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The Ebola Vaccine Team B: a model for promoting the rapid development of medical countermeasures for emerging infectious disease threats

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In support of accelerated development of Ebola vaccines from preclinical research to clinical trials, in November, 2014, the Wellcome Trust and the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota established the Wellcome Trust-CIDRAP Ebola Vaccine Team B initiative. This ongoing initiative includes experts with global experience in various phases of bringing new vaccines to market, such as funding, research and development, manufacturing, determination of safety and efficacy, regulatory approval, and vaccination delivery. It also includes experts in community engagement strategies and ethical issues germane to vaccination policies, including eight African scientists with direct experience in developing and implementing vaccination policies in Africa. Ebola Vaccine Team B members have worked on a range of vaccination programmes, such as polio eradication (Africa and globally), development of meningococcal A disease vaccination campaigns in Africa, and malaria and HIV/AIDS vaccine research. We also provide perspective on how this experience can inform future situations where urgent development of vaccines is needed, and we comment on the role that an independent, expert group such as Team B can have in support of national and international public health authorities toward addressing a public health crisis.

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Introduction

On Aug 8, 2014, the Director-General of WHO declared that the Ebola virus disease (EVD) outbreak in parts of west Africa represented a Public Health Emergency of International Concern (PHEIC) under the 2005 International Health Regulations.[1] Also in August, 2014, WHO called for fast-track development of Ebola vaccines as part of the Ebola Response Roadmap[2] and in October, 2014, WHO stressed that development of one or more Ebola vaccines was an urgent international public health priority.[3,4] In support of accelerated development of Ebola vaccines from preclinical research to clinical trials, in November, 2014, the Wellcome Trust and the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota established the Wellcome Trust-CIDRAP Ebola Vaccine Team B initiative (hereafter referred to as the Ebola Vaccine Team B). This ongoing initiative includes experts with global experience in various phases of bringing new vaccines to market, such as funding, research and development, manufacturing, determination of safety and efficacy, regulatory approval, and vaccination delivery. It also includes experts in community engagement strategies and ethical issues germane to vaccination policies, including eight African scientists with direct experience in developing and implementing vaccination policies in Africa. Ebola Vaccine Team B members have worked on a range of vaccination programmes, such as polio eradication (both in Africa and globally), development of meningococcal A disease vaccination campaigns in Africa, and malaria and HIV/AIDS vaccine research. The Ebola Vaccine Team B initiative has involved up to 28 members and four staff; all members (other than the two chairs [Osterholm and Farrar] and staff) volunteered their time and received no compensation for their efforts.

The Ebola Vaccine Team B was formed to rapidly assess challenges and opportunities related to Ebola vaccine development, to identify potentially overlooked aspects of the vaccine development process, and to synthesise information for distribution in the public domain as quickly as possible. To achieve these objectives, during the period from late November, 2014, to early February, 2015, working subgroups of Ebola Vaccine Team B experts met regularly via international conference calls to discuss and comment on various issues related to the development and delivery of Ebola vaccines. These discussions led to the release in February, 2015, of a set of recommendations and a draft target product profile (TPP) for Ebola vaccines.[5] At the time of writing, the Ebola Vaccine Team B is still engaged in constructive assessment and critique of the ongoing development and evaluation of Ebola vaccines. Here we outline key initial recommendations from the Ebola Vaccine Team B, provide an overview of the current Ebola vaccine landscape, discuss recommendations for future consideration, and present the TPP that was developed as part of the initial report. We also provide perspective on how this experience can inform future situations where urgent development of vaccines is needed, and we comment on the role that an independent, expert group such as Team B can have in support of national and international public health authorities toward addressing a public health crisis.

Selected recommendations from the initial Team B report

The Ebola Vaccine Team B was divided into nine workgroups, representing the key areas where challenges in Ebola vaccine development and delivery exist: manufacturing, research and development, safety, determination of efficacy or effectiveness, licensing, ethics, vaccination strategy, community engagement, and funding. Several of these areas were combined in the initial report because discussions and recommendations overlapped

substantially. A full list of recommendations can be found in the report;[5] selected key recommendations from the workgroups are outlined in table 1.

