

January 2017

Ebola Vaccine Team B

Completing the Development of Ebola Vaccines

CURRENT STATUS, REMAINING
CHALLENGES, AND RECOMMENDATIONS

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Team B Concept

Originating in government intelligence agencies in the mid-1970s, the concept of a Team B first referred to convening a team of outside experts to provide independent analyses of classified international security data. Since that time, the Team B concept has been applied to many other fields, but it still refers to the provision of independent expert review and analysis to support informed decision-making for a specific activity.

The Wellcome Trust and the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota established the Ebola Vaccine Team B in November 2014 to support international efforts to stop the rapid spread of Ebola virus disease in West Africa. The group's purpose is to provide a complementary and creative review of all major aspects of developing and delivering effective and safe Ebola vaccines, including funding, research, development, vaccine efficacy and effectiveness determination, licensure, manufacturing, and vaccination strategies. The Wellcome Trust-CIDRAP Ebola Vaccine Team B includes 25 international subject-matter experts involved in one or more areas of vaccine work.

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January 2017

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Foreword

This is the third major report from the Wellcome Trust–CIDRAP Ebola Vaccine Team B. The first report, [Recommendations for Accelerating the Development of Ebola Vaccines: Report and Analysis](#), was released in February 2015, and the second, [Plotting the Course of Ebola Vaccines: Challenges and Unanswered Questions](#), was released in March 2016. In this report, similar to our previous efforts, we have three primary objectives. The first is to track progress toward ensuring that safe, effective, and durable multivalent Ebola vaccines are readily available and can be rapidly deployed when the next outbreak occurs. The second is to identify challenges and barriers where additional efforts are needed, although some of the remaining issues are complex and will require substantial resources to resolve. Our third objective is to provide a set of high-level recommendations that we believe, if implemented, will facilitate the goal of having a robust Ebola virus disease (EVD) prevention program in place that allows prophylactic vaccination of high-risk frontline workers and provides well-maintained vaccine stockpiles to facilitate rapid control of Ebola outbreaks. High-risk frontline workers include healthcare workers, deploying international workers, and others at particularly high risk of EVD because of their profession, including ancillary staff and those dealing with burials.

This report includes information and perspectives obtained from a series of key informant interviews with Ebola vaccine manufacturers, regulators, and other key stakeholders. In addition, we conducted a comprehensive review of published literature and examined reports and documents from government agencies, private-sector companies, and nonprofit organizations.

As we reflect on progress to date and the remaining challenges we face, we are optimistic that the global community will devise creative strategies for overcoming the remaining barriers, such as through the activities of the newly formed Coalition for Epidemic Preparedness Innovations (CEPI), and will find the resources necessary to finish the job at hand. We can't predict when, where, or under what circumstances the next Ebola outbreak will occur; therefore, the global community needs to move quickly so we are not caught unprepared if an explosive Ebola outbreak occurs in the near future. We encourage our colleagues to maintain the sense of urgency that was present in 2014 and 2015 and complete the work toward vaccine development and delivery as expeditiously as possible so our collective vision of ending Ebola as a major threat to public health can be realized.

The work toward Ebola vaccine development serves as a valuable model and test case for novel vaccines to combat other neglected or emerging infectious diseases (EIDs) for which routine market forces do not generate the required financial resources for vaccine research, development, and introduction. Important examples include chikungunya virus disease, Crimean-Congo hemorrhagic fever, Lassa fever, Middle East respiratory syndrome (MERS), Rift Valley fever, severe acute respiratory syndrome (SARS), and West Nile virus infection. Our collective experience with Ebola vaccines provides critical lessons learned. In fact, the success of those other future efforts may depend on whether we successfully complete the development, production, procurement, and deployment of Ebola vaccines.

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Introduction

More than 2 years ago we witnessed a small outbreak of EVD in rural Guinea become within a few months an overwhelming medical, social, and economic crisis across Guinea and two of its interconnected and populous neighbors, Liberia and Sierra Leone, with additional spread into several other West African countries. We also know that the path the Ebola virus took in West Africa is not the only possible scenario for future Ebola epidemics. If a future Ebola outbreak occurs in a major sub-Saharan African megacity such as Kinshasa, Democratic Republic of the Congo, or Lagos, Nigeria, Ebola virus transmission could rapidly outpace the ability of traditional public health measures to curtail it. The potential is real for an even more disastrous public health emergency of international concern (PHEIC) than the 2013-16 West Africa epidemic.

Without ready availability of safe and effective vaccines (either monovalent Ebola vaccines or multivalent filovirus vaccines)—including for prophylactic immunization of frontline workers in advance of an outbreak—densely populated regions of Africa may be forced to rely on basic public health measures and existing healthcare services to cope with the severe morbidity and high mortality rates from EVD, an especially challenging task in low- and middle-income countries (LMICs) already struggling with inadequate healthcare facilities and workforce availability. Furthermore, a limited Ebola vaccine stockpile for ring vaccination likely will not be adequate to stop the spread of an explosive Ebola outbreak in a major African city. Finally, given recent evidence for long-term persistence of the virus in survivors and related risks of ongoing transmission, we need to have vaccines in place to stamp out these persistent disease foci.

After Aug 8, 2014, when the director-general of the World Health Organization (WHO) declared the Ebola epidemic in West Africa a PHEIC under the 2005 International Health Regulations, the WHO took a lead role in coordinating an accelerated international effort to develop and evaluate new Ebola vaccines, including direct involvement in conducting a phase 3 clinical trial in Guinea that demonstrated clinical vaccine efficacy before active transmission subsided ([Henao-Restrepo 2016a](#), [Henao-Restrepo 2016b](#)). In October 2014, during the height of the epidemic, the WHO convened a high-level emergency meeting of scientific, public health, regulatory, and industry officials, who agreed on the importance of Ebola vaccines for outbreak response and articulated a set of goals to overcome the obstacles to financing and accessing safe and effective vaccines ([WHO 2014a](#)). Two years later, however, several of the goals articulated at that meeting have not yet been achieved, despite the intense efforts of industry leaders, public health officials, research scientists, regulators, and public and private funders.

For example, the report states, “. . . all efforts to develop, test, and approve Ebola vaccines must be followed through to completion at the current accelerated pace, even if dramatic changes in the epidemic’s transmission dynamics meant that vaccines were no longer

needed.” Although much has been accomplished toward these goals over the past 2 years, critical steps remain incomplete.

In May 2016, the WHO published *An R&D Blueprint for Action to Prevent Epidemics: Plan of Action* ([WHO 2016a](#)). This document outlines goals for a number of the issues identified in this report; however, the focus of the WHO document is broader than Ebola and it doesn’t provide details on how we can address the immediate challenges of bringing Ebola vaccines to market. We assert that the need for Ebola vaccines (including multivalent filovirus vaccines) remains an urgent public health priority. Renewed and continued global leadership is required to complete the task of licensing and delivering safe, effective, and durable multivalent Ebola vaccines for prophylactic and reactive use. Achieving this outcome is critical not only for Ebola preparedness, but also for proof of concept that vaccines to protect against other neglected or EIDs can be successfully developed in the future. Resolving issues related to Ebola vaccines can also provide important lessons learned and steps forward toward meeting the goals of the WHO R&D Blueprint. To that end, this report summarizes progress in Ebola vaccine development, articulates the most critical remaining scientific challenges for vaccine candidates, and provides high-level recommendations to address the remaining obstacles to vaccine preparedness for the next inevitable Ebola outbreak.

Key Remaining Gaps in Ebola Vaccine Preparedness

Despite important progress to date (see next section), a licensed Ebola vaccine is still not available and important issues specific to Ebola vaccine preparedness require resolution so we can realize the goal of ensuring that monovalent Ebola and multivalent filovirus vaccines are available for use. These issues are further discussed later in this document and include:

- The WHO has not made determinations regarding the Emergency Use Assessment and Listing (EUAL) applications for Ebola vaccines from Merck (filing completed in December 2015) and Johnson & Johnson (filing completed in September 2016).
- Coordination of approvals for emergency use of vaccines remains a gap in preparedness against Ebola. For example, the WHO needs to clarify how vaccines with EUAL status will be granted approval for emergency use by local national regulatory authorities (NRAs). Ideally, a harmonized emergency use regulatory pathway across regulatory agencies should be in place.
- Plans and protocols for vaccine stockpile development, management, maintenance, deployment, and decisions for use have not been fully developed.
- High-level vaccination strategies for prevention and control of future Ebola epidemics have not been clarified and could benefit from additional scenario-based planning and modeling.
- If one Ebola vaccine is licensed for use, criteria are needed to determine if and how other investigational vaccines would be used during future outbreaks.
- Ongoing efforts are needed to define the circumstances in which clinical trials may be conducted during future Ebola outbreaks to evaluate vaccine candidates for which clinical efficacy data are lacking and to plan how such trials should be designed. These plans need to address methodologic, ethical, logistical, and feasibility issues. The WHO is working to design these types of clinical trials as part of its R&D Blueprint ([WHO 2016a](#)), but further effort is needed in this area.
- The role of reactive versus prophylactic use of the rVSV-ZEBOV vaccine has not been clarified.
- Clear plans for in-country pharmacovigilance monitoring after vaccine licensure are lacking, despite development of recent guidance from the WHO.
- Protocols for post-licensure observational studies of Ebola vaccines need to be developed and be ready for use when vaccines are deployed. For example, an important priority is to devise methods for assessing the duration of protection following vaccination.
- Identification of correlates of protection and standardization of immunologic assays and animal models are needed to facilitate licensure of vaccines when clinical efficacy studies are not feasible.
- Steps to address liability and indemnification issues for Ebola vaccines deployed outside of clinical trials are still needed.

- Strategies to mitigate the economic risks for manufacturers of candidate Ebola vaccines are needed, perhaps using a shared risk/shared reward model.
- Additional resources are needed for research and development (R&D) of multivalent filovirus vaccines, at least through the stockpiling process.

Progress to Date on Ebola Vaccine Development

On Mar 29, 2016, the WHO lifted the PHEIC declaration for Ebola in West Africa. The epidemic resulted in 28,616 confirmed, probable, and suspected cases reported in Guinea, Liberia, and Sierra Leone, and 11,310 deaths ([WHO 2016b](#)). More than 10,000 people who contracted EVD during the epidemic survived and are living in West Africa ([WHO 2016c](#)). Ongoing response efforts focus on identifying and interrupting any remaining chains of Ebola virus transmission and addressing residual Ebola-related health risks ([WHO 2015a](#)).

Some of the Ebola vaccine R&D programs that were initiated or expanded during the 2013-16 epidemic are continuing ([Keshwara 2016](#)). Remarkable progress has been made in moving Ebola vaccine candidates forward and addressing other critical issues necessary for delivery of Ebola vaccines in high-risk areas. Key accomplishments are summarized below. (*Note:* This summary is not intended to be comprehensive, but rather to highlight major areas of recent progress.)

