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Ebola vaccines: keep the clinical trial protocols on the shelf and ready to roll out

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Safe and effective vaccines to prevent Ebola infection would be useful in the fight against this devastating disease. Depending on their efficacy, onset of immunity, length of protection, and cost and ease of administration, these vaccines could contain or even prevent an outbreak.

During an outbreak, a vaccine could prevent infection of front-line health workers and staff who are engaged in patient transport and burial. In terms of containment action, vaccination of whole households of patients could prevent any tertiary cases that might occur from persons infected secondarily by caring for the initial household case. Populations at high risk, eg, villages or urban wards where multiple transmission chains have been identified, could also be targeted in a vaccination programme. Because exposure risk is time-limited in most outbreaks, these vaccination strategies might not need a vaccine that triggers long-lasting immunity.

An Ebola vaccine that induces long-lasting immunity could, however, find a place in outbreak prevention. Routine vaccination of health workers in areas where Ebola infection is known to be a risk within west and central Africa, could be a major intervention to prevent Ebola outbreaks. The majority of outbreaks, including the most recent outbreak in DR Congo in 2014, occurred after health workers became infected.[1–4] Infected heath workers inadvertently serve as a conduit of infection to their own family members or caretakers, and from these initial infections, transmission is sustained in the community by direct contact with patients or dead bodies. Some evidence indicates that if Ebola emerges and its transmission is not amplified by infection of health workers, outbreaks do not occur.[5,6] More widespread preventive vaccination in general populations living in high-risk areas would depend on cost-benefit analysis, operational feasibility, and acceptance.

Previous Ebola vaccines have been developed with financial aid of grants provided by various US defence and health agencies because of concern that the Ebola virus could be used deliberately for bioterrorism, but no public health call for such vaccines from WHO or other international organisations, African countries, or civil society was ever made prior to the current outbreaks. Although the Board of GAVI, the vaccine alliance, has approved plans of up to US$300 million for vaccine procurement and up to $90 million for the strengthening of infrastructure to provide vaccines, a long-term market will depend on the WHO recommendations[7] for vaccine use, once the vaccines have been shown to be safe and effective, and the ability of countries and the donor community to provide funding for procurement.

Phase 1 clinical trials have been completed for three candidate vaccines, and these vaccines are entering or are about to enter phase 2 and 3 clinical trials in countries where Ebola outbreaks are occurring. Time is of the essence because efficacy trials can only be completed while the Ebola virus continues to circulate. WHO is facilitating a process to devise an emergency regulatory pathway in these countries such that rapid introduction of vaccines for clinical trials and general distribution is feasible without compromising scientific standards and rigour.[8] With the support of UNICEF, WHO, and the clinical trial consortia, efforts to raise large-scale community engagement are underway in these countries to build trust and allay concerns about clinical trials. Ethical and human participant review processes in the countries where trials will be done are also underway, and final clearance is being sought from heads of state.

Logistically, clinical trials will not be easy. Vaccine formulations have yet to be optimised, and some vaccine preparations must be stored well below –20°C until use.[9] Without an understanding of the serological correlates of protection in humans, clinical trials to assess vaccine efficacy can only be done while the Ebola virus is circulating in human populations. Research consortia are now setting up logistical support platforms, training research assistants for clinical trial conduct, ensuring community engagement, and obtaining national ethical and regulatory clearance and other permissions required so that trials can begin. There is urgency to complete these efforts because Ebola incidence is decreasing as countries place more emphasis on surveillance and contact tracing and as communities build a better understanding of how to prevent transmission and spread.