Overview of the current Ebola vaccine landscape

Since the beginning of 2014, 35 clinical trials involving Ebola vaccines have been initiated, completed, or are about to begin.[39] 27 studies in 15 countries are phase 1 or phase 1–2 trials aimed at assessing vaccine safety (including reactogenicity) and immunogenicity, four studies in seven African or European countries are phase 2 trials aimed at assessing safety and immunogenicity in larger study populations, and four studies are phase 2–3 or phase 3 trials (three of which have been initiated in west Africa and a fourth is registered but has not yet begun). Seven reports involving these trials have been published so far.[40–46]

The three phase 2–3 or phase 3 clinical trials initiated in west Africa include[39,47] a phase 3 trial in Guinea involving a recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebola virus (rVSV-ZEBOV); a phase 2–3 trial in Liberia examining safety and efficacy of two candidate vaccines (rVSV-ZEBOV and recombinant chimpanzee adenovirus type 3-vectored vaccine [cAd3-EBOV]; the phase 3 portion of the trial was suspended in April, 2015, owing to the low incidence of Ebola virus disease [EVD] in Liberia); and a phase 2–3 safety and efficacy study in Sierra Leone involving a single dose of rVSV-ZEBOV.

As of August, 2015, only preliminary results of the Guinea study, which is an open-label, cluster-randomised, ring vaccination clinical trial, had been published.[41] In this study, participants were randomly assigned to immediate or delayed receipt of one dose of 2×10^7 plaque-forming units (pfu) of the rVSV-ZEBOV vaccine. On days 3 and 14 post-vaccination, study investigators obtained information about adverse events from participants or their next of kin. After 10 days post-randomisation, no cases of EVD occurred in those who received vaccine as part of the group randomly assigned to receive immediate vaccination compared with 16 confirmed cases among all eligible persons in the delayed vaccination group. The authors stated this analysis yielded a vaccine efficacy of 100% (95% CI 74·7–100·0; p=0·0036), based on assessment of 90 case clusters. This value also can be defined as a measure of total vaccine effectiveness,[48] because it is affected by conditions within the two populations, not only by the individuals in those populations. At the cluster level with the inclusion of all eligible participants, the authors estimated the vaccine effectiveness as 75·1% (95% CI –7·1 to 94·2; p=0·1791) because six cases of EVD happened in participants who were assigned to the immediate vaccination group but did not receive vaccine (apparently because they did not consent to be vaccinated or consent was not obtained). This value can also be considered a measure of overall effectiveness,[48] since the comparison involved all participants (vaccinated and not vaccinated) in the two randomised groups. 43 serious adverse events were reported; one serious adverse event was judged to be causally related to vaccination (a febrile episode in a vaccinated participant, which resolved without sequelae); assessment of serious adverse events is ongoing. Although these results are highly encouraging, because of clustering within the rings, participants are not statistically independent, which could affect the precision in this type of study design.[49,50] Although the authors suggested they accounted for this issue, further data are needed to validate the findings. The ring vaccination approach used in this trial is continuing in Guinea (but without randomisation to delayed vaccination) and, in late August, 2015, was expanded into Sierra Leone.[51,52]

Three other reports have assessed the safety and immunogenicity of the rVSV-ZEBOV vaccine.[40,42,45] In one multicentre study, 13 (25%) of 51 volunteers in Geneva, Switzerland, who were vaccinated with various doses containing at least 1×10^7 pfu, had fever and 11 (22%) had reactive arthritis, which led to a pause in the study.[40] The study was resumed using a lower dose of vaccine and a subsequent report noted that reducing the dose of rVSV-ZEBOV to 3×10^5 pfu led to lowered antibody responses and did not prevent vaccine-induced arthritis, dermatitis, or vasculitis.[42] A third report involved two phase 1 trials with 26 participants in each (52 total); 40 received an intramuscular injection of the rVSV-ZEBOV vaccine at a dose of either 3×10^6 pfu or 2×10^7 pfu and 12 received placebo.[45] Safety and immunogenicity were assessed for the 28 days after vaccination. No significant safety concerns were identified during the observation period and the vaccine was immunogenic in the participants tested.

Although the Guinea trial results are very promising, data reported in the Swiss trial raise questions about reactogenicity of rVSV-ZEBOV. An appropriate vaccination strategy for use of this vaccine might involve immediate protection among high-risk contacts in an outbreak setting. Additional data are needed to establish if this vaccine is appropriate in other situations, such as use in the general population or in people at risk of future exposure, including health-care workers (who would need relatively long-term immunogenicity). Furthermore, the rVSV-ZEBOV vaccine currently needs storage at –80°C, which presents logistical challenges for stockpiling and widespread use in remote areas of Africa.