Clinical Evaluation of Ebola Vaccine Candidates

- The current range of Ebola vaccine candidates includes products with different characteristics that may be relevant to their potential role in deployment in outbreak situations or at-risk populations, such as cold-chain requirements, route of administration (eg, intramuscular, intranasal), and dosing regimen (single-dose vs prime-boost strategies) ([Martins 2016](#)). Five categories of Ebola vaccines are under development:
 - Replication-competent, vectored vaccines (eg, rVSV-ZEBOV, VesiculoVax, HPIV3-EBOVZ)
 - Replication-incompetent, adenovirus-vectored vaccines (eg, cAd3-EBOZ, Ad26.ZEBOV, Ad5-EBOV)
 - Replication-incompetent poxvirus-vectored vaccines (eg, MVA-BN-Filo, MVA-EbolaZ)
 - DNA vaccines (eg, INO-4201, INO-4202, INO-4212)
 - Subunit vaccines (eg, EBOV GP nanoparticle vaccine with Matrix-M adjuvant)
- Initial clinical trials involving rVSV-ZEBOV, cAd3-EBOZ/MVA, Ad26.ZEBOV/MVA-BN-Filo, and Ad5-EBOV have been completed; published reports and a summary of their outcomes are shown in Table 1 in the [Appendix](#). Final results from the phase 3 rVSV-ZEBOV ring vaccination trial in Guinea, which was completed during active transmission in West Africa, have demonstrated that the vaccine was efficacious in preventing EVD in that setting ([Henao-Restrepo 2016a](#)).

Two other phase 2/3 efficacy trials, in Liberia ([Kennedy 2016](#)) and Sierra Leone ([Widdowson 2016](#)), were initiated, but their efficacy components were suspended as the epidemic subsided, while the safety and immunogenicity components continued.

- Additional safety and immunogenicity data are forthcoming from more than 30 active clinical trials (Table 2, [Appendix](#)), including a phase 2 study of Ad26.ZEBOV/MVA-BN-Filo in HIV-infected persons, a prospective observational cohort study on the immune durability of rVSV-EBOV vaccination, and a phase 1 study of an intranasally administered Ebola vaccine candidate (HPIV3-EbovZ GP). According to news reports, a new clinical trial of the safety and immunogenicity of the rVSV-EBOV vaccine in HIV-infected persons is being initiated in Canada, Senegal, and Burkina Faso ([IDRC 2016](#)). A phase 1 study assessing the safety and immunogenicity of a multivalent filovirus vaccine combining Ad26.Filo and MVA-BN-Filo is also under way. (*Note:* Other studies not addressed here may be in various stages of development.)
- New collaborative partnerships were formed for planning and conducting Ebola vaccine clinical trials in West Africa, North America, and Europe, led by international teams of researchers, public health officials, and industry leaders and supported by public and private funders. These include the EBOVAC projects ([Enria 2016](#); [Milligan 2016](#); [EBOVAC 2016](#)), the Ebola ça suffit ring vaccination trial consortium ([Henao-Restrepo 2015](#); [Henao-Restrepo 2016a](#), [Henao-Restrepo 2016b](#); [Camacho 2015](#)), the Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE) ([Widdowson 2016](#); [CDC 2016](#)), and the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL) ([Kennedy 2016](#); [Massaquoi 2016](#); [NIH 2015](#)).
- The Medical Countermeasures Initiative from the US Food and Drug Administration (FDA), which coordinates the development and availability of medical products needed to prepare for and respond to public health emergencies, issued a 3-year, \$3.2 million contract with Public Health England to establish correlates of protection to support potential licensure of new Ebola vaccines and analyze blood samples collected from patients with Ebola to create a reference database. The goal of the contract is to identify a unique set of EVD biomarkers and expected disease outcomes, which could provide reference points for developing and evaluating Ebola vaccines ([FDA 2015a](#)).

Target Product Profiles

- The WHO published an Ebola vaccine target product profile (TPP) to provide guidance on Ebola vaccine development for emergency use in outbreak situations and prophylactic use in advance of an outbreak to protect frontline workers and other at-risk groups ([WHO 2016d](#)). The TPP addresses indications for use, target populations, safety and reactogenicity, efficacy, dose regimen, durability, route of administration, species covered, product stability and storage, co-administration with other vaccines, presentation, production, and registration and prequalification.

- In November 2016, the WHO provided a second TPP on prophylactic use of multivalent filovirus vaccines ([WHO 2016e](#)). These vaccines would be used for active immunization of frontline workers considered at risk for disease caused by Ebola Zaire, Ebola Sudan, and Marburg viruses.

Funding

- In January 2016, Gavi, the Vaccine Alliance, and Merck completed an advance purchase commitment for the rVSV-ZEBOV vaccine, formalizing Merck's intent to file a licensing application before the end of 2017 and Gavi's commitment to provide \$5 million to Merck to support the production and stockpiling of 300,000 doses of pre-licensed rVSV-ZEBOV vaccine available for emergency or investigational use ([Gavi 2016](#)).
- Government agencies (eg, in the United States, Canada, United Kingdom, European Union), vaccine manufacturers (eg, Merck, GlaxoSmithKline, Johnson & Johnson, Bavarian Nordic), philanthropic organizations (eg, Gates Foundation, Wellcome Trust), non-governmental organizations (NGOs; eg, Gavi) and other key stakeholders have made substantial investments in Ebola vaccine development ([Policy Cures](#)). The primary US government agencies supporting Ebola vaccine R&D are the Biomedical Advanced Research and Development Authority (BARDA), the National Institutes of Health (NIH), the Joint Vaccine Acquisition Program (JVAP), the Defense Advanced Research Projects Agency (DARPA), and the Defense Threat Reduction Agency (DTRA). Examples of recently awarded US and European contracts include:
 - BARDA exercised its \$21.6 million option (added to the \$30 million initial award in December 2014) to support continued development of the rVSV-ZEBOV vaccine, including clinical bridging studies to further assess the vaccine's safety, immunogenicity, and efficacy in populations different from those in the original testing region. With this additional funding, NewLink Genetics Corporation received a total of \$74.6 million from BARDA for R&D of the rVSV-ZEBOV vaccine ([HHS 2016](#); [NewLink 2016](#)).
 - BARDA awarded \$28.5 million to Johnson & Johnson for development of its heterologous prime-boost regimen Ad26.ZEBOV/MVA-BN-Filo ([J&J 2015](#)).
 - DARPA awarded Inovio a \$45 million contract in 2015 for development of the INO-4212 Ebola vaccine ([Inovio 2015](#)).
 - JVAP, BARDA, and NIH support the development of Profectus BioSciences's highly attenuated VSV-vectored Ebola virus vaccine (VesiculoVax) ([Profectus 2016](#)).
 - The European Innovative Medicines Initiative (IMI) Ebola+ Programme is funding a series of Ebola vaccine projects focusing on Ad26.ZEBOV and MVA-BN-Filo vaccines, implemented by a public-private consortium that includes Johnson & Johnson, Bavarian Nordic, the University of Oxford, the London School of Hygiene and Tropical Medicine, the French National Institute of Health and Medical Research (INSERM), and others. The projects include: (1) EBOVAC, to conduct clinical trials; (2) EBODAC, to develop strategies to enhance the acceptance and uptake of these vaccines in West Africa; and

(3) EBOMAN, to accelerate the development and manufacturing of the vaccines for clinical trials and surge capacity ([EBOVAC Web site](#)).

Regulatory Activities

- In October 2016, the WHO Expert Committee on Biological Standardization released draft guidelines for NRAs and vaccine manufacturers on the development, manufacturing, quality control, and clinical evaluation of the safety and efficacy of Ebola vaccines for licensure ([WHO 2016f](#)).
- CEPI reviewed vaccine regulatory pathways for vaccines to address EIDs and analyzed the regulatory challenges in vaccine approval and emergency use ([CEPI 2016](#)), building on a series of efforts at the WHO, the FDA, and the European Medicines Agency (EMA) to consider available options for Ebola vaccines ([Russek-Cohen 2016](#); [FDA 2015b](#); [FDA 2015c](#); [Krause 2015](#); [Cavaleri 2016](#); [WHO 2014b](#)) and EID vaccines in general ([WHO 2016a](#); [Kieny 2016](#)). Examples of key mechanisms from the FDA and the EMA for licensure, emergency use, and purchasing applicable to Ebola vaccine development and delivery are outlined in Table 3 in the [Appendix](#).
- Merck intends to submit applications for licensure of the rVSV-ZEBOV vaccine to the FDA and the EMA. The application is expected to be reviewed on an expedited basis; the rVSV-ZEBOV vaccine candidate received Breakthrough Therapy Designation from the FDA and Priority Medicines (PRIME) status from the EMA ([Merck 2016](#)).
- Inovio announced that it intends to pursue licensing of the INO-4212 vaccine via the FDA’s animal rule procedure ([Inovio 2016](#)).
- The WHO developed the EUAL procedure to expedite the availability of investigational vaccines for deployment in a public health emergency ([WHO 2015b](#)). The EUAL process is intended to assess whether available data demonstrate a “reasonable likelihood” that quality, safety, and effectiveness of an investigational vaccine are acceptable and that the benefits of the vaccine “outweigh the foreseeable risks and uncertainties” in the context of a PHEIC. Merck and Johnson & Johnson have submitted applications to the WHO for EUAL status for the rVSV-ZEBOV vaccine ([Merck 2015](#)) and Ad26.ZEBOV/MVA-BN-Filo vaccines ([J&J 2016a](#)), respectively; the WHO has not yet announced decisions regarding these applications.

Deployment Planning

- As noted above, Gavi has supported the production and stockpiling of 300,000 doses of pre-licensed rVSV-ZEBOV vaccine for emergency or investigational use ([Gavi 2016](#)).
- Johnson & Johnson, in partnership with Bavarian Nordic, has produced approximately 2 million regimens of the Ad26.ZEBOV/MVA-BN-Filo prime-boost vaccine, with the capacity to produce several million regimens if needed ([J&J 2016b](#); [Shukarev 2016](#)). This vaccine is compatible with standard cold chain equipment for

vaccine distribution; ongoing studies suggest thermostability for both components of the regimen at -20°C for 12 months or longer and at 2° to 8°C for 6 months or more.

- In October 2015, the WHO's Strategic Advisory Group of Experts on Immunization (SAGE) reviewed available safety data from phase 1 studies of rVSV-ZEBOV and cAd3-ZEBOV and concluded that both vaccines had acceptable safety profiles for use in healthy adults, but that longer-term follow-up was needed to allow more extensive assessment of safety, particularly regarding joint and skin effects following rVSV-ZEBOV vaccination and safety in special populations, such as children, pregnant women, and persons with underlying medical conditions such as HIV infection. The SAGE concluded that rVSV-ZEBOV and cAd3-ZEBOV are immunogenic when provided in a single dose. The advisors also concluded that the two heterologous prime-boost regimens, cAd3-ZEBOV/MVA and Ad26.ZEBOV/MVA-BN-Filo, provide immunogenicity ([WHO 2015c](#)). The SAGE outlined a series of provisional recommendations, which were intended to be reviewed and revised as additional data become available, including:
 - Development of multivalent filovirus vaccines
 - Optimization of vaccine thermostability to meet WHO prequalification criteria
 - Development of preapproved and prepositioned research protocols for rapid implementation of clinical trials in countries at risk for future outbreaks
 - Modeling the impact of various vaccination strategies to control future outbreaks
 - Development by the Global Ebola Vaccine Implementation Team (GEVIT) of tools and deployment plans for vaccination
- The GEVIT, convened by the WHO, drafted initial plans and recommendations to enhance global, regional, and country-level preparedness for deploying licensed Ebola vaccines in response to a potential future outbreak ([WHO 2016g](#)). Additional efforts of the GEVIT include modeling demand for Ebola vaccine and providing scientific advice and technical briefings to enable the development of additional tools to prepare for EVD epidemic responses in at-risk countries ([WHO 2016k](#)).

