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CIDRAP
Center for Infectious Disease Research & Policy
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Fast-Track Development of Ebola Vaccines

Principles and Target Product Criteria

January 12, 2015

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The unprecedented morbidity and mortality from the 2013-2015 Ebola virus disease (EVD) epidemic in West Africa has challenged every aspect of our global ability to effectively detect, respond to, and control such a rapidly emerging infectious disease crisis. As the epidemiology of the EVD epidemic has become more apparent over recent months, it is clear that Ebola virus transmission can be reduced by employing traditional public health measures such as contact tracing and infection control practices aimed at barrier protection. Nonetheless, the potential for this epidemic to become an endemic situation, where ongoing virus transmission in West Africa occurs in the foreseeable future, is a real and very concerning possibility. As long as Ebola virus continues to be transmitted to humans by humans in these countries, the potential for sudden bursts of localized virus transmission will exist, and the risk of the Ebola virus expanding its range to other countries must be considered.

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

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

The Wellcome Trust–CIDRAP Team B includes 26 international subject matter experts involved in one or more areas of vaccine work. The first comprehensive report of Team B will be released later this month. In the meantime, we provide here an interim report: “Fast-Track Development of Ebola Vaccines: Principles and Target Product Criteria.” We hope this expert framework will serve as a “living document” and help accelerate the availability of effective and safe Ebola vaccines. Immediate consideration of the issues highlighted is critical to help bring an end to this epidemic and better prepare the world for inevitable future Ebola epidemics.

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Principles for Development and Distribution of Ebola Vaccines

The current, unprecedented EVD epidemic in West Africa requires an equally unprecedented public-private effort to develop vaccines that could be used in different scenarios: (1) to curtail the current epidemic, (2) to address the current or future potential of Ebola becoming endemic, and (3) to be deployed for reactive use during future outbreaks or for use in prophylactic vaccination campaigns, as appropriate to the future epidemiology of the disease. To bring Ebola vaccines to market, which is clearly in the greater common good given the global consequences of this epidemic, extreme measures are needed to ensure a massive coordinated effort among vaccine manufacturers, government regulatory authorities, government public health agencies, non-governmental organizations, and global, national, and local leaders. In considering the current situation, whereby new vaccines are being tested and will potentially be brought to market in West Africa and possibly elsewhere, a number of principles can be applied to support the process. Some are specific to the conditions of the current epidemic, and some also apply to future use of Ebola vaccines.

Lessons learned from the West Africa experience can be applied to future Ebola control efforts well in advance of outbreaks and can also provide a model for other emerging diseases, with a focus on preparedness, responsiveness, and rapid early engagement. Furthermore, this incident can serve as a catalyst for changing the international community's approach to major regional epidemics or pandemics in the 21st century.

These principles are intended to provide an ongoing framework that supports current endeavors and fosters useful dialogue as the process moves forward. This will serve as a "living document" that will be revised and refined as more information becomes available and additional input is sought and obtained.

1. Possible Changing Epidemiology of Ebola Virus

The epidemiology of Ebola virus in the 21st century may look very different from that seen during the latter half of the 20th century; if so, the West Africa Ebola epidemic could be a harbinger of things to come. The global public health community must therefore prepare for a number of different future Ebola-related scenarios ranging from small, infrequent focal outbreaks to large epidemics affecting major metropolitan areas and wide geographic regions. Furthermore, ongoing studies are needed to enhance our understanding of the epidemiology and ecology of Ebola virus. Vaccination will likely play a key role in the future control of EVD, complementing and strengthening existing public health measures known to interrupt transmission of Ebola virus. A sustained effort, therefore, is necessary to make Ebola vaccines a reality. In addition, one vaccine may not fit all potential scenarios, so ongoing research and development will be critical to overall long-term success in combatting this serious disease.

2. Sustained Funding for Ebola Vaccines

Ebola vaccine development and deployment will require a strong public-private sector partnership and commitment, because the scope of the effort is too complex for any single government, organization, or company. Sufficient and sustained funding is required on a long-term basis throughout the lifecycle of Ebola vaccines from development, licensure, manufacture, and delivery to post-market surveillance and maintenance of a strategic stockpile for future use. Public attention may recede from the current crisis in West Africa, but the likelihood of disease and death from future Ebola outbreaks will not. Therefore, a strategy for integrated global funding should be considered, particularly given the World Health Organization's (WHO's) authority to monitor global health and to declare a public health emergency of global importance. This approach—to triage the current situation and fill key gaps in a sustainable way—could serve as a roadmap for response to other emerging infectious disease threats.