What will happen if phase 3 trials have insufficient power to determine efficacy as or if incidence continues to wane as hoped? A logical conclusion would be that trials would need to rapidly reassume when and where the next Ebola outbreak occurs. Because emergence that leads to an outbreak is a random and unpredictable event, this emergence might not occur in the countries that are working to prepare for the trials at present. Lessons from the multicentre Mechanisms of Severe Acute Influenza Consortium (MOSAIC) project in the UK might be of use. Designed and funded to improve the understanding of clinical and immunological progression of H1N1 virus while it was circulating among UK populations, the MOSAIC project faced many delays in start-up. The conclusions were that expedited ethical approval, a single pre-existing template for any material transfer agreements, and research and

Lancet 2015; 385: 1913–15

Published Online
April 3, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60645-6

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For the **MOSAIC project** see http://www1.imperial.ac.uk/mosaic/about/

development approvals in advance of the expected influenza season of high transmission were crucial to the efficient management of an outbreak.

Much more must be done to ensure that vaccine trials can be rolled out again, if necessary, once the present outbreak is over and the next outbreak occurs. Vaccines already produced must be stored, optimised, and maintained in sufficient quantities; funders of clinical trials must maintain fluid funding to roll out trial operations when needed; countries at risk of an Ebola outbreak must provide ethical, regulatory, and other clearances in the period between outbreaks and maintain these clearances until future outbreaks occur; and scientists must keep the clinical trial protocols on the shelf and be ready to rapidly implement them when needed.

WHO, together with regulatory agencies in countries where vaccines will be studied and a wider group of African regulators has begun a process to address some of the above-mentioned challenges. Regulatory agencies in Africa, the US Food and Drug Administration (which already has a so-called animal rule policy when human vaccine efficacy trials are not possible), the European Medicines Agency, and other regulatory agencies should actively engage to jointly consider an accelerated licensure strategy that does not rely on vaccine efficacy, but is rather based primarily on adequate safety and immunogenicity in the relevant human populations.

Adequate safety data should include at least the amount and quality of data that would be expected under a normal licensure process. Typically, this would imply safety data from thousands of adult participants, paediatric and elderly age groups, and key populations regarded as at high risk (eg, pregnant women, persons who are malnourished, with HIV infection, or otherwise immune-compromised). A full complement of preclinical toxicology studies, including reproductive toxicity data, would also be expected.

Central to the approval process would be the establishment of a functional relation between immune responses in human beings and those obtained in vaccinated non-human primates protected against experimental challenge. Trust must also be built within the study populations to avoid counterproductive reactions ranging from rumours of adverse effects to full-blown conspiracy theories that could easily undermine this accelerated approach. Finally, accelerated licensure would need to come with a commitment that additional efforts to confirm efficacy would be undertaken post-licensure.

An accelerated approach could possibly lead to full registration of one or more Ebola vaccines within the next 12–18 months, with the understanding that post-approval commitments would be in place for confirmatory trials to establish vaccine efficacy in properly designed and executed clinical trials in time for a new outbreak. Large community-based trials would be far easier to do with a vaccine that was already registered and stockpiled, and for which policy recommendations for use were in place. With this approach in place, industry might be more inclined to scale up and dedicate manufacturing capacity for a vaccine that could be registered in the near term than it would be for a vaccine approved under traditional approaches. But it must be clear to all, including pharmaceutical companies, that accelerated licensure does not equate to accelerated marketing, but rather, that registration of an Ebola vaccine in advance would make it much simpler to introduce the vaccine for study in the event of a new outbreak.

Past experience suggests that post-licensure promises of further research by some companies, as indicated by a regulator, are ignored or not fully completed. If WHO's Strategic Advisory Group of Experts (SAGE) on Immunization were to provide a recommendation for GAVI to support purchase of stockpile vaccine for efficacy studies, there might be a way to decrease the risk of broken post-licensure promises. The vaccine stockpile would require periodic renewal as the vaccines are used up in trials or expire, and a contract to replenish or renew the stockpile could be made conditional on compliance with efficacy trials. An even stronger mechanism could be for a regulatory agency to block sales of vaccine to non-government purchasers or to put an expiration clause into the approval letter that would require the manufacturer to repeat safety tests. Post-approval safety monitoring also requires national pharmacovigilance systems, but such systems are fledgling or non-existent in most developing countries, and there is an urgent need to implement these systems. Even so, any commitment for post-approval efficacy studies will always be conditional upon there being another outbreak.