Remaining Challenges for the rVSV-ZEBOV Vaccine

Regulatory Approval

As noted earlier in this report, on the basis of data from the Guinea ring vaccination trial ([Henao-Restrepo 2015](#)) and other information, Merck is expected to apply for licensure by the end of 2017, as announced in its advance purchase commitment with Gavi ([Gavi 2016](#)). At this point, it is not clear whether or not the FDA or the EMA will determine that the efficacy data generated during the Guinea trial are sufficient to allow approval through the traditional licensure (FDA) or marketing authorization (EMA) pathways. If not, the rVSV-ZEBOV vaccine could be considered for approval via other specific frameworks, such as the FDA's accelerated approval pathway (provided a surrogate marker reasonably likely to predict clinical benefit can be established) or the EMA's conditional marketing authorization pathway, which covers the option of vaccine use during public health emergencies ([Krause 2015](#)).

Although progress is being made in understanding the humoral immune response to Ebola vaccination ([Khurana 2016](#)), immune correlates to predict protection against Ebola virus have not yet been identified for any of the vaccine candidates, which creates challenges for using the accelerated approval pathway or other alternatives to traditional approval pathways. Furthermore, the above-mentioned frameworks require that post-licensure clinical studies be conducted with due diligence to confirm clinical benefit. Merck will need to submit protocols for post-marketing studies during the marketing application review process for the vaccine. The FDA and the EMA generally advise that the protocols be as adaptive and flexible as possible, because there are so many uncertainties (eg, timing, location, size, and circumstances) in planning for future Ebola outbreaks. If a vaccine is licensed through the traditional approval pathway or marketing authorization, the need for post-marketing studies will be discussed on a case-by-case basis and may depend on a range of factors, such as the safety profile and risk-benefit of the vaccine.

If the rVSV-ZEBOV vaccine is not approved for licensure via one of the pathways noted above, the vaccine can still be used in an emergency setting through several mechanisms. One is under the US expanded-access investigational new drug (IND) provisions, which would require institutional review board (IRB) approval and informed consent. A second mechanism is through the WHO's EUAL process, which would be applicable during declared PHEICs. EUAL status, however, does not eliminate the need for in-country review from a local NRA. As noted earlier, Merck has applied to the WHO for EUAL status, which could facilitate the in-country approval process during an emergency ([WHO 2015b](#)). As of this writing, the WHO has not granted EUAL status for the rVSV-ZEBOV

vaccine. The EUAL procedure is relatively new, and uncertainty remains regarding the details of implementing an Ebola vaccination program under this procedure. Further clarification is needed on the requirements, review process, and timeline for the EUAL approval, and on in-country regulatory issues regarding emergency use once EUAL status is granted.

Pharmacovigilance Studies Post-licensure

At a minimum, once the vaccine is licensed, country-by-country pharmacovigilance systems will need to be in place to monitor rVSV-ZEBOV safety during and after periods of vaccine use. Currently, post-marketing surveillance systems are not well developed in the countries that were affected by the West Africa Ebola epidemic, and enhanced capacity for adverse event following immunization (AEFI) surveillance is needed across the region ([WHO 2016b](#)). The WHO is in the process of preparing a detailed guidance document for safety monitoring and pharmacovigilance activities following introduction of Ebola vaccines ([WHO 2016f](#)). Even with such guidance, however, an ongoing challenge will be ensuring that the involved countries have the resources and infrastructure necessary to carry out the recommended activities.

Approval From NRAs in Africa

If and when Merck obtains licensure and/or EUAL status for the rVSV-ZEBOV vaccine from the FDA or the EMA, another major hurdle is gaining approval for use in African countries at high risk for Ebola. As with other vaccines, Merck will need to apply for licensure, and each country's NRA will need to approve the vaccine. To date, Ebola cases have occurred in the following African countries: Democratic Republic of the Congo, Gabon, Guinea, Liberia, Mali, Nigeria, Republic of Congo, Senegal, Sierra Leone, South Africa, South Sudan, and Uganda. A number of other countries in sub-Saharan Africa also are at risk of Ebola outbreaks because they share a border with one of the high-risk countries (ie, are "Ebola-facing"). Merck may need to navigate this complex and diverse regulatory landscape post-licensure to ensure preparedness for the next Ebola outbreak. During a future outbreak, some African countries could choose to accept WHO EUAL status or WHO prequalification (PQ) of the vaccine in lieu of additional in-country registration. WHO PQ, however, requires vaccine storage at -20°C or warmer ([WHO 2014c](#)); the rVSV-ZEBOV vaccine currently requires storage at -80°C. This issue needs to be addressed before WHO PQ can be obtained. In the meantime, officials are working on a mechanism to provide compassionate use of rVSV-ZEBOV in 12 at-risk countries, in case the vaccine is needed before licensure.

Determining Indications for rVSV-ZEBOV Vaccine Use

According to the WHO TPP for Ebola vaccines, the indications for use are as follows ([WHO 2016d](#)):

- **Reactive use:** For immunization of at-risk persons residing in the area of an ongoing outbreak to protect against EVD caused by circulating species of filovirus; to be used in conjunction with other control measures to curtail or end an outbreak. (The vaccine should provide at least 3 months—and preferably 1 year—of protection.)
- **Prophylactic use:** For active immunization of persons considered at risk based on specific risk factors to protect against EVD caused by species of filoviruses that have the potential to cause outbreaks. (The vaccine should provide at least 1 year—and preferably 5 years—of protection after a primary series and can be maintained by booster doses.)

Even though rVSV-ZEBOV is a monovalent vaccine, it could be used prophylactically, at least until acceptable multivalent vaccines are available. Currently, however, limited data are available on the durability and risk-benefit profile of the rVSV-ZEBOV vaccine, and evidence is lacking to support an indication for disease prevention in the absence of an ongoing outbreak. Without such information, it is difficult to determine whether the vaccine should be indicated for prophylactic use in addition to reactive use. This determination will be made during the regulatory review process. Merck has ongoing studies aimed at assessing the durability of protection offered by the vaccine; however, it's not clear how durability will be assessed, since correlates and thresholds of protection have not been elucidated.

Some experts believe that once an Ebola vaccine is licensed, public health officials should seriously consider implementing prophylactic vaccination programs for a cadre of frontline workers across the at-risk region as soon as possible ([Skrip 2016](#)). More than 500,000 healthcare workers currently provide care in African countries considered at high to moderate risk for Ebola outbreaks. Experts have argued that this approach would not only protect those workers (along with other frontline workers) but also mitigate nosocomial spread of the virus during an outbreak ([Skrip 2016](#)). Further discussion, assessment, and decision-making are needed to clarify indications of use for the rVSV-ZEBOV vaccine (assuming the vaccine is licensed), particularly related to prophylactic versus reactive vaccination approaches.

Vaccine Stockpiling

As noted earlier, Gavi has committed to purchasing 300,000 doses of rVSV-ZEBOV vaccine, which is a significant step in creating an Ebola vaccine stockpile. Important questions still need to be addressed, however, regarding development and maintenance of Ebola vaccine stockpiles, including the following:

1. What level of vaccine preparedness is optimal (or feasible) for stopping future outbreaks, and what are the vaccination strategies for achieving that level of preparedness?
2. How large do vaccines stockpiles need to be to meet the desired level of preparedness?
3. What role will stockpiles play in future outbreak management to meet disease control requirements versus initiation of vaccine production on a just-in-time basis?
4. Will there be more than one vaccine stockpile? If there are multiple stockpiles, how will different global stockpiles be interrelated or their use coordinated?
5. Will there be a centralized system for stockpile storage and maintenance (eg, storing vaccine in a temperature-controlled environment, ensuring that vaccine is viable over time), or will each manufacturer be responsible for its own stockpile (assuming that stockpiling is approved for more than one vaccine)?
6. Where will vaccine stockpiles be stored?
7. What resources (eg, financial, logistical, technical expertise) are needed to maintain vaccine stockpiles, and are those resources available?
8. Who will pay to replenish vaccine stockpiles?
9. Who will determine when and how stockpiles will be used?

Participants at the GEVIT Regional Workshop, held in October 2015, discussed the possibility of using an International Coordinating Group (ICG) mechanism for managing an Ebola vaccine stockpile ([WHO 2015e](#)). According to the GEVIT workshop report, “the ICG mechanism components include stock management, storage, management of applications, and decision-making.” The existing ICG, which includes representation from the WHO, Médecins sans Frontières (MSF), the International Federation of Red Cross and Red Crescent Societies (IFRC), and the United Nations International Children's Emergency Fund (UNICEF), currently manages stockpiles for yellow fever, cholera, meningitis, and smallpox vaccines. Additional discussion is ongoing to determine how this ICG approach can be used for Ebola vaccine stockpiles and how it will be implemented. In addition, the GEVIT plans to pursue research and modeling efforts to estimate future Ebola vaccine demands.

Manufacturing Capacity Challenges

Once the rVSV-ZEBOV vaccine is licensed, substantial manufacturing capacity challenges will still exist for preparing and delivering Ebola vaccines; examples include the following:

- A limited ongoing commercial market exists for a vaccine that may primarily be intended for emergency use. (This could change if a large military purchase from the US or other government occurs, which might affect indications for use and size of stockpiles, or if extensive prophylactic use is recommended.)
- The forecast for vaccine needs is uncertain, since the timing and size of future outbreaks is unpredictable and decisions regarding prophylactic use have not been made.
- The low vaccine volumes required for stockpiling may not be in line with the most efficient use of one or more manufacturing plants. Even if the vaccine is approved for

prophylactic use in frontline workers, it is unlikely that the demand will be high enough to support optimal use of a manufacturing plant.

- If an outbreak occurs, additional vaccine doses likely will be needed, either to replenish the stockpile or to control the outbreak. The surge capacity required could create challenges for maintaining manufacturing expertise and capacity, and result in large opportunity costs to the manufacturer. In addition, this mismatch creates a potential risk of adequate vaccine supplies not being available when needed owing to a lack of just-in-time manufacturing capability.