3. Community Engagement

Community engagement will require careful attention throughout the full spectrum of Ebola vaccine efforts and should be interpreted broadly to include local traditional, cultural, religious, and community leadership among affected populations; universities, teaching hospitals, and healthcare workers in the field; and ministries of health. To be successful, vaccination campaigns should be part of a multifactorial approach that is unique and appropriate to each country affected by the disease (during this epidemic or in future scenarios). In the current situation, specific strategies will depend on vaccine characteristics and targeted populations; these factors should be communicated through the appropriate channels (ie, the WHO, the United Nations Children's Fund [UNICEF], Médecins Sans Frontières [MSF], Red Cross and Red Crescent, and others) as quickly as possible to affected countries so that realistic plans can be developed. Community engagement activities need to be implemented from the start and in parallel with all other efforts so involved communities are part of the process and develop ownership regarding outcomes. In addition, community engagement efforts must be ongoing during interepidemic periods.

Past experience—both negative and positive—with other vaccination campaigns in Africa (such as yellow fever, measles, meningococcal A meningitis, and polio) should be reviewed and used to inform development of robust community engagement strategies for Ebola vaccination that can be put in place as quickly as possible in West Africa. For example, the role of the WHO in providing leadership during planning and triage for meningococcal A vaccination campaigns across the "meningitis belt" has been critical to the success of that effort.

4. Ethics and Regulatory Oversight

Closely tied with community engagement efforts, ethics oversight before and during the Ebola vaccine clinical trials and eventual vaccination strategy will require bolstering in areas where ethics and regulatory structures have been depleted because of civil warfare, disease, or other factors. Engagement of local ethics and regulatory expertise is of the highest priority, followed by assistance from experts within Africa or from outside experts as requested by affected countries. To ensure consistent, structured ethical oversight of the clinical-trial process and implementation of vaccination strategies in Ebola-affected countries, the global community should provide adequate resources to achieve this goal. Such resources may include training to build local capacity and technology transfer, as well as funding for travel and information technology resources needed by experts from outside the affected countries.

5. Inclusion of Candidate Vaccines in Clinical Trials

Selection of vaccine candidates for randomized controlled clinical trials of efficacy determination should be based on a set of minimum criteria: evidence of functional immunogenicity, relative safety as demonstrated in phase 1 trials, and availability (adequate manufacturing capability and capacity to rapidly deliver sufficient product to West African countries affected by the Ebola epidemic). Other desirable (but not essential) characteristics include easy route of administration, simple dosing schedule, and manageable cold-chain requirements. Any candidate vaccine, regardless of funding status or proprietary ownership, that meets this set of minimum criteria should be included in plans for phase II/III clinical trials in West Africa. As part of this process, legal issues around intellectual property need to be addressed that allow for development of a rapid-response product for global use that employs technologies developed within the competitive marketplace of developed countries.

6. Clinical Trial Design

Planning for Ebola vaccine clinical trials should include innovative ways to address the challenges and opportunities of conducting studies during this epidemic, such as fluctuating, decreasing, or seasonally moderated incidence rates and the need to ensure sufficient sample sizes for adequate statistical power, especially in multi-arm trials. In addition, clinical trials should collect as much data as possible across multiple products. Also, the clinical trial process should be flexible enough to address rare serious adverse events that may emerge during implementation of clinical studies. Because of the unprecedented mortality seen with EVD, the risk-benefit ratio will likely always be beneficial, which could deter or undermine efforts to better understand possible emerging safety signals. Furthermore, if a candidate vaccine shows efficacy in a trial, the impact this has on ongoing trials of other vaccines, or of the same vaccine in other trials, may pose

challenges. While it is highly desirable to have more than one efficacious vaccine developed, the wisdom of continuing other trials may be challenged if sufficient doses of a vaccine with demonstrated efficacy are available for widespread use. Planning for such a scenario is an urgent priority because if a premature down-selection to a single vaccine candidate occurs, this could create a significant point of vulnerability if that vaccine eventually encounters obstacles (eg, manufacturing, changed tolerability, early waning immunity) or fails. Finally, additional innovations are needed to continue evaluation of new product candidates when clinical trials are no longer feasible owing to lack of disease, particularly if a serologic correlate of protection is not identified quickly.

