Perspectives

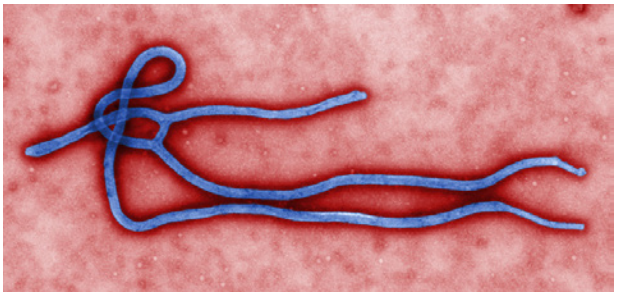
Ethical Considerations for Use of Vaccines in the Current West African Ebola Outbreak

Jon S. Abramson, MD[1]

Ebola virus is one of several viruses that cause hemorrhagic fever disease and can be confused clinically with other hemorrhagic diseases including Lassa fever, yellow fever and dengue fever. With the exception of Dengue fever, these viruses cause outbreaks of disease associated with a high mortality rate (20 – 90%). In the case of Ebola hemorrhagic fever (EHF) symptoms usually occur 8 – 10 days (range 2 – 21 days) after exposure to Ebola virus. As of beginning of April 2015 there have been 24, 872 reported cases of EHF with 10,311 deaths (~41% mortality rate). These numbers substantially underestimate the total number of Ebola cases and deaths in west Africa because many patients do not come to treatment centers. Furthermore, the diversion of resources away from other diseases (e.g., malaria) is likely leading to additional deaths.

The World Health Organization (WHO) in collab-oration with various governments and partners (e.g., Doctors Without Borders), is working intensely to develop an effective response to the current Ebola outbreak. Previous Ebola outbreaks had been contained within a relatively short period of time using available interventions including early detection and isolation, contact tracing and adherence to rigorous infection control (Table). However, the current outbreak has been much harder to control due to multiple factors including an inadequate healthcare infrastructure to care for large numbers of very ill people in the affected countries, shortages of infection control equipment (e.g., gloves, gowns) and fear and mistrust of many in the population regarding how they will be cared for. On August 8, 2014, the WHO formally declared the Ebola epidemic an "international public-health emergency of international concern".

Given the inability to control the outbreak to date, effective treatment or preventive modalities would be very helpful.



During the past decade, research efforts to develop drugs and vaccines for EHF have been ongoing. Some of these have shown promising results in the laboratory and/or in animal models, but they have not yet been evaluated for safety and efficacy in humans and all are unlicensed (i.e., the modality has not been approved for use by a globally recognized regulatory agency such as the Food and Drug Administration [FDA]). Due to the continuing severity of the Ebola outbreak and the desire of leadership in affected countries to consider use of experimental interventions, on August 11, 2014, the WHO convened a panel of outside ethicists to consider the ethical implications of the potential use of unlicensed products. The panel reached consensus that given the severity of the current Ebola outbreak, it is ethical to offer therapies and vaccines with as yet unknown efficacy and adverse effects as potential treatment or prevention modalities. The group noted that ethical criteria must guide the provision of such interventions including obtaining informed consent, transparency on all aspects of care, confidentiality, preservation of dignity and community involvement. There was unanimous agreement that there is a moral duty to evaluate these interventions, using the best possible clinical trials that can be designed under the circumstances, in order to prove the safety and efficacy of the various interventions or provide evidence to stop their use. The panel also discussed the ethical criteria to prioritize who

should receive unlicensed experimental therapies or vaccines and for achieving fair distribution within communities and amongst countries, in the face of a growing number of possible new interventions, all of which are unlikely to be produced in sufficient quantities in the short term to meet demand.

The issue of whether to use an unlicensed vaccine is pertinent to the Strategic Advisory Group of Experts on Immunizations (SAGE) that is tasked with making recommendations to the WHO Director General on the use of vaccines. SAGE on occasion has recommended the off-label use of a licensed vaccine after assessing the risk versus benefit (e.g., in 2012 SAGE recommended the licensed yellow fever vaccine be considered for off-label use in pregnant women in the setting of a yellow fever outbreak). However, the set of circumstances for consideration of using an unlicensed Ebola vaccine are substantially different than using a licensed vaccine off-label. There are no efficacy or safety data in humans for the experimental Ebola vaccines under development (e.g., a chimpanzee adenoviral vector-based filovirus vaccine containing the *Zaire ebolavirus* species [ChAd3] and a recombinant Vesicular Stomatitis Virus vaccine containing both the *Zaire and the Sudan ebolavirus* species [rVSV] are two of the vaccines being considered for use in phase 3 clinical studies).

While one of the unlicensed modalities that could potentially be effective for treating EHF (i.e., ZMapp, a combination product composed of three different monoclonal antibodies that bind to different epitopes of the Ebola virus glycoprotein) has already been given to a small number of infected healthcare workers (HCWs), there are important differences in the ethical consideration for the use of a treatment modality versus a vaccine used to prevent disease. The most important difference is that the treatment modality is only being used in those already infected with the Ebola virus and therefore at very high risk of dying. In contrast, the vaccine would initially most likely be given to healthy people who are at increased risk for contracting disease (e.g., HCWs, household contacts of an infected person, etc). Another very important consideration is there is already a proven alternative for preventing the spread of Ebola virus (i.e., effective implementation of infection control measures including contact tracing).