Challenges for Vaccines that Lack Clinical Efficacy Data

Manufacturers of Ebola (or other filovirus) vaccines other than the Merck rVSV-ZEBOV vaccine face the same challenges outlined above and also have the additional challenges of either meeting the criteria for vaccine licensure in the absence of clinical efficacy data or developing plans for conducting additional clinical efficacy trials when the next Ebola outbreak occurs. At this point, it's not clear how decisions will be made regarding research priorities during future Ebola outbreaks. Also, the financial incentives and resources for bringing other vaccines to market will likely be diminished if one vaccine is already licensed. Finally, future outbreaks will offer limited opportunities for additional clinical trials, and planning is needed to set priorities.

Vaccine Licensure Without the Ability to Generate Clinical Efficacy Data

Licensure of one Ebola vaccine candidate does not preclude licensure of additional candidates, particularly if an alternative candidate offers different vaccine characteristics. Vaccine manufacturers who do not have efficacy data from a clinical trial using a clinical end point to support the use of their vaccine can still explore alternative pathways to obtain licensure in advance of the next Ebola outbreak. Options for regulatory approval in the absence of clinical efficacy data include the FDA accelerated approval pathway, approval via the FDA animal rule, the EMA conditional market authorization pathway, and the EMA marketing authorization under exceptional circumstances ([Appendix](#), Table 3). If a vaccine is approved via one of these alternative pathways, an additional question is whether or not local NRAs will authorize in-country use of the vaccine or will impose additional requirements on the vaccine manufacturer. Such decisions likely will be influenced by the availability of the vaccine that has shown clinical efficacy.

As noted earlier in this report, obtaining approval via the FDA accelerated approval pathway requires availability of a surrogate end point (ie, immune marker) that is reasonably likely to predict clinical benefit. The FDA has used the accelerated approval provisions for several vaccines, including influenza vaccines and the 13-valent pneumococcal conjugate vaccine (PCV13) for use in adults 50 years of age and older ([FDA 2011](#); [FDA 2015d](#)). Points for consideration include the following:

- If one Ebola candidate vaccine is licensed and the manufacturer has identified, in agreement with the FDA, a surrogate marker that is reasonably likely to predict protection for that vaccine, then an additional Ebola vaccine candidate can be compared with the licensed vaccine in non-inferiority immunogenicity studies on the basis of that immune marker, provided the immune marker is applicable to the investigational candidate vaccine.

- If the immune marker from the licensed vaccine is not applicable to the candidate vaccine, then the candidate vaccine still could be licensed through the accelerated approval pathway. Because the applicability of immune correlates of protection and surrogate immunologic end points—and FDA acceptance of them—depends on several factors, including vaccine characteristics, a manufacturer would need to conduct studies to identify markers specifically applicable to its candidate vaccine. This poses a number of important challenges, including the need for validation of immunologic assays for Ebola vaccines and animal models to assess predictability of immunologic markers for different platforms.

The accelerated approval pathway includes a requirement to confirm the clinical benefit through phase 4 confirmatory trials after the vaccine is approved. Such studies would need to have adequate statistical power, be well controlled, and be conducted with due diligence ([Krause 2015](#)). Unless a large outbreak occurs with high case counts, it may not be feasible for a manufacturer to complete this requirement. Furthermore, the design of such studies poses significant challenges. The FDA encourages manufacturers to work with governments in high-risk areas to determine how these studies can best be conducted and under what circumstances. More discussion is needed with regulators to address the methodologies, ethics, logistics, and feasibility of how to comply with this requirement for vaccines licensed through this pathway when the timing, location, and size of future outbreaks cannot be predicted.

Obtaining approval via the FDA’s animal rule is also an option. The FDA’s animal rule approval pathway was used to support a post-exposure prophylaxis indication for BioThrax (Anthrax Vaccine Adsorbed) ([FDA 2015e](#)). To date, however, the animal rule has not been used to license a vaccine for prophylactic use. Approval of a vaccine under the animal rule requires: (1) challenge studies in appropriate animal models that demonstrate the efficacy of a candidate vaccine and (2) data demonstrating that the immune responses induced in the animals can be bridged to human immune responses induced by the same vaccine. Significant challenges remain in applying the animal rule pathway for Ebola vaccines, including the lack of standardized immunological assays, the need for qualified animal models, and the more aggressive nature of Ebola disease in non-human primates (the sole currently well-established animal model comparable to natural infection in humans). Approval of an Ebola vaccine via the animal rule would potentially require a large investment in time and resources to conduct the requisite animal studies, which could result in substantial delay and financial risk for manufacturers. As with the accelerated approval pathway, post-marketing studies would be needed; this requirement could be met with field trials that provide additional information about effectiveness and safety ([Krause 2015](#)).

The EMA offers several licensing options that may be applicable for Ebola vaccines that lack complete sets of clinical efficacy data. The first is the EMA’s conditional market authorization pathway. This pathway requires that all of the following conditions be met: (1) the benefit-risk balance of the product is positive, (2) it is likely that the applicant will be able to provide comprehensive data, (3) unmet medical needs will be fulfilled, and (4)

the benefit to public health of the product's immediate availability on the market outweighs the risks associated with the need for further data ([EMA 2016a](#)). Conditional market authorization may be relevant for certain products to be used in emergency situations, is valid for 1 year, must be approved annually, and requires that outstanding data be provided. This approach was used recently to approve a pandemic preparedness influenza vaccine ([EMA 2016b](#)); however, the applicability of this pathway for Ebola vaccines needs to be clarified, given uncertainties regarding future Ebola outbreaks.

Another option is the EMA's marketing authorization under exceptional circumstances. This approach requires at least one of the following grounds that would prevent the ability of the applicant to provide comprehensive efficacy and safety evidence: (1) the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence; (2) in the present state of scientific knowledge, comprehensive information cannot be provided; or (3) it would be contrary to generally accepted principles of medical ethics to collect such information. Given this set of specifications, a marketing authorization under exceptional circumstances would not be expected to be converted to a standard market authorization.

Conducting Additional Phase 3 Clinical Trials During the Next Outbreak

Rather than pursuing vaccine licensure in the absence of clinical efficacy data, vaccine manufacturers could decide to stockpile their vaccines and wait until the next Ebola outbreak to conduct additional phase 3 clinical trials under an IND protocol. Given that the results of the Guinea trial support efficacy for the rVSV-ZEBOV vaccine, and that the vaccine may be licensed on the basis of those data, it may be more difficult for other manufacturers to conduct pre-licensure clinical trials because such vaccines may not be approved for emergency use by in-country NRAs. It is conceivable, however, that a shortage of the licensed vaccine may stimulate willingness to use an investigational vaccine, depending on the level of safety data available for the unlicensed product. Even if an alternative candidate vaccine is approved for use in an emergency setting, a relatively large outbreak with adequate case counts would need to occur to generate enough statistical power to allow meaningful comparisons between a licensed and an unlicensed vaccine. Also, manufacturers would need to bear the cost of maintaining an adequate vaccine stockpile of a candidate vaccine to be used during future studies, with the risk of expiration of the stockpiled vaccine.

If one Ebola vaccine is licensed for use, criteria would need to be determined for use of an investigational vaccine during future outbreaks. One approach would be to compare efficacy of the investigational vaccine with efficacy of the licensed product in a head-to-head clinical trial. This raises ethical and political concerns about comparing a vaccine that has been determined to be efficacious with one for which there is less certainty about efficacy. This scenario would require preliminary evidence that the alternative vaccine is likely also to be effective, and therefore it is ethically acceptable to compare it with the first licensed

vaccine. This approach may be most appropriate if the alternative vaccine provides rapid protection (necessary in an outbreak setting) and also may confer some advantage over the first licensed vaccine (eg, has longer durability or is a multivalent preparation). While clinical trial designs for assessing additional Ebola vaccines during the next outbreak are under discussion, no clear approach has been agreed upon, and ethical considerations still require further resolution.

Overarching Challenges for Vaccine Manufacturers

In addition to the challenges identified above, several overarching challenges that apply to all Ebola vaccine manufacturers deserve mention.

Identifying Strategies for Vaccine Use During Future Outbreaks

During a meeting in October 2015, the SAGE indicated, “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....When more data are available, more precise recommendations on the choice of vaccination strategy will be considered” ([WHO 2015d](#)). These statements are intentionally vague, owing to the lack of specific information; however, if an outbreak were to occur “tomorrow,” responders would have limited guidance for using vaccine and decisions would need to be made on a just-in-time basis.

Efforts to model the effects of various vaccination strategies have been developed, and several scenario-based exercises have been conducted ([Kucharski 2016](#); [Wells 2015](#); [WHO 2015e](#)). Results of one modeling study suggest that a ring-vaccination strategy would not have been adequate to stop the West Africa Ebola epidemic at its outset ([Kucharski 2016](#)); the authors postulate that a combination of ring vaccination and mass vaccination may be necessary to curtail future large Ebola outbreaks. Another modeling study, based on outbreak conditions in Sierra Leone, suggests that ring vaccination can successfully contain an outbreak in situations where the effective reproduction number is 1.6 or lower ([Merler 2016](#)). For EVD flare-ups and small outbreaks, early case detection, along with ring vaccination, may be adequate for disease control, but broader approaches, such as regional population-based vaccination or regional targeted vaccination of frontline workers, could be needed to manage larger outbreaks ([Shukarev 2016](#)). Additional scenario-based planning may be useful for identifying best strategies for different situations. As noted earlier, different scenarios may require vaccines that differ with regard to safety profile, benefit-risk balance, durability of immunity, and viral species covered. For example, which vaccines could be used (likely in clinical trials) for managing outbreaks caused by viruses other than Zaire ebolavirus, including Marburg virus, Sudan ebolavirus, or Bundibugyo ebolavirus? The SAGE Working Group on Ebola Vaccines and Vaccinations is still active and intends to review recommendations for Ebola vaccine use this year; hopefully, different scenarios can be discussed during this review process.

Liability and Indemnification

The issue of liability and indemnification for using Ebola vaccines in African countries continues to be a potential barrier. Most high-income countries have governmental mechanisms in place that provide liability protection and indemnification to vaccine manufacturers for licensed vaccines, providing no wrongdoing is identified. Most developing countries, however, lack national laws that institutionalize these protections. Instead, governments of developing countries can use ad hoc contractual indemnity agreements to assume risks for vaccine manufacturers (ie, “hold harmless” agreements) ([Attaran 2015](#)). This process, though, does not completely remove the risk of litigation. It also puts a potential burden on the governments of the involved LMICs. Another option is for the global community to establish a no-fault compensation fund for vaccines released on an emergency basis to LMICs during emergencies ([Attaran 2015](#)). At a WHO meeting on financing Ebola vaccines, held in October 2014, participants proposed that the World Bank develop a pool of financial donors that could relieve responsibility for both vaccine manufacturers and the affected governments ([WHO 2014a](#)). In addition, the WHO is exploring insurance options to indemnify potential recipients of not-yet registered vaccines and provide liability protection to industry in such cases. A possible insurance solution is outlined in the WHO R&D Blueprint ([WHO 2016a](#)). Another option would be to create a new public-private partnership to address this issue, such as through the newly formed CEPI. Options should look not only at emergency use, but also at addressing these issues for licensed Ebola vaccines.