7. Efforts to Determine Correlates of Protection

Despite the potential biosafety challenges involved, clinical trials should include blood sampling of study subjects to identify correlates of protection, which can serve as surrogate immunogenicity endpoints to predict vaccine benefit. Identifying correlates of protection may have an immediate benefit of providing an alternative path to licensure if sufficient efficacy data cannot be obtained because of declining disease incidence or other challenges in the field. Furthermore, determining correlates of protection can provide a mechanism for "bridging" to other populations (such as different age-groups or populations in geographic regions) and could be critical to assessing next-generation Ebola vaccines that may be developed in the future during non-outbreak situations. Finally, studying the immune response of recovered patients may provide valuable insight into understanding mechanisms of protection, which may inform identification of appropriate correlates.

8. Standardization of Serologic Assays

Assays for evaluating serologic response to various vaccine candidates should be standardized using consensus reference standards and validated across different vaccines and different projects to allow for meaningful comparisons between products and to establish serologic correlates of protection. Different products may have different correlates of protection and standardization may not be possible in all situations.

9. Regulation and Licensure

If an Ebola vaccine is to have significant benefit in the current epidemic, any vaccine considered for licensing and use should be evaluated expeditiously using pre-established and pre-approved criteria, if possible, while maintaining the highest quality safety and efficacy standards. With key support from the WHO, national regulators, and the African Vaccine Regulatory Forum, transnational public-private partnerships should continue efforts to streamline and harmonize approval requirements. Once a vaccine is licensed and recommended for use, it should be manufactured and distributed on a fast-track basis to the West African countries most affected by the current epidemic.

In addition to accelerating the pathway to an approved vaccine, regulatory mechanisms that authorize the use of unapproved vaccines can also be accessed under limited, carefully monitored circumstances during a public health emergency. For example, the US Food and Drug Administration (FDA) allows products to be accessed under Emergency Use Authorization (EUA) when certain criteria are met, including the absence of adequate, approved, and available alternatives for preventing the disease and the determination that known and potential benefits of the vaccine outweigh its known and potential risks. A similar mechanism, known as conditional marketing authorization, exists through the European Medicines Agency (EMA). Such mechanisms can facilitate rapid deployment of an unapproved vaccine; this type of approach may be useful in the current epidemic, whereby urgency is paramount. Furthermore, strategies to overcome the legal and logistical hurdles to transport unapproved products between countries are needed. In this case, a memorandum of understanding (MOU) or other mechanism for import/export special licenses or waivers should be considered. Finally, in December 2014, the US Department of Health and Human Services issued a declaration to provide liability protection (indemnity) for activities related to EVD vaccines; similar actions should be considered by other leading governments around the globe, such as the European Union (EU), Japan, India, China, and Brazil.

10. Manufacturing Capacity and Ease of Use

The ability to rapidly produce an Ebola vaccine will depend on a number of critical factors that will affect manufacturing capacity, such as vaccine dose requirements, the need for booster doses, fill-and-finish requirements, and storage requirements (including considerations for diluent if a lyophilized product is delivered). These factors should be taken into consideration when determining the most optimal vaccine for mass production to ensure that key manufacturing barriers can be overcome quickly enough to address the current epidemic. Furthermore, implementation of an effective vaccination campaign will need to consider factors that influence ease of use for different vaccines under typical field conditions in West Africa, such as cold-chain requirements.

11. Vaccine Access

Providing vaccine access to populations in low-income countries in an emergency situation such as the current epidemic represents the interest of the common good, but it also poses significant economic challenges. Vaccine pricing, therefore, must balance the economic realities and costs associated with vaccine production and distribution with the urgent and critical public health objective of curtailing the current epidemic. Developing Ebola vaccines and bringing them to market will require a strong financial commitment of international governments and the global public health community. One strategy that can mitigate the economic challenges is use of appropriate advance market commitments, which could be put forward by consortia organizations such as the Gavi, the Vaccine

Alliance. Such efforts also could help ensure sustainability of vaccine-production capabilities over time by offering a degree of short- to mid-term market stability, which may enhance the potential for creating adequate vaccine stockpiles for future use. Building local capacities to allow regional production of Ebola vaccines in West Africa also should be considered.