Three reports have involved adenovirus-vectored vaccines, including the cAd3-EBOV vaccine and a recombinant adenovirus type 5 vector-based vaccine.[43,44,46] For the cAd3-EBOV trials, both were phase 1, dose-escalation, open-label studies. The first trial, which involved 20 participants in the USA, identified no safety concerns, although transient fever developed within 1 day after vaccination in two participants who had received a 2×10^{11} particle-unit dose.[43] The second trial involved 60 volunteers in Oxford, UK, who received a single dose of

cAd3-EBOV vaccine at one of three dose levels (1×10^{10} viral particles, $2\cdot5\times10^{10}$ viral particles, and 5×10^{10} viral particles); 20 participants were included in each group.[44] No safety concerns were identified and the cAd3-EBOV vaccine was immunogenic at the doses tested. A final report involved a randomised, double-blind, placebo-controlled, phase 1 trial using two different doses of an adenovirus type-5 vector-based Ebola vaccine (one high dose and one low dose).[46] 120 participants were enrolled, with 40 in each arm of the study. The authors determined the high-dose vaccine was immunogenic and no serious adverse events were noted, although 82 participants (68%) reported at least one adverse reaction within 7 days of vaccination (19 in the placebo group, 27 in the low-dose group, n=36 in the high-dose group [p=0·0002]).

Recommendations for future consideration: where to go from here

Assessment of vaccine attributes

Ongoing and continued assessment of vaccine attributes is needed to inform long-term use of Ebola vaccines to control or prevent future outbreaks.[6,53,54] First-generation

	Recommendations
Need to accelerate manufacturing	Ebola vaccine manufacturing could be accelerated by streamlining the vaccine production process using existing platform technologies,[6–9] thereby using specific know-how to improve cost-effectiveness, and focusing on monovalent formulations in the near term to address vaccination needs of the current epidemic in west Africa.
Completion of phase 2/3 clinical trials	Phase 2/3 clinical trials of Ebola vaccines should be done even if an efficacy endpoint cannot be guaranteed, because substantial safety and immunogenicity data will be needed for licensing and decision making regarding further vaccine development.[10]
Crucial role of international coordination	WHO should continue to coordinate international efforts to identify appropriate options for accelerated regulatory approval of Ebola vaccines and provide expert guidance (such as through the WHO prequalification process).[11] Key goals include developing consensus recommendations regarding emergency approval or authorisation pathways, identifying opportunities for reciprocity to expedite approvals among multiple national regulatory authorities, and clarifying the role of the US Food and Drug Administration, Health Canada, or the European Medicines Agency in facilitating approvals in the west African vaccine regulatory process.[12–15]
Need for additional clinical trials	The clinical trial process needs to be innovative and flexible to provide opportunities for the assessment of new product vaccine candidates when disease prevention cannot reliably be assessed because of low disease incidence. Furthermore, to the extent possible, all promising vaccines should be assessed in clinical trials, even if one vaccine shows early efficacy, since it is not clear which vaccines might ultimately prove to be most effective and safe for different populations or circumstances. If an early vaccine shows efficacy, researchers might be able to identify a correlate of protection for the vaccine.[16] If that correlate of protection is generalisable to other candidate vaccines, later clinical trials could be done using an accepted immunogenicity correlate as an approval endpoint rather than measuring clinical protection in an outbreak or epidemic setting.[16] If no generalisable correlate of protection can be identified, clinical trials with later vaccines are still possible, particularly if evidence (from animal data or other markers) suggests that such vaccines are reasonably likely to predict clinical benefit or might be superior to the first-generation vaccine. In such situations, clinical trials would likely be done by comparing the new candidate vaccine against the first-generation vaccine.[17,18] This might apply to the development of future vaccines for other diseases as well, such as malaria and dengue, where second-generation vaccines are compared with partly efficacious first-generation vaccines.[19]