Mitigating Economic Risks for Ebola Vaccine R&D

Another major challenge for vaccine manufacturers is the economic risk for developing an Ebola vaccine that does not have a clear commercial market, particularly if one vaccine is already licensed. The direct costs of vaccine development, combined with the associated opportunity costs, can lead to substantial economic uncertainty and risk for manufacturers if a clear path for return on investment cannot be demonstrated. Currently, no clear mechanism is in place to mitigate economic risks for manufacturers who expend resources to develop and test additional Ebola or multivalent filovirus vaccines. Ongoing support from governments or other organizations is needed to offset these economic uncertainties and risks.

A new global non-profit public-private partnership, CEPI—founded in 2016 by the government of Norway, the government of India, the Bill & Melinda Gates Foundation, the Wellcome Trust, and the World Economic Forum—is exploring and developing approaches for coordinating resources from a range of sources (eg, industry, governments, philanthropic organizations, NGOs) to advance the development of vaccines for EIDs, including filovirus infections ([CEPI 2016](#)). CEPI is primarily focused on funding and coordinating R&D activities up through phase 2 clinical trials and on the development of pilot vaccine stockpiles for use during future outbreaks. CEPI’s preliminary business plan for 2017 to 2021, however, also indicates that it will work with other organizations to

support additional clinical testing, approval of products for epidemic situations, and vaccine stockpiling and distribution ([CEPI 2016](#)).

One of CEPI's key participating organizations is Gavi, which is a public-private partnership created in 2000 to improve access to new and underused vaccines for children living in lower-income countries. Gavi receives direct contributions from donor governments and private-sector philanthropic organizations to support its mission. As noted above, Gavi entered into an advance purchase commitment with Merck to procure a stockpile of the rVSV-ZEBOV vaccine. Gavi could use this framework to support development of other Ebola or filovirus vaccines beyond phase 2 clinical trials. In addition, Gavi could play an important role in ensuring that stockpiles of Ebola or multivalent filovirus vaccines are procured and available on an ongoing basis; however, Gavi would need additional funding commitments from donors to support this role.

GSK has produced 300,000 doses of cAd3-EBOZ for emergency use but recently halted its vaccine development program owing to challenges of obtaining licensure and concerns about financial risks, given market uncertainties. As an alternative approach, GSK is proposing to create a permanent Biopreparedness Organization (BPO) that would develop new vaccines against EIDs and would operate on a no-profit, no-loss basis, with funding from outside sources. GSK made this proposal at the WHO 2nd Technical Workshop on ideas for potential platforms to support development and production of health technologies for priority infectious diseases, held in July 2016 ([GSK 2016](#); [WHO 2016j](#)). The BPO would be based at a GSK facility and would make its proprietary technologies available for use within the organization.

Johnson & Johnson is now reflecting on the best path forward for its monovalent Ebola vaccine, considering current uncertainties on the regulatory pathway and the remaining cost, time, and resources required to full development. This planning also is taking into account the ultimate aim to develop a multivalent filovirus vaccine; a candidate vaccine is currently being assessed in a phase 1 trial through a partnership with the NIH.

Lack of Regulatory Harmonization Among NRAs in Africa

Lack of harmonized dedicated regulatory pathways for authorizing the use of Ebola vaccines during an outbreak remains an important overarching preparedness gap. Several organizations and initiatives are in place to improve regulatory harmonization across Africa and streamline the approval process, although making progress in this area will take time, posing an important challenge for vaccine manufacturers for the foreseeable future. A key organization in this domain is the African Vaccine Regulatory Forum (AVAREF), which is a regional regulatory network founded by the WHO in 2006. The AVAREF promotes communication and collaboration between African NRAs and ethics committees and played an important role in advancing clinical trials of Ebola vaccines during the 2013-16 Ebola epidemic ([Akanmori 2015](#)). AVAREF has developed a new governance structure, strategy, and operating model, which will align with the African Medicines Regulatory Harmonization (AMRH) Initiative ([WHO 2016i](#)). The AMRH's goal is to establish the

African Medicines Agency, which will operate under the authority of the AMRH. According to the New Partnership for African Development ([NEPAD 2016](#)), the African Medicines Agency “will oversee the registration of a selected list of medicines and coordinate regional harmonization systems on the continent” ([NEPAD 2016](#)). This agency apparently will operate under a similar paradigm as the EMA in Europe.

Leadership and Coordination

We acknowledge the WHO for the many efforts it has undertaken in response to the 2013-16 Ebola crisis and for moving epidemic response preparedness forward, as evidenced by the WHO R&D Blueprint ([WHO 2016a](#)). While the agency has worked diligently and has had many successes toward improving public health preparedness for future Ebola epidemics, important gaps remain in finishing the job and ensuring that safe and effective multivalent filovirus vaccines are available as soon as possible.

Despite the WHO's leadership role, it is not in a position to manage and fund all of the complexities associated with bringing Ebola vaccines to market. While the WHO can generate guidance documents, lead collaborations, and convene stakeholders through workshops and other platforms, the organization lacks the authority and extensive resources necessary to surmount some of the biggest remaining challenges associated with Ebola vaccine development. The process of bringing Ebola and multivalent filovirus vaccines to market requires commitment and coordination from many different public and private stakeholders with varying agendas, expertise, and capabilities. In addition, the world faces a post-epidemic diminished sense of urgency for Ebola preparedness and a lack of “pull” from the governments of at-risk countries for vaccine development and delivery.

While the WHO can continue to offer critical leadership to ensure that Ebola preparedness remains an important priority across the globe, perhaps a focused consortium of key stakeholders may be able to offer a more concentrated effort necessary to keep Ebola preparedness on the international agenda of important public health concerns so that a crisis response to the next inevitable outbreak can be averted. This may require a designated Ebola vaccine “champion group” to synthesize a set of specific goals and responsibilities, set clear parameters regarding which vaccines will be prioritized for use and additional research during future outbreaks (in accordance with characteristics defined in the WHO Ebola vaccine TPPs), identify milestones in the overall strategy toward vaccine readiness, maintain the R&D process for Ebola or broader filovirus vaccines with other needed characteristics, manage risks and share costs, and monitor progress toward the overarching goal of Ebola public health preparedness.

Recommendations

The Ebola Vaccine Team B has generated the following high-level recommendations for the WHO and other appropriate international organizations, governmental agencies, and private companies to consider and resolve. Many of these recommendations need to be addressed to ensure that the global community has sustainable and readily available access to Ebola vaccines (including coverage for Marburg and Ebola Sudan viruses) that can be deployed whenever and wherever the need arises. Some of the issues identified here may be addressed through implementation of the WHO R&D Blueprint, but there currently is no single entity that has the authority, responsibility, and capability to move all of them forward and ensure successful completion of Ebola vaccine development. Also, details are lacking regarding how and by whom some of these issues are being addressed and what the expected outcomes are; further elaboration from the WHO on specific accomplishments or plans would assist in tracking progress.

1. ***Reassess the leadership structure for Ebola vaccine preparedness.*** While the WHO has made great strides toward moving Ebola vaccines forward, additional gaps remain. To address these gaps, consideration should be given to establishing a dedicated consortium focused on “championing” Ebola vaccines and resolving the remaining key issues related to global Ebola emergency preparedness (similar to what has been done with meningococcal and malaria vaccine initiatives). This group could represent a new public-private partnership that would operate independent of the WHO, but with WHO input and guidance.
2. ***Develop strategies for mitigating the financial uncertainties and risks for vaccine manufacturers.*** Financial uncertainty and risk is a critical barrier to innovative vaccine development, particularly for vaccines involving agents such as Ebola and other filoviruses, where a commercial market is unclear and minimal. This likely requires a novel public-private partnership model, possibly through CEPI, but the approach should go beyond phase 2 clinical trials up through the licensure and stockpiling process.
3. ***Address liability and indemnification issues for vaccine manufacturers.*** The WHO should continue to pursue a solution to this issue, as outlined in the WHO R&D Blueprint. Alternatively, a public-private partnership, such as CEPI, could assume responsibility for this activity and develop a plan for addressing these issues—for emergency use vaccines and for licensed vaccines. This may require establishment of a dedicated fund that provides financial support to cover potential liability costs.

4. ***Promote scientific collaboration to facilitate licensure of filovirus vaccines in situations for which it is not possible to generate clinical efficacy data.*** Multiple alternative pathways to support licensure without the possibility to generate efficacy data are highlighted in this document. However, important gaps in the regulatory science for Ebola vaccines remain. It is not clear, for example, what regulatory pathways are most suitable if clinical efficacy data cannot be obtained. Furthermore, all alternative pathways to licensure will rely to some extent on immunologic end points and efficacy data generated in animal models. Standardization of both immunologic assays and animal models would strongly facilitate assessment of the likelihood of different vaccine candidates to provide clinical benefit. Finally, further work is needed to ensure that multivalent vaccines are prioritized in future R&D efforts. The WHO and organizations such as CEPI should further stimulate collaboration between manufacturers, regulators, and academic experts to establish which data are required to support alternative regulatory pathways of filovirus vaccines, also taking into account the selection of animal models that best mimic the course of disease observed in humans following natural exposure.
5. ***Explore the feasibility of predeployment of any licensed Ebola vaccine.*** The decision to use vaccines prophylactically in advance of any outbreak requires data to support disease prevention, a favorable benefit-risk balance, and evidence demonstrating duration of the immune response—possibly including need and applicability of booster doses. Defining indications for use primarily lies within the purview of regulatory agencies. The issue of prophylactic use, however, has important public health implications that should be considered in the decision-making process. This work also should be aligned with GEVIT planning.
6. ***Clarify regulatory approval and policies for emergency use of unlicensed Ebola vaccines.*** This issue involves several components. First, clarification is needed to explain how EUAL status will affect regulatory review of a vaccine. Second, even with the new EUAL procedure, planning regarding emergency use of unlicensed vaccines remains an important preparedness gap for Ebola. Consideration should be given to developing a harmonized emergency use framework, approved by multiple regulatory authorities, that addresses regulatory approval and policies for emergency use of Ebola vaccines during outbreak settings.
7. ***Consider additional scenario-based planning for vaccination strategies in advance of future outbreaks.*** High-level vaccination strategies for prevention and control of future Ebola epidemics have not been clarified and could benefit from additional scenario-based planning or modeling. For example, under what scenarios would each of the primary vaccination strategies (ring vaccination, targeted vaccination of frontline workers, and regional population-based vaccination), or a combination of strategies, be used?

8. ***Plan for additional clinical trials.*** If one Ebola vaccine is licensed for use, criteria are needed to determine if and how other investigational vaccines would be used during future outbreaks. Additional clinical trials would likely be necessary for Ebola monovalent or multivalent vaccines not licensed and not approved for emergency use. Steps should be taken to ensure that such trials are ready to be implemented if another large Ebola outbreak occurs. This process should include addressing trial-related technical, ethical, financial, and social issues. This will require a collaborative effort among a number of key partners, including the WHO, African NRAs and ethics committees, manufacturers, and other stakeholders. Research priorities for additional clinical studies need to be clarified, along with prioritizations for which vaccines should be included in future clinical trials.

