approximately $33 million came from the public sector (74% from the US government and the rest from the European Commission and the governments of the United Kingdom, Norway, Canada, and France); $2 million from philanthropies; and $34 million from the private sector.[56] In 2015, funding for Ebola vaccine development was one item among many in the $6.18 billion in emergency funding requested by President Obama on Nov 5, 2014.[57] This one-time appropriation included $238 million to the NIH's National Institute of Allergy and Infectious Diseases (NIAID) for clinical trials for Ebola vaccines and treatments; $25 million to the FDA for development, review, and regulation of Ebola vaccines and treatments; and $157 million to the Biomedical Advanced Research and Development Authority (BARDA) to bring Ebola vaccines and treatments developed under NIH and Department of Defense contracts to advanced development and manufacture for clinical trials.[58] The amount of funding specifically for vaccine development within the emergency appropriation has not been identified. Likewise, aggregate funding data from non–US government or industry sources for Ebola vaccine development in 2015 have not yet been reported.

Initial decisions by pharmaceutical companies to invest in Ebola vaccine development during the early phases of the epidemic were driven by recognition of the global public health urgency of the situation as well as expectation of external support for cost-sharing, such as stated commitments to procure and deliver vaccines that were shown to be safe and effective.[49,59] Now that the West Africa epidemic is essentially over and further financial support for Ebola vaccine R&D may not be readily available, industry participation becomes increasingly tenuous because of commercial realities. Key issues include uncertain

demand for the vaccine in the short term, unclear pathways to licensure in the absence of clinical efficacy data, absence of a sustainable vaccine market over the longer term, potential need for technical refinement of vaccine constructs, opportunity costs of investing in Ebola vaccines instead of more marketable products, potential loss of intellectual property rights, cumbersome contracting issues, and remaining (potentially unreimbursed) costs of current or next-generation vaccines through clinical trials and regulatory review.[60]

Key Unresolved Issues

A clear commitment for continued support for Ebola vaccine R&D is essential, given that a successful outcome of the 2-year effort has not yet been achieved and resources will likely shift to the next emerging infectious disease crisis. While several companies are still actively engaged in Ebola vaccine development, it is important to identify and establish realistic options for maintaining those efforts through to completion of one or more final vaccine products, as needed. The stakes are high: Success or failure of this effort affects not only future Ebola response capabilities but also the willingness of critical partners in vaccine manufacturing to participate in other urgent but financially risky initiatives.

Recent comprehensive assessments of the global public health response to the West Africa Ebola epidemic have highlighted the need for an international cooperative mechanism to prioritize, accelerate, and finance development of vaccines and other countermeasures with low market potential and high public-health consequences.[48,61–63] These issues are not unique to Ebola vaccines. Plotkin et al proposed the establishment of a $2 billion strategic fund, supplied by donor governments, multilateral banks, pharmaceutical companies, philanthropies, and nontraditional sources, to facilitate the development of new and improved vaccines to address emerging infectious diseases that disproportionately affect developing nations.[64] The goal of the proposed fund is to remove barriers to the development of vaccines with low market potential and complement existing support for basic research and early R&D (eg, NIH and BARDA) and procurement and delivery of childhood vaccines in impoverished countries (eg, Gavi and UNICEF).[65]

At the heart of this issue is the importance of managing financial risks and technical uncertainties of Ebola vaccine development, so that no single company or organization bears a prohibitive share. An upfront commitment is needed to knit together the resources and bridge the liabilities to make it feasible for companies to complete the development of rVSV-ZEBOV and continue to develop other Ebola vaccines if they offer advantages. The Gavi-Merck agreement is an important step in this direction but may not be sufficient, even for the Merck vaccine. One or more of the other current vaccine candidates may also have a valid and necessary role to play in future Ebola prevention and control efforts.

Unacceptable risks can be defined as any factor a vaccine manufacturer has not anticipated and/or cannot control or influence that (1) is likely to introduce unbudgeted expenses,

including delays; (2) could lower budgeted return on investment; (3) may cause unmanageable reputational harm; (4) could impede needed growth; (5) is likely to unduly complicate or undermine proven and efficient business systems or processes; or (6) cannot be justified to shareholders. At some point, persistent uncertainties become unacceptable risks.