Importance of post-marketing adverse event reporting	Post-marketing surveillance should be done once vaccines are approved or authorised for use, using techniques applicable to under-resourced countries.[20] Consideration should be given to determining if applicable baseline data are available from in-country epidemiological sources for anticipated potential adverse events.[21,22] Furthermore, community engagement strategies should be developed for addressing vaccine adverse events (that are either causally or coincidentally related to vaccination). Public health officials need to specify the entities (governments, vaccine manufacturers, others) responsible for post-marketing surveillance studies and how vaccine-related adverse events will be handled and documented. They need to clarify and communicate broadly how and to whom vaccine-related harms should be reported, the process for addressing them, and who is accountable for any reparations.
Involvement of African scientists in ethical decisions	African stakeholders should be at the forefront of ethical decisions that affect the safety, wellbeing, and resilience of the populations hardest hit by the west Africa Ebola epidemic.[23,24] This includes conduct of clinical trials and vaccination strategies once vaccines are brought to market.
Aligning vaccine strategies with the epidemiology of disease	The key framework for developing a post-licensure vaccination strategy should be based on initial targeting of those at highest risk of exposure. The strategy can be phased in, according to vaccine availability, and might evolve. Leaders in the affected countries need to be central to the decision making and determination of priority groups for vaccination. A number of vaccination strategies have been used to control infectious diseases or have been considered as potential control options.[25–32] Vaccination strategies applicable to Ebola include the following: • *Targeted vaccination to at-risk groups.* Health-care workers, Ebola response teams, and funeral workers should be considered a priority once vaccine is available. Such front-line workers are essential to the care of the ill or handling of deceased victims and are at increased risk of acquiring infection. Vaccination of this group should be feasible with a single-dose or multi-dose vaccine. • *Ring vaccination.* Contacts of cases, along with their potential secondary contacts and others in geographic proximity to cases, also should be a priority. For these groups, a single-dose vaccine will be desirable. • *Geographically targeted mass vaccination.* The pattern of disease occurrence in the west Africa Ebola epidemic has shown geographic hot spots;[33] therefore, population-based vaccination in targeted areas is a potential strategy. A vaccine requiring only a single dose will be most suitable in this setting. If mass vaccination is considered, the safety profile will need to be established for special populations, such as children, elders, pregnant women, and immunocompromised persons and ongoing pharmacovigilance data will be essential.
Early initiation of community engagement with inclusion of local leadership	Efforts should be underway as early as possible to address any perceived barriers to vaccine acceptance, as well as to build trust, promote awareness, and provide any needed information.[34] Trusted leaders from the affected countries should drive community engagement, with support from external partners as appropriate and requested.[35] Traditional leaders and others selected by their communities, rather than imposed on them by others, are essential to community engagement efforts that are culturally informed, practical, and trust-building. Engagement of local scientific communities also should be considered. For example, hardest-hit countries should consider creating structures similar to the Nigerian Northern Traditional Leaders Committee for Primary Care and Polio Eradication as a way to formally engage with traditional and religious institutions and influential individuals who can reduce misinformation and stigmatisation and bring transparency to ethical aspects of Ebola vaccine assessment and deployment.[36,37] Another example of successful community engagement occurred in Burkina Faso to promote use of the new meningococcal A conjugate vaccine.[32]
Vaccine costs need to ensure a fair price point	Governments and manufacturers should ensure transparency in financial transactions that affect pricing as well as decisions regarding distribution of doses, especially if vaccine supplies are limited. Deployment of Ebola vaccines also should reflect a rational pricing system.[38] Ideally, a purchase price for Ebola vaccines should reflect the direct costs to manufacture sufficient amounts, account for the public and charitable investments in their development, and assume limited ability of affected countries to secure funding for vaccine supplies.