12. Vaccination Strategies for the Current Epidemic

Depending on vaccines developed, several strategies may be appropriate for combatting EVD during the current epidemic. For example, a ring vaccination strategy aimed at case contacts may be suited to stamping out disease occurrence by targeting persons exposed to disease transmitters. Alternatively, vaccination aimed at high-risk groups, such as healthcare workers, funeral workers, or religious or community-based Ebola response teams may be most appropriate, particularly if vaccine is in short supply. In addition, targeted vaccination could be considered for persons who maintain critical infrastructures (such as military personnel, police, government officials, etc). A population-based approach, perhaps geographically targeted, similar to what has been accomplished with meningococcal type A disease or yellow fever across regions of Africa, may ultimately be required to end the epidemic and prevent EVD from becoming endemic in West Africa. Future efforts also should include cost-effectiveness evaluations of short-term strategies that may be enhanced with longer term prophylactic use; information to conduct such assessments may be limited and gaps in data will exist, but attempts to assess cost-effectiveness of various strategies remain worthwhile.

13. Vaccination Strategies for Control of Future Epidemics or Endemic Disease

Strategies to control future outbreaks or endemic disease may involve immediate deployment of existing vaccine stockpiles during outbreaks or prophylactic vaccination of specific high-risk groups, such as healthcare workers, or vaccination of larger segments of the population, depending on the evolving epidemiology of the disease. Such strategies can draw from and perhaps be integrated with vaccination approaches for other infectious diseases. Furthermore, several vaccines, each with different vaccine characteristics, may be needed to accommodate various short- and long-term objectives.

14. Development of Robust Post-Market Surveillance

Since regulatory approval for Ebola vaccines will likely undergo an accelerated licensing process or possibly an emergency expanded access approach, development of a robust post-market surveillance system will be a critical component of any vaccination strategy aimed at curtailing the current outbreak or controlling future outbreaks. Post-market surveillance will provide an additional opportunity to assess vaccine safety and identify any rare or uncommon serious adverse events not identified through the accelerated approval process. Such surveillance also can be used to: (1) ascertain the incidence of disease in relation to vaccination, (2) provide vaccine effectiveness information, (3) provide additional information about the potentially evolving epidemiology of EVD, and (4) assess the risk of endemicity, which might need to be augmented by targeted population-based seroprevalence surveys. To effectively complete post-market surveillance objectives, biosafety level-3 (BSL-3) laboratory capacity for diagnostic purposes needs to be strengthened and maintained in affected countries.

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

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

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

	vaccine and, if the vaccine is efficacious, will provide a highly favorable risk-benefit ratio, ideally with only mild or transient side effects (ie, grade 1 AEs) and lacks evidence of serious AEs[g] ▪ If fever is an AE, it should be of short duration (preferably resolving within 24 hours)	vaccine and, if the vaccine is efficacious, will provide a favorable risk-benefit ratio (primarily grade 1 AEs, with grades 2-4 AEs occurring rarely)[g] ▪ If fever is an AE, it should be of short duration	any safety concerns ▪ Safety profile demonstrates only mild transient health effects (ie, grade 1 AEs) and lacks evidence of serious AEs[g c]	any safety concerns ▪ Safety profile demonstrates primarily mild transient health effects (ie, grade 1 AEs) and serious AEs (grades 2-4) are rare[g]
Efficacy/ Effectiveness	▪ Interrupts disease transmission ▪ Greater than 90% efficacy in preventing disease in healthy children and adults[d] ▪ Rapid onset of immunity ▪ Evidence for post-exposure efficacy in primate challenge experiments	▪ Interrupts disease transmission ▪ Greater than 50% efficacy in preventing disease in healthy older adolescents and adults[d] ▪ Rapid onset of immunity	▪ Greater than 90% efficacy or effectiveness in preventing disease in healthy children and adults	▪ Greater than 50% efficacy or effectiveness in preventing disease in healthy older adolescents and adults[d]
Dose Regimen	▪ Single-dose regimen	▪ Prime-boost regimen with booster dose no more than 1 month following initial dose	▪ Single-dose regimen	▪ Single-dose regimen or prime-boost regimen with additional booster doses as needed ▪ Booster dose schedule is designed to achieve optimal long-term protection
Durability of Protection	▪ Confers at least 2 years of protection[h]	▪ Confers at least 1 year of protection[h]	▪ Confers long-lasting protection of 10 years or more (with booster doses as necessary to maintain durability over time)[h]	▪ Confers protection of at least 3 years (with booster doses as necessary to maintain durability over time)[h]
Criteria Applicable for Production and Distribution of Ebola Vaccines				
Route of Administration	▪ Injectable (IM, ID, or SQ) or other formulation, such as ingestible, nasal, or transdermal patch, if available	▪ Injectable (IM, ID, or SQ) or other formulation as available	▪ Injectable (IM, ID, or SQ) or other formulation, such as ingestible, nasal, or transdermal patch, if available	▪ Injectable (IM, ID, or SQ) or other formulation as available
Formulation	▪ Monovalent vaccine effective against Zaire ebolavirus[i] ▪ Does not require an adjuvant	▪ Monovalent vaccine effective against Zaire ebolavirus[i]	▪ Trivalent vaccine effective against Zaire ebolavirus, Sudan virus, and Marburg virus ▪ Does not require an adjuvant	▪ Monovalent vaccines effective against Zaire ebolavirus, Sudan virus, and Marburg virus