Lessons from WHO's attempts to ensure that stockpiled smallpox vaccine could be used urgently, should smallpox be reintroduced, might also be applicable. WHO defined the criteria for release of unlicensed vaccine from its stockpile, and a vaccine request form was provided to countries that met those criteria, along with a disclaimer and a letter about the regulatory needs for use of the vaccine, such that when vaccine was released from the stockpile, it could be immediately licensed and used.[10] Such measures would facilitate a release of the vaccine for efficacy trials into the field as early as possible.

In the past, a continuum of vaccine research and development activities for emerging pathogens once outbreaks have ended was difficult and almost impossible to maintain. During the outbreak of severe acute respiratory syndrome (SARS), vaccine developers began research and development, only to see the outbreak fade and funding decreased.[11] Continued funding could have resulted in a vaccine candidate effective in animal models infected with SARS and possibly other coronaviruses, such as the Middle East respiratory syndrome coronavirus, which is now emerging and re-emerging in the Middle East. And continued readiness for clinical vaccine trials

by specific countries and the international community could have facilitated vaccine efficacy trials in the Middle East and led the world closer to an effective coronavirus vaccine.

Serious consideration should also be given to the creation of an internationally supported facility dedicated to rapidly developing vaccines against known emerging pathogens, such as a multivalent Filovirus vaccine that could protect against multiple Ebola virus strains and the Marburg virus.

Once the west Africa Ebola outbreak is over and the generous and innovative national and international response has drawn to an end, the challenge might again be to maintain the continuum of vaccine studies that lead to an effective vaccine. This time the opportunities must not be lost.

Contributors

All authors contributed equally to planning, writing, and revising this report.

Declaration of interests

We declare no competing interests.

References

1 Maganga G, Kapetshi J, Berthet N, et al. Ebola virus disease in the Democratic Republic of Congo. *N Engl J Med* 2014; **371:** 2083–91.

2 Lamunu M, Lutwama J, Kamugisha J, et al. Containing a haemorrhagic fever epidemic: the Ebola experience in Uganda (October 2000–January 2001). *Int J Infect Dis* 2004; **8:** 27–37.

3 Khan A, Tshioko F, Heymann D, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. *J Infect Dis* 1999; **179** (suppl 1)**:** S76–86.

4 Report of an International Commission. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ* 1978; **56:** 271–93.

5 Jezek Z, Szczeniowski M, Muyembe-Tamfum J, McCormick J, Heymann D. Ebola between outbreaks: intensified Ebola hemorrhagic fever surveillance in the Democratic Republic of the Congo, 1981–1985. *J Infect Dis* 1999; **179** (suppl 1)**:** S60–S64.

6 Heymann D, Weisfeld J, Webb P, Johnson K, Cairns T, Berquist H. Ebola hemorrhagic fever: Tandala, Zaire, 1977–1978. *J Infect Dis* 1999; **142:** 372–76.

7 WHO. WHO Ebola R&D effort—vaccines, therapies, diagnostics. 2015. http://www.who.int/medicines/ebola-treatment/ebola_r_d_effort/en/ (accessed Feb 23, 2015).

8 GAVI Vaccine Alliance. Gavi commits to purchasing Ebola vaccine for affected countries. Dec 11, 2014. http://www.gavi.org/Library/News/Press-releases/2014/Gavi-commits-to-purchasing-ebola-vaccine-for-affected-countries/ (accessed Feb 23, 2015).

9 Wellcome Trust. Recommendations for accelerating the development of Ebola vaccines. Feb 17, 2015. http://www.wellcome.ac.uk/News/Media-office/Press-releases/2015/WTP058692.htm (accessed March 26, 2015).

10 WHO. Recommendations for the production and quality control of smallpox vaccine, revised 2003. WHO Technical Report Series 926, annex 1. Geneva: World Health Organization, 2004

11 Cassels FJ. Severe acute respiratory syndrome. The Jordan Report 2012. Bethesda, MD: National Institute of Allergy and Infectious Diseases, 2012: 98–104.