Table 1: **Examples of initial recommendations of Ebola Vaccine Team B by issue**

Ebola vaccines might or might not have the attributes needed for different scenarios.[55] Hypothetically, an Ebola vaccine candidate that provides rapid development of immunity after a single administration, but has limited duration of protection, could be very useful for controlling an outbreak. Conversely, an Ebola vaccine candidate that requires multiple doses over several months before protective immunity is achieved, but has a long duration of protection, might be necessary in protecting health-care workers and response and burial team members in advance of future outbreaks.

Regulatory review

In preparation for a future public health emergency, WHO should consider creating a permanent capability within the organisation to facilitate the development of consensus regulatory recommendations and guidelines by national regulatory authorities (NRAs) for addressing public health emergencies.

Manufacturing capacity

The development of in-region manufacturing capacity could potentially enhance access to Ebola vaccines in low-income and middle-income countries in the longer term.[56–58] Technology transfer to a reliable developing-country vaccine manufacturer could also provide an alternative source of vaccine if an originator manufacturer cannot commit to continued production.[56,59] Technology transfer, however, would be extremely challenging and resource intensive in west Africa, because reliable capacity currently does not exist in the region.

Improving vaccines

The risk-benefit profile for the rVSV-ZEBOV is unclear beyond ring vaccination around known cases in the current outbreak in Guinea, so future randomised trials of other vaccines or strategies should remain a high priority. Furthermore, developers of next-generation Ebola vaccines should consider the need to protect against other filovirus infections in addition to Zaire Ebola virus (such as Marburg virus, and Sudan Ebola virus), which will require development of multivalent or multifunctional vaccines.[7] Finally, antigenic drift might be an issue over time—particularly with ongoing evolutionary pressure—and future efforts will need to monitor the effect of antigenic drift or selection for vaccine-resistant strains on vaccine effectiveness. Ensuring candidate vaccines are on-the-shelf and ready for assessment during future outbreaks might be a useful approach to address development of future-generation Ebola vaccines.[60]

Stockpiling vaccines

Once the west Africa epidemic is controlled, stockpiling vaccines to be used for future outbreaks should be considered.[55] Vaccines could be used during outbreaks (eg, by employing the reactive vaccination strategies outlined above) in coordination with traditional public health measures to achieve rapid control. Public health officials currently maintain vaccine stockpiles for use during yellow fever outbreaks in Africa (in combination with mass vaccination campaigns)[61,62] and cholera vaccine also is stockpiled for outbreaks,[63] demonstrating the potential viability of this approach. Furthermore, stockpiling of candidate vaccines for further testing in phase 3 clinical trials during outbreaks should be considered, as noted above.[60]

New funding strategies

Key stakeholders should consider creating an integrated funding strategy that prioritises public health as a primary driver over solely commercial considerations.[38,64,65] Although public attention might recede from the current crisis in west Africa as the epidemic abates, the likelihood of disease and death from future Ebola outbreaks will not. Because of the animal reservoir of Ebolavirus, future outbreaks are inevitable, and work must begin to explore a strategy for integrated global funding, including support for the WHO's authority to monitor global health, declare a public health emergency of international concern, and coordinate a timely response to any such emergencies.

Partnerships

Engagement of the pharmaceutical industry is very important for developing, licensing, and manufacturing any new, emerging infectious disease vaccines; therefore, industry needs and drivers must be understood and accommodated. There is a very real risk that in the future pharmaceutical companies will not be willing to participate in vaccine development efforts aimed at responding to public health crises such as the west Africa Ebola epidemic unless industry needs are addressed.[66] This situation raises the role of public–private partnerships in creating funding models that allow new vaccines to move forward while simultaneously addressing industry needs and requirements.[64,65,67] A comprehensive assessment of existing public–private partnerships should be done with the goal of identifying strengths that can be used to establish economic models for vaccine development that are driven by public health priorities, particularly on behalf of populations where resources are most limited.

Summary of recommendations

Numerous crucial issues in the development of Ebola vaccines still remain: the limitations of single-source vaccine supplies and the need to keep multiple pharmaceutical companies engaged in the process; the need to pursue development of vaccines that can be used in larger inter-epidemic or endemic situations; the need for continued funding for development of other Ebola vaccine candidates until final products with appropriate risk-benefit profiles are available for use under different circumstances; the need to provide actionable information to African countries about Ebola vaccine availability and use in the future; and the need to derive benefit from the

wide range of clinical trials that are currently ongoing or planned to start in the near future. The Ebola Vaccine Team B initiative will continue to address these issues and others that arise in the months to come.

Target product profile for Ebola vaccines

Although TPPs have traditionally been used in industry or as part of the regulatory process, a TPP also can drive discussions about optimal and minimal vaccine characteristics and production capabilities, which ultimately can be used to generate suitable products for the prevention and control of EVD. A TPP can be used as a tool for ongoing assessment of vaccine attributes[68] and can take into consideration a broad range of other issues, including how the vaccine will be used, the target populations, vaccine production, and vaccine distribution.[69–71] The Ebola Vaccine Team B created a TPP for Ebola vaccines that includes criteria for reactive use and proactive use (table 2). This TPP was released to the WHO in April, 2015, for use as a starting point for a WHO-approved TPP for Ebola vaccines.

Lessons learned from the Ebola Vaccine Team B experience

The Ebola Vaccine Team B has provided an opportunity to discuss and address several crucial issues related to Ebola vaccine development and dissemination. Several key lessons, however, are generalisable to the broader issue of global infectious disease prevention and control. First, the current market-driven approach for vaccine development is not adequate to protect impoverished populations from emerging infectious diseases of epidemic or pandemic potential. Creative funding strategies are needed that ensure vaccines move efficiently from discovery and research through clinical trials and licensure to manufacturing and delivery, even when ongoing profitability for vaccine manufacturers is not assured. Second, the west Africa Ebola epidemic illustrates the need for enhanced international coordination and transparency, particularly regarding approval processes for doing clinical trials in developing countries and addressing international regulatory issues for licensure of new vaccines. As part of this process, better preparedness plans need to be in place to address community engagement needs in advance of a crisis situation. Finally, the west Africa Ebola epidemic highlights the need to further strengthen disease surveillance systems in the region as well as in other geographical areas within the continent and globally.