Product Stability and Storage	▪ Shelf life of at least 36 months ▪ Does not require storage at -80°C to prevent degradation ▪ The need for a preservative is determined and any issues are addressed ▪ Product is stable at refrigeration temperatures (2°- 8°C) ▪ Heat stability should be maximized to allow product to be used in a CTC (ie, with storage out of cold chain at room temperature for up to several days)	▪ Shelf life of at least 24 months ▪ The need for a preservative is determined and any issues are addressed ▪ Storage conditions comply with cold-chain capabilities; product may be stored at -80°C or at -20°C, if stable for some period of time (hours to a few days) at 2°- 8°C or at room temperature (to allow for shipment and storage in the field)	▪ Shelf life of at least 36 months ▪ Does not require -80°C to prevent degradation ▪ The need for a preservative is determined and any issues are addressed ▪ Product is stable at refrigeration temperatures (2°- 8°C) ▪ Heat stability should be maximized to allow product to be used in a CTC (ie, with storage out of cold chain at room temperature for up to several days)	▪ Shelf life of at least 24 months ▪ The need for a preservative is determined and any issues are addressed ▪ Storage conditions comply with cold-chain capabilities; product may be stored at -80°C or at -20°C, if stable for some period of time (hours to a few days) at 2°- 8°C or at room temperature (to allow for shipment and storage in the field)
Coadministration with Other Vaccines	▪ The vaccine will be given as a stand-alone product not coadministered with other vaccines.	▪ The vaccine will be given as a stand-alone product not coadministered with other vaccines.	▪ The vaccine can be coadministered with other licensed vaccines without clinically significant impact on immunogenicity or safety.	▪ The vaccine will be given as a stand-alone product not coadministered with other vaccines.
Presentation	▪ In an outbreak setting, the simplest presentation is likely best (ie, a mono-dose, liquid product that does not require reconstitution); however, other options noted in the bullets below are acceptable. ▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent	▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent	▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent	▪ Vaccine is provided as a liquid or lyophilized product in mono-dose or low multi-dose (10-20) presentations[j,k] ▪ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies ▪ Lyophilized vaccine will need to be accompanied by paired separate vials of the appropriate diluent
Production	▪ Can be produced efficiently and as expeditiously as possible after an engendered and validated scale-	▪ Can be produced efficiently and as expeditiously as possible after an engendered and validated scale-up	▪ Can be produced efficiently and as expeditiously as possible The dose of antigen required for protection	▪ Can be produced in quantities sufficient for prophylactic use in at-risk regions or populations

	up that allows for maximum production yields; the dose of antigen required for protection allows for high production yield (which will affect cost and availability) ▪ 5 million doses can be produced by third quarter 2015 ▪ Ideally, production involves a single bulk-substance product (without requiring a separate booster product or diluent [needed for lyophilized vaccines]) ▪ If a booster with an alternative product is needed, that product also can be produced quickly and without significant manufacturing barriers or supply-chain issues ▪ If an adjuvant is needed, it can be formulated with the vaccine instead of combined at the time of use	▪ The dose of antigen required for protection allows for high production yield (which will affect cost and availability) ▪ 5 million doses can be produced by first quarter 2016 ▪ If a booster with an alternative product is needed, that product also can be produced quickly and without significant manufacturing barriers or supply-chain issues	allows for high production yield (which will affect cost and availability) ▪ Can be produced in quantities sufficient for prophylactic use in at-risk regions or populations ▪ If an adjuvant is needed, it can be formulated with the vaccine instead of combined at the time of use	
Licensure	▪ Meets criteria for licensure or accelerated licensure pathway ▪ Recommendation for vaccine use by WHO	▪ Meets criteria for accelerated licensure pathway or expanded access (such as EUA), with full licensure potentially to follow[l] ▪ Criteria for expanded access or EUA are acceptable to EMA, FDA, and the NRAs of countries affected by the epidemic[l] ▪ Conditional recommendation for vaccine use by WHO	▪ Meets criteria for licensure ▪ Product is prequalified by WHO	▪ Meets criteria for licensure