9. ***Create a set of policies around vaccine stockpiles.*** A number of important questions remain regarding funding, maintaining, deploying, and replenishing Ebola vaccine stockpiles. The WHO and other key stakeholders should implement an ICG approach for the stockpile; the ICG and appropriate partners should work collaboratively to address remaining questions and ensure that effective policies for stockpiling are developed and implemented. This set of policies should address stock management, storage, management of applications, and decision-making for how, and under what conditions, stockpiles will be used and who will make decisions for use. These policies should be mutually aligned with the GEVIT plans and tools.

10. ***Review the pharmacovigilance capabilities within at-risk countries and strengthen them as needed.*** Although the WHO has developed guidance on surveillance systems for monitoring adverse events following Ebola immunization, in-country capacity to conduct such surveillance may be limited. The WHO should continue, and enhance, its support of capacity assessment and capacity building in LMICs at risk for Ebola to ensure that such systems are functioning adequately when needed. The benefits of this support will go beyond Ebola preparedness toward enhancing overall public health infrastructure in the involved countries.

11. ***Develop protocols for post-licensure observational studies.*** After a vaccine is introduced, additional observational studies of vaccine effectiveness likely will be necessary. Protocols should be in place to conduct post-marketing studies to: (1) ensure that vaccine effectiveness is consistent with available efficacy data, (2) identify risk factors for vaccine failure, and (3) monitor for safety issues.

Appendix

Table 1. Summary of Published Data on Safety, Immunogenicity, and Efficacy of Current Ebola Vaccine Candidates

STUDY	SAFETY	IMMUNOGENICITY	EFFICACY
rVSV-ZEBOV (Merck)			
<p>Regules JA, Beigel JH, Paolino KM, et al. A recombinant vesicular stomatitis virus Ebola vaccine — preliminary report. <i>N Engl J Med</i> 2015 (published online Apr 1) [Full text]</p>	<p>Among 52 healthy adult participants in the US, no safety concerns were identified after low-dose (3×10^5 PFU) or high-dose (2×10^7 PFU) vaccination. The most common AEs were injection-site pain, myalgia, and fatigue. Transient VSV viremia was noted in all the vaccine recipients.</p>	<p>Immunogenicity, as measured by IgG ELISA, was concordant with antibody responses measured via functional (neutralization) assay. IgG ELISA results indicated a dose response: significantly higher IgG and neutralizing antibody levels were detected after single administration of the vaccine at the higher dose than at the lower dose.</p>	<p>Not designed to evaluate.</p>
<p>Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. <i>Lancet</i> 2015 Aug 29;386(9996):857-66 [Full text]</p> <p>Ebola ça suffit ring vaccination trial consortium. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. <i>BMJ</i> 2015 Jul 27;351:h3740 [Full text] (See footnotes for related commentary and correspondence.)</p>	<p>In an open-label, cluster-randomized ring vaccination trial, 90 clusters (4,394 adult participants) were enrolled in Guinea during the Ebola epidemic to receive immediate vaccination or delayed (21 days later) vaccination (via a single dose of 2×10^7 PFU). 43 serious AEs were reported, 1 of which (a febrile episode, which resolved without sequelae) was considered to be vaccine-related.</p>	<p>Not evaluated.</p>	<p>In an interim analysis of data from the 90 clusters, 16 cases of EVD from 7 clusters were reported in the observation period in 42 clusters (2,380 people) assigned to delayed vaccination, compared with no cases in the 48 clusters (2,014 people) who received immediate vaccination, yielding a point estimate of 100% efficacy (95% CI, 74.7%-100.0%; $P = 0.0036$). No new cases of EVD were diagnosed in vaccinees from the immediate or delayed groups from 6 days post-vaccination.</p>
<p>Huttner A, Dayer J-A, Yerly S, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. <i>Lancet Infect Dis</i> 2015 Oct;15(10):1156-66 [Full text] (Note: this paper focuses on safety and immunogenicity data from the Swiss trial, one of four trials included in the report by Agnandji et al, 2016, below.)</p>	<p>In the Swiss cohort (in which high-dose rVSV-ZEBOV vaccination led to detectable viremia in almost all vaccinees and viral dissemination with secondary arthritis in up to 22% of vaccinees), dose reduction from 10^7 PFU or greater to 3×10^5 PFU reduced the occurrence and magnitude of viremia and reactogenicity, but did not prevent vaccine-induced arthritis, dermatitis, or vasculitis.</p>	<p>The data also show a dose effect on the immunogenicity of rVSV-ZEBOV. Titers of EBOV-GP-binding and neutralizing antibodies were significantly weaker in low-dose (3×10^5 PFU) recipients.</p>	<p>Not designed to evaluate.</p>

<p>Agnandji ST, Huttner A, Zinser ME, et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe. <i>N Engl J Med</i> 2016 Apr 28;374(17):1647-60 [Full text] (<i>A preliminary version of this paper was published Apr 1, 2015.</i>)</p>	<p>Among 158 healthy adults in 4 trials in Gabon, Kenya, Germany, and Switzerland, no serious vaccine-related AEs were reported. However, a safety-driven study hold was implemented in the Swiss cohort, following preliminary data indicating that among participants vaccinated with at least 1×10^7 PFU, 11/51 (22%) developed oligoarthritis, with pain lasting a median of 8 days. The Swiss trial resumed using a lower dose (3×10^5 PFU). Follow-up data indicated that the unexpected viral dissemination in skin and joints, mostly identified in the Swiss cohort, could persist for up to 2 to 3 weeks; at 6 months, 10/11 participants with arthritis were symptom-free.</p>	<p>Vaccine-induced Ebola-Zaire GP-specific antibody responses were detected in all participants at all doses ranging from 3×10^5 PFU to 5×10^7 PFU, with similar GP-binding antibody titers but significantly higher neutralizing antibody titers at higher doses. GP-binding antibody titers were sustained through 180 days in all participants.</p>	<p>Not designed to evaluate.</p>
<p>Goldstein S, Samai M, Fofanah A-B, and the STRIVE Study Team. The Sierra Leone trial to introduce a vaccine against Ebola (STRIVE): evolution of a clinical trial during an outbreak (Abstract 131), presented at IDWeek, Oct 27, 2016, New Orleans. <i>Open Forum Infect Dis</i> (Fall 2016);3(suppl 1) [Abstract]</p>	<p>Among more than 8,000 healthcare and frontline Ebola response workers in Sierra Leone vaccinated during the epidemic, no serious AEs were reported during 6 months of follow-up.</p>	<p>Evaluation of baseline seroprevalence and immune response to vaccination is ongoing among ~500 of the study participants enrolled in an immunogenicity sub-study.</p>	<p>VE could not be evaluated, given the declining incidence of EVD during the study period and changes to the study protocol based on outcome data from Henao-Restrepo et al, 2015, above.</p>
<p>Henao-Restrepo AM, Camacho A, Longini IM, et al. [2016a] Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). <i>Lancet</i> 2016 (published online Dec 23) [Full text] (<i>Final analysis of the clinical trial reported in preliminary form by Henao-Restrepo et al, 2015, listed above.</i>)</p>	<p>Among 5,837 participants (5,643 adults and 194 children) in Guinea, 53.0% reported at least 1 AE within 14 days of vaccination; these were typically mild (eg, headache, fatigue, and/or muscle pain). Of 80 serious AEs identified, 2 were judged to be related to vaccination (1 febrile reaction and 1 anaphylaxis), and 1 was possibly related (influenza-like illness); all 3 resolved without sequelae. Overall, the data indicate no safety concerns in adults or children.</p>	<p>Not evaluated.</p>	<p>In this final report of the <i>Ebola Ça Suffit!</i> clinical trial in Guinea during the West Africa Ebola epidemic, the inclusion of data from 27 additional clusters supports the authors' interim estimates and conclusions regarding VE (Henao-Restrepo et al, 2015). Final data from all trial clusters showed that at 10 days or more after randomization, there were no cases of EVD among immediately vaccinated contacts and contacts of contacts, ie, 100% protection.</p>
cAd3-EBO-Z (GlaxoSmithKline) with or without MVA-BN-Filo (Bavarian Nordic)			
<p>Ledgerwood JE, DeZure AD, Stanley DA, et al. Chimpanzee adenovirus vector Ebola vaccine – preliminary report. <i>N Engl J Med</i> 2014 (published online Nov</p>	<p>Among 20 healthy adults in the US, no serious AEs were reported in 4 weeks of follow-up; transient fever developed within 1</p>	<p>Reactogenicity and immune responses to single vaccination with cAd3-EBO (bivalent) were dose-dependent. GP-</p>	<p>Not designed to evaluate.</p>

<p>26) [Full text] (See footnotes for related correspondence.)</p>	<p>day after vaccination in 2 participants who had received the higher of the two doses (2×10^{11} pu); no fevers developed after vaccination with the lower dose (2×10^{10} pu).</p>	<p>specific antibodies were induced in all 20 participants, with higher titers in the group receiving the higher vaccine dose. CD4 and CD8 T-cell responses were also more frequent among those who received the higher dose.</p>	
<p>Tapia MD, Sow SO, Lyke KE, et al. Use of ChAd3-EBO-Z Ebola virus vaccine in Malian and US adults, and boosting of Malian adults with MVA-BN-Filo: a phase 1, single-blind, randomised trial, a phase 1b, open-label and double-blind, dose-escalation trial, and a nested, randomised, double-blind, placebo-controlled trial. <i>Lancet Infect Dis</i> 2016 Jan;16(1):31-42 [Full text]</p>	<p>Among 91 adults in Mali and 20 adults in the US, no safety concerns were identified within 7 days of follow-up for either vaccine at any of the doses evaluated; most AEs were mild (eg, fever lasting less than 24 hours or injection-site pain or tenderness), with no unexpected serious adverse reactions suspected.</p>	<p>A single 1×10^{11} pu dose of cAd3-EBO-Z elicited strong anti-GP antibody responses in all participants, suggesting that it could suffice for phase 3 efficacy trials of ring-vaccination containment needing short-term, high-level protection to interrupt Ebola virus transmission. MVA-BN-Filo booster vaccine given 11 to 16 weeks after priming with cAd3-EBO-Z was strongly immunogenic (as measured by antibody and T-cell responses), potentially conferring long-term protection to subgroups (eg, healthcare and frontline workers)</p>	<p>Not designed to evaluate.</p>
<p>De Santis O, Audran R, Pothin E, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. <i>Lancet Infect Dis</i> 2016 Mar;16(3):311-20 [Full text] (See footnotes for related commentary.)</p>	<p>Among 120 healthy adults in Switzerland, no vaccine-related serious AEs were reported during 6 months of follow-up. Most reported AEs were mild and self-limited, arising during the first 24 hours after injection and lasting less than 48 hours; 7 grade 3 AEs were recorded, and all resolved within 3 days without residual effects.</p>	<p>Results showed that vaccination induced an Ebola virus-specific antibody response and polyfunctional CD8-specific T-cell response; a single vaccination with monovalent cAd3-EBO-Z induced antibody responses in 96% of participants, independently of the dose and follow-up at 6 months showed that antibody titers were maintained at a significantly increased concentration.</p>	<p>Not designed to evaluate.</p>
<p>Ewer K, Rampling T, Venkatraman N, et al. A monovalent chimpanzee adenovirus Ebola vaccine boosted with MVA. <i>N Engl J Med</i> 2016 Apr 28;374(17):1635-46 [Full text] (Preliminary version published Jan 28, 2015, at nejm.org as: Rampling T, Ewer K, Bowyer G, et al. A monovalent chimpanzee adenovirus Ebola vaccine—preliminary report.)</p>	<p>Among 60 healthy adults in the UK, no safety concerns were identified at any dose level or interval evaluated for cAd3-ZEBOV or MVA. Most AEs were self-limited and mild. Local pain was the most common local AE (with 1 case reported as severe). Moderate systemic AEs were fever, myalgia, arthralgia, headache, fatigue, nausea, and</p>	<p>The cAd3 vaccine boosted with MVA elicited B-cell and T-cell immune responses to ZEBOV that were superior to those induced by the cAd3 vaccine alone. Antibody responses remained positive 6 months after vaccination above a threshold associated with efficacy in humans. A 1-week interval between</p>	<p>Not designed to evaluate.</p>