At the onset of the Ebola epidemic in west Africa, several Ebola vaccines were in preclinical development, owing to substantial investments by various government agencies, the pharmaceutical industry, and private foundations. Prior work on product development platforms allowed relatively rapid progression to clinical trials for several vaccine candidates, but delivery of efficacious licensed products to affected areas has yet to happen. More rapid efficacy assessment of these vaccines would have been possible if they had been assessed for initial safety and immunogenicity in phase 1–2 studies before the onset of the epidemic, and if there had been greater consensus before the epidemic on the feasibility and appropriateness of study designs to assess efficacy. An improved process is needed to identify infectious diseases of epidemic or pandemic potential and to ensure that more robust research is initiated and supported to develop vaccines and other medical countermeasures for such pathogens. The most obvious example is vaccines for emergent novel influenza viruses with pandemic potential. Other pathogens of importance include paramyxoviruses, such as Nipah virus and Hendra virus; emergent coronaviruses, such as severe acute respiratory syndrome coronavirus and Middle Eastern respiratory syndrome coronavirus; other haemorrhagic fever viruses such as Marburg virus, Rift Valley fever virus, and Crimean-Congo haemorrhagic fever virus; emergent enteroviruses, such as EV71, EV68 (or D68), and Coxsackie A16 (or CA16); hepatitis E virus; and chikungunya virus. In addition to research and development, more efforts are needed to ensure that such vaccines are supported through clinical trials, manufacturing, and delivery to potential at-risk populations.

Team B as a model for future infectious disease emergencies

A Team B approach can augment traditional public health efforts in several ways. First, a Team B can include non-governmental international experts with a wide range of past experience from the private and public sectors and from academia. In the case of this Team B, the broad range of expertise allowed the group to cover all areas of Ebola vaccine development and deployment. In particular, the participation of African scientists allowed the group to delve into issues specific to west Africa and provided a so-called ground zero perspective, which was crucial for the success and credibility of the initiative. Team B staff also contacted additional experts who provided further valuable insights. Government processes, by contrast, might be more limited in engaging partners from the private sector because of the regulatory role that some governmental agencies have, which can generate concerns about potential conflicts of interest. Second, a Team B can be organised quickly and can retain its autonomy. This allows a Team B to generate outputs rapidly because the process does not depend on government or private-sector review or approval and is not hamstrung by issues such as concerns about antitrust (which, for example, could arise with any consortium of pharmaceutical companies). In this situation, the Ebola Vaccine Team B was able to rapidly generate a TPP and share it with the WHO for its future use. Finally, a Team B can be more flexible and nimble than most government bodies and can respond to a changing landscape more quickly by adjusting programmatic priorities.

Several challenges also exist with developing and sustaining a Team B. First, a need exists for adequate staffing of the Team B to conduct research and draft documents. Second, a Team B must rely on volunteer engagement of relevant experts. Even in situations where financial support can be provided, the support will not be commensurate with the hours of service needed. Third, a Team B must balance the desire to be of service without encroaching on the work of government entities and global organisations, and without being overly critical of efforts underway. This entails walking a fine line and engaging public-sector