Abbreviations: AE, adverse event; CTC, controlled temperature chain; EMA, European Medicines Agency; EUA, Emergency Use Authorization (applicable to regulations in the US); EVD, Ebola virus disease; FDA, US Food and Drug Administration; ID, intradermal; IM, intramuscular; NRA, National Regulatory Authority; SQ, subcutaneously; WHO, World Health Organization.
*This assumes vaccine candidates already have met regulatory requirements for phase I clinical trials.

[a]Optimal and minimal criteria for vaccines to be used in the current epidemic are similar to considerations for vaccines that may be used in future outbreaks or epidemics if a reactive vaccination strategy is employed. Vaccines developed and produced now or in the future may be stockpiled for reactive use in future situations.
[b]Optimally, a vaccine should be available for all age-groups; however, some vaccines may not be able to be given to the pediatric population because of general reactogenicity or interference with safety or efficacy of co-administered products.

[c]Ideally, a vaccine will be safe and effective in special populations, such as immunocompromised persons or pregnant women; however, obtaining efficacy and safety data for such populations will require special studies that take extensive time to design and conduct; therefore, this feature is not realistic for the current epidemic, but may be a consideration for a future time, if appropriate.
[d]Initial vaccination of older adolescents and adults is a potentially viable strategy because: (1) this will encompass most high-risk persons (eg, healthcare workers, Ebola community workers, funeral workers, and in-home care providers as well as many case contacts); (2) the epidemiology of EVD in West Africa indicates that the largest burden of disease occurs in this age-group, and (3) by targeting this population, enough herd immunity might be achieved to stop the outbreak when combined with other control measures.
[e]A tiered strategy targeted initially to healthcare workers, adults, and adolescents, then later to children and the elderly over time may be considered (depending on the vaccination strategy), with more than one vaccine product being appropriate for different populations and different usages.
[f]Safety profiles for vaccines used in an outbreak/epidemic setting may potentially be lower than the safety profiles for vaccines used on a prophylactic basis to prevent endemic disease or future outbreaks, since the risk/benefits in the two settings may be different.
[g]A system for grading adverse events is as follows. Grade 1 (mild): symptoms cause no or minimal interference with usual social and functional activities; grade 2 (moderate): symptoms cause greater than minimal interference with usual social and functional activities; grade 3 (severe): symptoms cause inability to perform usual social and functional activities; grade 4 (potentially life threatening): symptoms cause inability to perform basic self-care functions, or a medical or operative intervention is indicated to prevent permanent impairment, persistent disability, or death.
[h]Investigators will not be able to determine durability of protection in the current clinical trials; this will require additional observation and follow-up studies.
[i]A monovalent vaccine against Zaire ebolavirus is adequate to control the current West Africa epidemic; however, strategic use of a reactive vaccination strategy aimed at controlling future filovirus disease outbreaks will likely also require development of monovalent vaccines against Sudan virus and Marburg virus (or a trivalent vaccine against all three pathogens).
[j]Liquid vaccines are easy to administer because they don't need reconstitution. Lyophilized vaccines may be more temperature stable, but require reconstitution with an appropriate diluent. These two different forms of vaccine each have advantages and disadvantages that will need to be weighed based on conditions in the field.
[k]Single-dose vials potentially decrease safety risks. Single-dose or low multi-dose vials also decrease vaccine wastage, which is an important factor when considering cost of administration; however, they require increased storage space. The optimal number of doses per vial, therefore, will need to take into consideration field conditions and the vaccination strategy (eg, 50 or more doses per vial may be appropriate for a mass vaccination strategy).
[l]Issues around accelerated licensure and expanded access apply predominantly to this epidemic. Ideally, before any future outbreaks or epidemics occur, time will permit the full licensure process.

EBOLA VACCINE TEAM B*

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