	malaise. No severe systemic solicited AEs were reported.	administration of the prime and booster vaccines provided CD8+ T-cell immunogenicity 2 weeks after the prime dose.	
rVSV-ZEBOV (Merck) or cAd3-EBOZ (GlaxoSmithKline)			
Bolay F, for the Partnership for Research on Ebola Vaccines in Liberia (PREVAIL 1) Team. A randomized controlled trial of the safety and immunogenicity of two Ebola vaccines (Abstract 76LB), presented at the Conference on Retroviruses and Opportunistic Infections (CROI), Feb 22-25, 2016, Boston [Abstract]	Among 1,500 adults (5.2% of whom were HIV+) in Liberia during the Ebola epidemic randomized to rVSV-ZEBOV, cAd3-EBO, or a placebo, “differences with placebo in injection site reactions, targeted symptoms (headache, muscle pain, feverishness, fatigue) and lymphocyte counts were noted at week 1, but not month 1 for both vaccines.”	“Antibodies, measured using the FANG ELISA assay for 50% of participants, show that 8% had an antibody response to Ebola at baseline. Excluding these individuals, an antibody response at month 1 was noted in >85% of participants in each of the vaccine arms and <10% of participants in the placebo arm (p<0.001).”	VE could not be evaluated, given the declining incidence of EVD during the study period.
Ad26.ZEBOV (Johnson & Johnson) with MVA-BN-Filo (Bavarian Nordic)			
Milligan ID, Gibani MM, Sewell R, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia Ankara-vectored Ebola vaccines: a randomized clinical trial. JAMA 2016 Apr 19;315(15):1610-23 [Full text]	Among 87 healthy adult participants in the UK, no Ad26.ZEBOV (monovalent) or MVA-BN-Filo (multivalent) vaccine-related serious AEs occurred.	More than 90% of participants generated Ebola GP-specific IgG 4 weeks after a priming dose of Ad26.ZEBOV, and 55% (95% CI, 35%-74%) developed specific T cells; these responses were enhanced by administration of an MVA-BN-Filo booster dose and were sustained at 8 months after the prime vaccination.	Not designed to evaluate.
Ad5-EBOV (Tianjin CanSino Biotechnology)			
Zhu FC, Hou LH, Li JX, et al. Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomised, double-blind, placebo-controlled, phase 1 trial. Lancet 2015 Jun 6;385(9984):2272-9 [Full text]	Among 120 healthy adult participants in China, 19/40 in the placebo group, 27/40 in the low-dose group, and 36/40 in the high-dose group ($P = 0.0002$) reported at least one solicited AE within 7 days of vaccination, most commonly, mild pain at the injection site, with a significantly higher incidence of pain at the injection site in the high-dose group. No serious AEs recorded during 28-day follow-up.	<i>Vaccine-matched 2014 Zaire Ebola GP-specific humoral response:</i> 95% in the low-dose group and 100% in the high-dose group showed significant increase by day 14 and continued to increase up to day 28. <i>T-Cells (CD4 or CD8):</i> responses peaked at day 14. Both types of immune responses were partly blunted by the presence of pre-existing anti-adenovirus type-5 immunity, especially in the low-dose group; high-dose vaccine could overcome the negative effects of preexisting adenovirus type-5 immunity.	Not designed to evaluate.

<p>Zhu FC, Wurie AH, Hou LH, et al. Safety and immunogenicity of a recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in Sierra Leone: a single-centre, randomised, double-blind, placebo-controlled, phase 2 trial. <i>Lancet</i> 2016 (published online Dec 22) [Full text]</p>	<p>Among 500 healthy adults in Sierra Leone, 54/125 in the placebo group, 60/125 in the low-dose vaccine group, and 132/250 in the high-dose vaccine group reported at least one solicited AE within 7 days of vaccination; most AEs were mild and self-limiting. Solicited injection-site AEs were significantly more frequent in vaccine recipients than in those receiving placebo. Three serious AEs (malaria, gastroenteritis, and a fatal asthma episode) were reported in the high-dose vaccine group, but none was deemed related to the vaccine.</p>	<p>Vaccine recipients had high humoral immune responses of GP-specific antibodies that peaked at day 28 and decreased significantly by 85% at day 168 following injection. High- and low-dose vaccine participants showed no difference in post-vaccination antibody responses. T-cell immune responses to vaccination were not measured.</p>	<p>Not designed to evaluate.</p>
<p>Li JX, Hou LH, Meng FY, et al. Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial. <i>Lancet Glob Health</i> 2016 (published online Dec 22) [Full text]</p>	<p>Reporting on follow-up data from the preliminary study by Zhu et al, 2015 (above), 120 healthy adults in China were re-recruited to receive at month 6 a homologous booster at the same low or high dose as the initial vaccine or placebo; both groups who received vaccine showed significantly higher incidence of mild or moderate AEs than the placebo group. No severe safety concerns were raised; 2 serious AEs were reported (pneumonia and duodenal ampulla ulcers), both of which resolved after treatment and were deemed unrelated to the vaccination.</p>	<p>Vaccination with a second dose of the same vaccine (homologous prime-boost regimen) at a 6-month interval elicited greater GP-specific antibody responses with longer duration, compared with a single prime dose alone. Effects of the homologous booster vaccination at 6-month interval on T-cell immunogenicity were relatively weak.</p>	<p>Not designed to evaluate.</p>
<p>Abbreviations: AE, adverse event; CI, confidence interval; EVD, Ebola virus disease; ELISA, enzyme-linked immunosorbent assay; GP, glycoprotein; PU, particle unit; PFU, plaque-forming unit; VE, vaccine efficacy</p>			
<p>Related commentary and correspondence on Henao-Restrepo et al, 2015</p> <ul style="list-style-type: none"> o Krause PR. Interim results from a phase 3 Ebola vaccine study in Guinea. <i>Lancet</i> 2015 Aug 29;386(9996):831-3 [Full text] o Ledgerwood JE. Use of low dose rVSV-ZEBOV: safety issues in a Swiss cohort. <i>Lancet Infect Dis</i> 2015 Oct;15(10):1117-9 [Full text] o Fitzgerald F, Yeung S, Gibb DM, et al. Ebola vaccination. (Letter) <i>Lancet</i> 2015 Dec 19;386(10012):2478 [Full text] o Longini IM, Egger M, Dean NE, et al. Authors' reply. <i>Lancet</i> 2015 Dec 19;386(10012):2480 [Full text] o Zhang Y, Feng S, Cowling BJ. Changes in the primary outcome in Ebola vaccine trial. (Letter) <i>Lancet</i> 2016 Apr 9;387(10027):1509 [Full text] o Kieny MP, Longini IM, Henao-Restrepo AM, et al. Authors' reply. <i>Lancet</i> 2016 Apr 9;387(10027):1509-10 [Full text] <p>Related commentary on Henao-Restrepo et al, 2016a</p> <ul style="list-style-type: none"> o Geisbert TW. First Ebola virus vaccine to protect human beings? <i>Lancet</i> 2016 (published online Dec 22) [Full text] <p>Related correspondence on Ledgerwood et al, 2014</p> <ul style="list-style-type: none"> o Zhang Q, Seto D. Chimpanzee adenovirus vector Ebola vaccine—preliminary report. (Letter) <i>N Engl J Med</i> 2015 Aug 20;373(8):775-6 [Full text] o Ledgerwood JE, Sullivan NJ, Graham BS. Author's reply. <i>N Engl J Med</i> 2015 Aug 20;373(8):775-6 [Full text] 			

Related commentary on De Santis et al, 2016

- **Falzarano D.** Ebola vaccines: we have options. *Lancet Infect Dis* 2016 Mar;16(3):267-8 [[Full text](#)]

Related commentary on Zhu et al, 2016

- **Grobusch MP, Goorhuis A.** Safety and immunogenicity of a recombinant adenovirus vector-based Ebola vaccine. *Lancet* 2016 (published online Dec 22) [[Full text](#)]

Table 2. Clinical Trials of Ebola Vaccines, Currently Active as Listed in Clinical Trials Registries (as of December 2016)