	Prevention of EVD in the current or future epidemics (reactive use)*		Protection against endemic EVD (prophylactic use)	
	Optimal	Minimal	Optimal	Minimal
Criteria applicable to characteristics of Ebola vaccines				
Indication for use	For active immunisation of at-risk people 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 immunisation of at-risk people 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 immunisation of people 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 immunisation of people 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 given to all age groups and populations, including special populations (immunocompromised people, pregnant women, people with underlying chronic disease, and malnourished people)†,‡	The vaccine can be given to healthy older adolescents and non-pregnant adults§	The vaccine can be given to all age groups and populations, including special populations (immunocompromised people, pregnant women, people with underlying chronic disease, and malnourished people) †,‡	The vaccine can be given to healthy older adolescents and non-pregnant adults¶
Safety‖	A safety profile that is consistent with expectations for a licensed vaccine and, if the vaccine is efficacious, will provide a highly favourable risk-benefit ratio, ideally with only mild or transient side-effects (ie, grade 1 AEs) and lacks evidence of serious AEs** If fever is an AE, it should be of short duration (preferably resolving within 24 h)	A safety profile that is consistent with expectations for a licensed vaccine and, if the vaccine is efficacious, will provide a favourable risk-benefit ratio (primarily grade 1 AEs, with grades 2–4 AEs occurring rarely)**	Robust safety profile whereby vaccine benefit clearly outweighs any safety concerns Safety profile demonstrates only mild transient health effects (ie, grade 1 AEs) and lacks evidence of serious AEs**,‡	Robust safety profile whereby vaccine benefit clearly outweighs any safety concerns Safety profile demonstrates primarily mild transient health effects (ie, grade 1 AEs) and serious AEs (grades 2–4) are rare**
Efficacy/ effectiveness	Interrupts disease transmission Greater than 90% efficacy in preventing disease in healthy children and adults§ Rapid onset of immunity Evidence for post-exposure efficacy in primate challenge experiments	Greater than 50% efficacy in preventing disease in healthy older adolescents and adults§ 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§
Dose regimen	Single-dose regimen	Prime-boost regimen with booster dose no more than 1 month after 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††	Confers at least 3 to 6 months of protection††	Confers longlasting protection of 10 years or more (with booster doses as necessary to maintain durability over time) ††	Confers at least 2 years of protection after completion of the vaccination regimen††
Criteria applicable for production and distribution of Ebola vaccines				
Route of administration	Injectable (intramuscular, intradermal, or subcutaneous) or other formulation, such as ingestible, nasal, or transdermal patch, if available	Injectable (intramuscular, intradermal, or subcutaneous) or other formulation as available	Injectable (intramuscular, intradermal, or subcutaneous) or other formulation, such as ingestible, nasal, or transdermal patch, if available	Injectable (intramuscular, intradermal, or subcutaneous) or other formulation as available
Formulation	Monovalent vaccine effective against Zaire Ebola virus‡‡ Does not require an adjuvant	Monovalent vaccine effective against Zaire Ebola virus‡‡	Trivalent vaccine effective against Zaire Ebola virus, Sudan Ebola virus, and Marburg virus Does not require an adjuvant	Monovalent vaccines effective against Zaire Ebola virus, Sudan Ebola 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 maximised to allow product to be used in a CTC (ie, with storage out of cold chain at room temperature for up to several days)	Shelf life of at least 12 months The need for a preservative is determined and any issues are addressed Storage conditions comply with cold-chain capabilities; product may be stored at –80°C or at –20°C, if stable for some period of time (hours to a few days) at 2–8°C or at room temperature (to allow for shipment and storage in the field)	Shelf life of at least 36 months Does not require storage at –80°C to prevent degradation The need for a preservative is determined and any issues are addressed Product is stable at refrigeration temperatures (2–8°C) Heat stability should be maximised 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)

(Table 2 continues on next page)

	Prevention of EVD in the current or future epidemics (reactive use)*		Protection against endemic EVD (prophylactic use)	
	Optimal	Minimal	Optimal	Minimal
(Continued from previous page)				
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 lyophilised product in mono-dose or low multi-dose (10–20) presentations§§,¶¶ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies Lyophilised vaccine will need to be accompanied by paired separate vials of the appropriate diluent	Vaccine is provided as a liquid or lyophilised product in mono-dose or low multi-dose (10–20) presentations§§,¶¶ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies Lyophilised vaccine will need to be accompanied by paired separate vials of the appropriate diluent	Vaccine is provided as a liquid or lyophilised product in mono-dose or low multi-dose (10–20) presentations§§,¶¶ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies Lyophilised vaccine will need to be accompanied by paired separate vials of the appropriate diluent	Vaccine is provided as a liquid or lyophilised product in mono-dose or low multi-dose (10–20) presentations§§,¶¶ Multi-dose presentations should be formulated, managed, and discarded in compliance with multi-dose vial policies Lyophilised 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 a validated scale-up that allows for maximum production yields; the dose of antigen required for protection allows for high production yield (which will affect cost and availability) 5 million doses can be produced by the end of 2015 (for the current epidemic) Ideally, production involves a single bulk-substance product (without requiring a separate booster product or diluent [needed for lyophilised vaccines]) If a booster with an alternative product is needed, that product also can be produced quickly and without substantial manufacturing barriers or supply-chain issues If an adjuvant is needed, it can be formulated with the vaccine instead of combined at the time of use	The dose of antigen required for protection allows for high production yield (which will affect cost and availability) 5 million doses can be produced during 2016 (for the current epidemic) If a booster with an alternative product is needed, that product also can be produced quickly and without significant manufacturing barriers or supply-chain issues	Can be produced efficiently and as expeditiously as possible; the dose of antigen required for protection allows for high production yield (which will affect cost and availability) Can be produced in quantities sufficient for prophylactic use in at-risk regions or populations If a booster with an alternative product is needed, that product also can be produced quickly and without significant manufacturing barriers or supply-chain issues If an adjuvant is needed, it can be formulated with the vaccine instead of combined at the time of use	Can be produced in quantities sufficient for prophylactic use in at-risk regions or populations
Licensure	Meets criteria for licensure or accelerated licensure pathway Recommendation for vaccine use by the WHO	Meets criteria for accelerated licensure pathway or expanded access (such as EUA), with full licensure potentially to follow|||| Criteria for expanded access or EUA are acceptable to EMA, FDA, and the NRAs of countries affected by the epidemic|||| Conditional recommendation for vaccine use by the WHO	Meets criteria for licensure Product is prequalified by the WHO	Meets criteria for licensure