Direct input from vaccine manufacturers also is needed to clarify the industry's current perspectives on managing the financial and technical risks in Ebola vaccine development and its commitment for continuing to develop the Ebola vaccines currently in preclinical or clinical trials. Based on this approach, an effective business model for Ebola vaccines will address several interrelated issues, including the following:

- Explicitly prioritizing public health over customary profitability as the driver for Ebola vaccine development.
- Recognizing the importance of pharmaceutical companies as essential partners with essential resources and practical financial constraints.
- Recognizing the importance of managing risk in engaging and sustaining pharmaceutical companies in Ebola vaccine R&D, for example, sharing any financial risks for development costs of vaccines that may not end up being used.
- Creating a clear line-of-sight for financial support and minimizing gaps and uncertainties from early vaccine development through the critical "valley of death" to vaccine procurement (ie, the gulf between finding a promising new agent and demonstrating its safety and efficacy in humans).[66]

Recommendations

One of the goals of the WHO's R&D Blueprint[67] is to ensure that vaccines will be available in a timely manner for the next infectious disease threat and that the global health research infrastructure is primed for immediate response during a health emergency. While tremendous progress has been made toward developing and deploying safe and effective vaccines against Ebola, the work is not complete. We urge the global public health community to take the steps necessary to ensure readiness to respond with vaccines to the next Ebola outbreak. High-level discussions have shifted away from the Ebola response in Africa to how to reform the international capacity to respond to and develop medical countermeasures for future infectious disease outbreaks around the globe. Without renewed commitment to completing work on Ebola vaccines, these broader priorities are likely to delay progress on Ebola vaccine development. To ensure the availability of safe, effective Ebola vaccines and the capacity to deploy them for future outbreaks in Africa or elsewhere, the Ebola Vaccine Team B recommends addressing the following objectives:

1. ***Renew the global commitment to developing and deploying one or more Ebola vaccines.*** As the authoritative leader of major global public health initiatives, the WHO should continue to focus attention on developing, deploying, and financing Ebola vaccines as a global health priority and to actively coordinate public- and private-sector stakeholders in this effort. We hope that the recommendations and action plan outlined in this report provide a useful framework for promoting a productive dialog and resolving the remaining challenges.

2. ***Complete current clinical trials using rVSV-ZEBOV and other promising Ebola vaccine candidates.*** Additional safety, efficacy, and immunogenicity data, beyond the existing published data, may be required for regulatory and EUAL approval of rVSV-ZEBOV. In addition, further data on safety, immunogenicity, and duration of protection for the other current vaccine candidates will be needed to determine if these candidates offer significant advantages over rVSV-ZEBOV. When additional data become available, the features of rVSV-ZEBOV should be compared with those of other vaccine candidates in light of the optimal characteristics outlined in the Ebola Vaccine Target Product Profile.[68] Upon completion of the current clinical trials, all data (including negative data) should be published. One of the key outcomes of these trials may be identification of immunologic markers following vaccination, which might help to identify correlates of protection and potentially allow vaccines without clinical end point efficacy data to be licensed and made available for deployment.

3. ***Continue to conduct animal studies to elucidate Ebola vaccine characteristics and provide data on correlates of protection against infection.*** Further preclinical studies in

animal models, such as nonhuman primates, using rVSV-ZEBOV and other vaccine candidates may provide valuable data to identify key immunologic markers and the duration of protection, as well as to determine whether existing monovalent vaccines provide cross-protection to other species of Ebolavirus and to Marburg virus.

4. ***Identify the basis for regulatory approval for rVSV-ZEBOV and other Ebola vaccines.*** Requirements and expectations for nontraditional regulatory pathways (such as the FDA's accelerated approval or Animal Rule) applicable to Ebola vaccine approval should be clearly defined and harmonized across relevant NRAs, if necessary. Optimal regulatory pathways for Ebola vaccines may involve surrogate efficacy data (such as immune markers that are reasonably likely to predict protection from Ebola infection) and comparison with rVSV-ZEBOV immunologic and field efficacy data. Identifying the optimal basis for regulatory approval may facilitate the preparation of dossiers and expedite review.