VACCINE CANDIDATE	CLINICAL TRIAL TITLE	ID NUMBER	STATUS
rVSVN4CT1-EBOVGP1 (VesiculoVax)	Trial to Evaluate Safety and Immunogenicity of an Ebola Zaire Vaccine in Healthy Adults	NCT02718469	Active, not recruiting
INO-4212 INO-9012	Open-Label Study of INO-4212 With or Without INO-9012, Administered IM or ID Followed by Electroporation in Healthy Volunteers	NCT02464670	Recruiting
rVSV-ZEBOV, ChAd3-EBOZ	Partnership for Research on Ebola Vaccines in Liberia (PREVAIL)	NCT02344407	Active, not recruiting
cAd3-EBO and/or MVA	Clinical Trial of Ebola Vaccines cAd3-EBO, cAd3-EBOZ and MVA-EbolaZ in Healthy Adults in Uganda	NCT02354404	Active, not recruiting
	A Phase I Study to Assess Ebola Vaccines cAd3-EBO Z and MVA-EBO Z	NCT02451891	Active, not recruiting
	A Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Children	NCT02548078	Active, not recruiting
	A Study to Evaluate the Safety and Immunogenicity of a Candidate Ebola Vaccine in Adults	NCT02485301	Active, not recruiting
	Ebola CVD-Mali #2000 (Bivalent) VRC-EBOAdc069-00-yp (cAd3-EBO)	NCT02368119	Active, not recruiting
	Safety, Tolerability, and Immunogenicity of the Ebola Chimpanzee Adenovirus Vector Vaccine (cAd3-EBO), VRC-EBOADC069-00-VP, in Healthy Adults	NCT02231866	Active, not recruiting
	VRC 208: Dose, Safety and Immunogenicity of a Recombinant Modified Vaccinia Virus Ankara Ebola Vaccine, VRC-EBOMVA079-00-VP (MVA-EbolaZ), Administered Alone or as a Boost to cAd3-Ebola Vaccines in Healthy Adults	NCT02408913	Active, not recruiting
	A Study to Assess New Ebola Vaccines, cAd3-EBO Z and MVA-BN Filo	NCT02240875	Recruiting
	Phase 1 Trial of Ebola Vaccine in Mali	NCT02267109	Active, not recruiting
rVSV-ZEBOV-GP	Ebola Vaccine Ring Vaccination Trial in Guinea	PACTR201503001057193	Not recruiting, immunogenicity analyses ongoing
	Evaluation of the Safety and Immunogenicity of Three Consistency Lots and a High-Dose Lot of rVSV-ZEBOV-GP (V920 Ebola Vaccine) in Healthy Adults (V920-012)	NCT02503202	Active, not recruiting
	A Study to Find Out if the New Ebola Vaccine is Safe and Stimulates Immunity That Might Protect Adults in Kilifi, Kenya.	NCT02296983	Active, not recruiting
	Immunogenicity of Recombinant Vesicular Stomatitis Vaccine for Ebola-Zaire (rVSV[Delta]G-ZEBOV-GP) for Pre-Exposure Prophylaxis (PREP) in People at Potential Occupational Risk for Ebola Virus Exposure	NCT02788227	Recruiting
	STRIVE (Sierra Leone Trial to Introduce a Vaccine Against Ebola)	NCT02378753 PACTR201502001037220	Active, not recruiting
	Immune Durability After VSV-EBOV Vaccination	NCT02933931	Not yet recruiting
rVSV-ZEBOV-GP, Ad26.ZEBOV, MVA-BN-Filo	Partnership for Research on Ebola VACCinations (PREVAC)	NCT02876328	Not yet recruiting
Ad26.ZEBOV, MVA-BN-Filo	Long-term Safety Follow-up of Participants Exposed to the Candidate Ebola Vaccines Ad26.ZEBOV and/or MVA-BN-Filo	NCT02661464	Recruiting
	Safety, Tolerability and Immunogenicity Study of 3 Prime-boost Regimens for Ebola Vaccines Ad26.ZEBOV/MVA-BN-Filo in Healthy Adults, Children and Human Immunodeficiency Virus Positive (HIV+) Adults	NCT02564523	Recruiting

	MVA-BN-Filo and Ad26.ZEBOV Vaccines in Healthy Volunteers	NCT02891980	Not yet recruiting
	Safety, Tolerability and Immunogenicity Study of 2 Prime-boost Regimens for Ebola Vaccines Ad26.ZEBOV/MVA-BN-Filo	NCT02598388 PACTR201608001734218	Recruiting
	A Safety and Immunogenicity Study of Heterologous and Homologous Prime-Boost Ebola Vaccine Regimens in Healthy Participants	NCT02325050	Active, not recruiting
	Staged Phase 3 Study to Assess the Safety and Immunogenicity of Ebola Candidate Vaccines Ad26.ZEBOV and MVA-BN-Filo During Implementation of Stages 1 and 2 (EBOVAC-Salone)	NCT02509494	Recruiting
	A Study to Assess Safety Tolerability and Immunogenicity of Three Prime-boost Regimens of the Candidate Prophylactic Vaccines for Ebola in Healthy Adults	NCT02416453	Recruiting
	A Study to Evaluate the Immunogenicity, Safety and Tolerability of Ad26.ZEBOV and MVA-BN-Filo in Healthy Adult Participants	NCT02543268	Active, not recruiting
Ad26.Filo, MVA-BN-Filo	A Study to Evaluate Safety, Tolerability, and Immunogenicity of Heterologous Prime-boost Regimens Using the Multivalent Filovirus Vaccines Ad26.Filo and MVA-BN-Filo Administered in Different Sequences and Schedules in Healthy Adults	NCT02860650	Recruiting
cAd3-EBO-Z, Ad26.ZEBOV	A Study to Assess Ebola Vaccines ChAd3-EBO-Z and Ad26.ZEBOV	NCT02495246	Active, not recruiting
GamEvac	Open Study of the Duration of Immunity After Vaccination With GamEvac-Combi	NCT02911415	Recruiting
	Open Study of the Duration of Immunity After Vaccination With GamEvac	NCT02911428	Recruiting
HPIV3-EbovZ GP	Evaluating the Safety of and Immune Response to a Human Parainfluenza Virus Type 3 Ebola Virus Vaccine (HPIV3-EbovZ GP) in Healthy Adults	NCT02564575	Active, not recruiting
Sources: NIH. ClinicalTrials.gov database [Web site]; WHO. International Clinical Trials Registry Platform [Web site]; PACTR. Pan African Clinical Trials Registry [Web site]			

Table 3. Overview of Key Procedures Relevant to Ebola Vaccine Licensure Pathways, Regulatory Review, Unlicensed Use, and Purchasing

Summarized here for general reference only; please refer to FDA, EMA, and WHO Web sites and sources listed below for complete, detailed information on these procedures.

Authority	Procedure	Assessment	Outcome
US Food and Drug Administration (FDA)	<i>Traditional Approval</i>	Demonstration of safety and effectiveness against clinical disease (or based on immunogenicity studies if a well-established correlate of protection is available), and ability to meet applicable manufacturing requirements	Licensure
	<i>Accelerated Approval</i>	Demonstration of effectiveness based on a surrogate end point that is reasonably likely to predict clinical benefit; ability to meet applicable manufacturing requirements; demonstration of clinical safety	Licensure with a requirement for adequate and well-controlled post-marketing studies to verify and describe clinical benefit during a current or future outbreak
	<i>Approval via the Animal Rule</i>	Clinical safety data, ability to meet applicable manufacturing requirements, and demonstration of reasonable likelihood to predict clinical benefit, based on adequate and well-controlled efficacy studies in relevant animal models, provided that clinical efficacy studies are not feasible or ethical and no other approval pathway is feasible	Licensure with a requirement for post-marketing field studies when feasible and ethical during a current or future outbreak to verify clinical benefit
	<i>Emergency Use Authorization (EUA)*</i>	Assessment that the known and potential benefits outweigh the known and potential risks of the vaccine, in the absence of an adequate, approved, and available alternative product	Authorized use of an unapproved vaccine during an HHS-declared or potential public health emergency affecting the health and security of US citizens living abroad
Example of FDA Process to Expedite Development and Review	<i>Breakthrough Therapy Designation</i>	Preliminary clinical evidence that indicates substantial improvement over existing interventions on one or more clinically significant end points	Potential for expedited development and review
European Medicines Agency (EMA)	<i>Marketing Authorization</i>	Demonstration of safety and efficacy against clinical disease; compliance with quality and manufacturing requirements per European Union (EU) law	Authorization for use within the EU (if the centralized procedure is used, which is mandatory for certain vaccines such as viral-vectored vaccines)
	<i>Conditional Marketing Authorization</i>	Data on safety and efficacy of products sufficient for establishing a positive benefit/risk balance, despite the lack of a comprehensive clinical data package; compliance with quality and manufacturing requirements per EU law; possible use in public health emergencies; can be converted to a “standard” marketing authorization if the required data confirm its efficacy, safety, and positive benefit/risk balance	Annually renewable authorization, subject to requirements for provision of post-authorization data within an agreed timeframe; could include collecting data during future outbreaks
	<i>Marketing Approval Under Exceptional Circumstances</i>	Safety and efficacy of products deemed to provide a sufficiently positive benefit/risk ratio, when comprehensive data on efficacy and/or safety cannot be generated under normal conditions due to feasibility concerns (eg, rarity of the disease or ethical concerns); compliance with quality and manufacturing requirements per EU law	Marketing authorization subject to requirements for provision of post-authorization data, which could include collecting data during future outbreaks; annual reassessment of the benefit/risk balance; dossier expected to remain non-comprehensive and therefore not expected to convert to a “standard” marketing authorization

	<i>Article 58, in Collaboration with the EU and WHO</i>	Quality, safety, and efficacy of products for human use exclusively outside the EU (using the same standard as for use within the EU) to prevent or treat diseases of major public health interest, applicable to vaccines against a WHO-designated “public health priority disease” or part of a WHO-managed stockpile for emergency response	Scientific opinion to support national marketing authorization in targeted countries; may be subject to requirements for provision of post-authorization data, including data collected during a future outbreak
Examples of EMA Processes to Expedite Development and Review	<i>Accelerated Assessment</i>	Restricted to products of “major public health interest” representing therapeutic innovation	Marketing authorization within 150 days
	<i>Priority Medicines (PRIME) Designation</i>	Enhanced provision of scientific advice and assessment to optimize the generation of robust data on benefits and risks and speed up evaluation of products that target an unmet medical need	Eligibility for accelerated assessment when applying for marketing authorization
World Health Organization (WHO)	<i>Emergency Use Assessment and Listing</i>	Demonstration of reasonable likelihood of vaccine safety, quality, effectiveness; the benefits of the vaccine outweigh the foreseeable risks and uncertainties in the context of a WHO-designated public health emergency of international concern (PHEIC) in the absence of an available licensed vaccine; and the vaccine is manufactured in compliance with Good Manufacturing Practice (GMP) standards	Assessment, based on available quality, safety, and efficacy data, of whether the use of a specific vaccine is acceptable in the context of a public health emergency on a time-limited basis while further data are being gathered and evaluated; the relevant national authorities retain responsibility for authorizing the use of any Emergency Use Assessment and Listing (EUAL)-approved vaccines in their countries.
	<i>Prequalification</i>	Initial evaluation and reassessment of a licensed vaccine at regular intervals thereafter to assess: vaccine quality (eg, production process and quality control methods; international GMP compliance; compliance with specifications; complaints monitoring; assurance of data to support product safety, efficacy, and country program suitability); and programmatic suitability for use	Support for purchasing decisions by vaccine procurement agencies (eg, UNICEF, Gavi), based on determination that a licensed vaccine meets global standards of quality, safety, and efficacy
<p>*According to the FDA, making an Ebola vaccine candidate available to persons at risk from Ebola disease under an EUA would require a determination by the Secretary of Health and Human Services of a public health emergency or a significant potential for a public health emergency that affects, or has a significant potential to affect, national security or the health and security of US citizens living abroad. The criteria for issuance of an EUA are: (1) the agent can cause a serious or life-threatening disease or condition; (2) based on the totality of evidence, including from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in preventing such disease or condition; (3) the known and potential benefits of the use of the product outweigh the known and potential risks of the product; and (4) there is no adequate, approved, and available alternative to the product for preventing such disease or condition. Informed consent and ethics review are not required. However, to the extent practicable under the emergency circumstances, authorization for use should include conditions to protect recipients.</p>			
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