AE=adverse event. CTC=controlled temperature chain. EMA=European Medicines Agency. EUA=emergency use authorisation (applicable to regulations in the USA). EVD=Ebola virus disease. FDA=US Food and Drug Administration. NRA=national regulatory authority. *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. †Optimally, a vaccine should be available for all age groups; however, some vaccines might not be able to be given to young children because of general reactogenicity or interference with safety or efficacy of EPI (Expanded Program on Immunization) vaccines. ‡Ideally, a vaccine will be safe and effective in special populations, such as immunocompromised people 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. §Initial vaccination of older adolescents and adults is a potentially viable strategy because: this will encompass most high-risk people (eg, health-care workers, Ebola community workers, funeral workers, and in-home care providers as well as many case contacts); the epidemiology of EVD in west Africa indicates that the largest burden of disease occurs in this age group, and by targeting this population, enough herd immunity might be achieved to stop the outbreak when combined with other control measures. ¶A tiered strategy targeted initially to health-care workers, adults, and adolescents, then later to children and the elderly over time might be considered (depending on the vaccination strategy), with more than one vaccine product being appropriate for different populations and different usages. ||Safety profiles for vaccines used in an outbreak/epidemic setting might 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. **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. ††Investigators will not be able to determine durability of protection in the current clinical trials; this will require additional observation and follow-up studies. ‡‡A monovalent vaccine against Zaire Ebola virus is adequate to control the current west Africa epidemic; however, strategic use of a reactive vaccination strategy aimed at controlling future filovirus disease outbreaks will likely also require development of monovalent vaccines against Sudan Ebola virus and Marburg virus or a trivalent vaccine against all three pathogens. §§Liquid vaccines are easy to administer because they don't need reconstitution. Lyophilised vaccines may be more temperature stable, but require reconstitution with an appropriate diluent. These two different forms of vaccine each have advantages and disadvantages that will need to be weighed based on conditions in the field, including stability, transport, and disposal constraints. ¶¶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). ||||Issues around accelerated licensure and expanded access apply predominantly to this epidemic. If the current phase 3 clinical disease endpoint studies are inconclusive, one or more Ebola vaccines could potentially be licensed via FDA's accelerated approval pathway (if correlates of protection are identified) or via FDA's Animal Rule pathway (if correlates of protection cannot be identified).

Table 2: **Target product profile for Ebola vaccines in epidemic and endemic settings**

partners as appropriate. Finally, Team B members might not always have an insider's perspective on information because of a lack of direct involvement with government entities or companies, which can limit the ability to obtain a full and accurate situational assessment.

Conclusion

The Ebola Vaccine Team B was able to leverage the experience of a group of dedicated individuals who represent a wide range of expertise applicable to the generation and deployment of Ebola vaccines. As a result, the Ebola Vaccine Team B has been able to provide valuable ongoing commentary on the Ebola vaccine development process and serves as a mechanism to enhance the greater good by providing independent, informed support to traditional public health processes.

Wellcome Trust-CIDRAP Ebola Vaccine Team B members

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Contributors

MO, KM, JO, KK-B, and JF contributed to the concept and design of the project. MO facilitated Team B conference calls. KM, JO, and KK-B wrote sections of the initial Team B recommendations report, which served as a basis for much of the manuscript. MO, KM, JO, and JF contributed to drafts of the manuscript. MO and KM reviewed and approved all edits from Team B members. MO, KM, JO, KK-B, and JF reviewed and approved the final version of the manuscript.

Declaration of interests

JF is Director of the Wellcome Trust, which has funded clinical trials of two Ebola vaccines, cAd3 (in the UK and Mali) and rVSV-EBOV (in Geneva, Gabon, Kenya, and Guinea). MO, KM, JO, and KK-B declare no competing interests.

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