5. ***Plan to launch phase 3 efficacy studies and/or phase 4/post-marketing studies of licensed or emergency-authorized Ebola vaccines at the outset of the next outbreak.*** Effective coordination and follow-through will be needed to meet this objective. Key components of the process include the following:
    - *Develop protocols to further assess the safety and efficacy of rVSV-ZEBOV vaccine.* Protocols need to be in place in advance of the next Ebola outbreak to collect ongoing data for the first-generation rVSV-ZEBOV vaccine in phase 4 studies (if the vaccine is licensed) or phase 3 studies (if the vaccine is emergency-authorized). Institutional and ethical approvals should be obtained in advance to prevent delays once an outbreak begins. Clear prioritization of studies is also needed at the international level.[43] Investigators should review lessons learned from the recent experience in West Africa and address critical issues proactively in advance of any future public health crisis.[44,69–73]
    - *Determine whether or not to conduct clinical trials with Ebola vaccines other than rVSV-ZEBOV.* Public health officials need to grapple with the issue of whether or not clinical trials using other Ebola vaccines are ethical during future Ebola outbreaks in light of the available efficacy data for rVSV-ZEBOV. This issue requires careful study by ethicists and discussion with officials in countries that are at high-risk of future Ebola outbreaks (including, but not limited to, countries in West Africa). It is imperative that these discussions include robust input from African leaders. If suitably designed studies are deemed ethical and feasible, then protocols and institutional reviews need to be in place to initiate such studies as soon as an outbreak is recognized.
    - *Ensure availability of vaccine stockpiles.* Adequate doses of vaccine need to be available in advance of the next outbreak in order to rapidly implement public health vaccination programs and initiate further studies. Gavi's advance purchase commitment with Merck will provide 300,000 doses of rVSV-ZEBOV,[35] which should ensure an adequate stockpile of this vaccine. Mechanisms (including

financial incentives) also need to be in place to ensure availability of adequate doses of other vaccines for future study, if decisions are made to continue such research.

- *Consider scenarios for determining appropriate vaccination strategies.* Potential strategies include, among others, risk-based targeting (ring vaccination), geographic targeting of an area (mass vaccination), and vaccination of front-line workers, depending on a number of factors, such as the extent of the spread of disease, disease incidence when vaccination is initiated, status of implementation of other control measures, effectiveness of contact tracing, and available supply of vaccine.[13] To enhance preparedness, public health officials—both at the international level and in Africa—should consider various scenarios for the next Ebola outbreak in advance and develop appropriate vaccination strategies to ensure rapid implementation. Key considerations include the conditions appropriate for reactive ring vaccination approach versus prophylactic vaccination and geographic versus risk-based targeting (including locally defined high-risk individuals, occupational groups, and communities).

6. ***Develop strategies for rapid collaborative partnership and community engagement.*** Prepare health promotion messages to be used before vaccination and discuss ethical issues regarding vaccine trials (eg, randomization, inclusions, informed consent, proxy consent, liability, and compensation for adverse events).

7. ***Strengthen engagement with and involvement of African public health officials to ensure effective vaccine deployment.*** Successful development and deployment of Ebola vaccines in African countries depends critically on effective engagement with African ministries of health and other public health officials in all aspects of the effort, from identifying appropriate vaccines for stockpiling and determining demand in at-risk countries, to conducting clinical trials and devising effective vaccination strategies. With the Ebola crisis ending, attention is understandably shifting to other urgent health priorities in West Africa. Proactive efforts are needed to re-engage African leaders across the continent to discuss their perspectives and feedback on the ongoing clinical trials and plans for further efficacy evaluation and vaccine deployment in response to the next Ebola outbreak.

8. ***Develop an action plan for addressing the financial structure and process for further development of Ebola vaccines.*** Key steps include the following:
    - *Clarify industry perspectives and commitments* for continuing to develop Ebola vaccines and submit dossiers for regulatory review. It may be useful for an independent group to interview vaccine manufacturing leaders to identify major obstacles (technical and financial) to completing development of Ebola vaccines and solutions for addressing them. De-identified findings from these interviews should be made available for open discussion.

- *Collect and analyze financial information* on: (1) major public or philanthropic financial support awarded for Ebola vaccine R&D and direct and opportunity costs incurred by industry; (2) estimated costs for continued development of vaccine candidates, including the role, if any, of "pull" incentives such as FDA priority review vouchers (potentially worth US $100 million to $350 million to promote innovation for neglected-disease medical countermeasures); and (3) comparative costs to purchase different vaccine products, maintain a stockpile, and ensure sufficient surge capacity in the event of an outbreak.
- *Establish a fund*, based on a public-private partnership, to share the costs of continuing R&D, regulatory review, manufacturing, stockpiling, and deployment of Ebola vaccines.
- *Consider options for the plan's scope.* This could involve a targeted option versus a broader approach, such as: (1) a limited option to bridge the remaining gaps and identify pathways to approval and deployment of safe and effective Ebola vaccines or (2) a comprehensive process to enhance vaccine development and deployment for emerging infectious diseases including, but not limited to, Ebola.
- *Organize a multilateral framework* under WHO auspices to guide the process and commit to completing it, involving the Ebola vaccine manufacturers, African public health leaders, NRA officials, Gavi, government research and public health agencies, Medecins Sans Frontieres, and philanthropies.

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