Decisions on how best to care for individuals and populations are made even harder when the needed data about the proposed intervention are scant and are being considered under the pressure of a large outbreak causing high mortality and great suffering. In addition to ZMapp, passive immunization with serum from patients who had recovered from Ebola infection has been tried as a therapeutic intervention in a small number of patients with EHF. The use of these types of untested therapies to treat EHF is understandable, although doing so raises a number of important ethical considerations (e.g., how to equitably and transparently distribute a scarce resource). The risk versus benefit consideration for someone with EHF getting an experimental therapeutic modality is very different than giving an unlicensed preventive vaccine to someone who is currently well.

My own opinion is that an unlicensed Ebola vaccine used in a preventive mode should only be given within the boundaries of well-designed human studies with appropriate safety monitoring. One possible exception would be if Ebola vaccine can prevent disease when given soon after a high risk exposure to the virus. Very preliminary animal data suggest that this may be the case, and if confirmed with additional studies use of the vaccine might be considered in those at high risk of infection due to a known exposure to the virus (e.g., a HCW stuck with a needle from a patient with EHF).

Even if a highly effective Ebola vaccine can be developed, it will take additional time before a vaccine program could be

Year	Country	Ebola virus species[@]	Reported Virulence			Description
			Cases	Deaths	Fatality rate	
1976	Zaire	EBOV	318	280	88%	First recognition of EHF. Disease was spread by close personal contact and by use of contaminated needles and syringes in hospitals/clinics.
1976	Sudan	SUDV	284	151	53%	Many HCWs were infected.
1995	Zaire	EBOV	315	250	79%	Outbreak traced to index patient working in forest. Epidemic spread through families and hospitals.
2000–2001	Uganda	SUDV	425	224	53%	Occurred in four districts of Uganda. The three greatest risks associated with EHF were attending funerals of other cases, contact with patients in one's family, and HCWs caring for patients without using adequate personal protective measures.
2001–2002 Oct–Jul	Gabon Congo	EBOV	122	96	79%	Occurred over the borders of Gabon and the Republic of the Congo.
2002–2003 Dec–Apr	Congo	EBOV	143	128	90%	Occurred in two districts in Cuvette Ouest Département.
2007	DR Congo	EBOV	264	187	71%	Last confirmed case on October 4, 2007 and last death on October 10. The outbreak was declared over on November 20.
2007–2008 Dec–Jan	Uganda	BDBV	149	37	25%	First recognition of BDBV. Occurred in in western Uganda.
2013–2014 Dec–present	Guinea Liberia Sierra Leone Nigeria Senegal	EBOV	5,232	2,630	50%	The most severe Ebola outbreak ever recorded in regards to the number of human cases and fatalities. It began in Guéckédou, Guinea and spread to Sierra Leone, Liberia, and Nigeria.

Table. Epidemiologic and clinic findings in major EHF outbreaks in Africa.

Table modified from List of Ebola Outbreaks. August 28, 2014. http://en.wikipedia.org/wiki/List_of_Ebola_outbreaks. While there have been a total of 22 Ebola outbreaks in Africa only those that involve >100 people are noted in this table.
The International Committee on Taxonomy of Viruses currently recognizes four species of the ebolavirus: Zaire ebolavirus (EBOV), Sudan ebolavirus (SUDV), Reston ebolavirus (RESTV), and Taï Forest ebolavirus (TAFV). One additional species or type of Ebola is often recognized by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) as Bundibugyo ebolavirus (BDBV) or Ebola-Bundibugyo, following the outbreak in Uganda in 2007.

expected to help impact the Ebola outbreak. Therefore, we must use those interventions we currently know are effective and not pin our hopes on the development of an Ebola vaccine. The WHO in collaboration with its partners, needs to continue to fully implement the Ebola Response Roadmap plan which calls for a coordinated international response to improve the healthcare infrastructure in the affected countries including, effective contact tracing of infected patients; improving the medical management capacity of healthcare centers; providing HCWs with further training and adequate quantities of personal protective equipment; and effective communication with the population in affected areas to correct their misconceptions about the disease and care that is being provided.

Authors

Author Affiliations: Professor, Department of Pediatrics, Wake Forest School of Medicine, Winston-Salem, NC 27157

[1]The author is an advisor to the WHO. The opinions expressed in this article are those of the author and do not necessarily represent those of the WHO.

Sources of Funding: There was no funding for this project.

Conflicts of Interest: The authors have no conflicts of interest to report.

Address correspondence to:

Jon S. Abramson, M.D.
Department of Pediatrics
Wake Forest School of Medicine
Winston-Salem, NC 27157
Phone: 336-716-2415
email: jabrams@wakehealth.edu

References

Casillas AM[1], Nyamathi AM, Sosa A, Wilder CL, Sands H. A current review of Ebola virus: pathogenesis, clinical presentation, and diagnostic assessment. Biol Res Nurs. 2003;4:268-75.

World Health Organization Ebola virus disease outbreak west Africa. Update September 4 2014. http://www.who.int/csr/don/2014_09_04_ebola/en/

Andrea Marzi A, Feldmann H. Ebola virus vaccines: an overview of current approaches. Expert Review Vaccines. 2014;13:521-531.

World Health Organization Ebola Response Roadmap.

August 29, 2014. http://apps.who.int/iris/bitstream/10665/131974/1/roadmapsitrep1_eng.pdf?ua=1

Estimating the Future Number of Cases in the Ebola Epidemic-Liberia and Sierra Leone, 2014–2015. MMWR. September 26, 2014. Vol. 63 / No. 3