

# How the Current West African Ebola Virus Disease Epidemic Is Altering Views on the Need for Vaccines and Is Galvanizing a Global Effort to Field-Test Leading Candidate Vaccines

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(See the major article by Sarwar et al on pages 549–57.)

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## ACCUMULATED DOGMA ON EBOLA

Since it first appeared as a clinical syndrome in Central Africa in the mid-1970s, accompanied by isolation of the causative virus, Ebola virus disease has fascinated infectious disease clinicians, virologists, and epidemiologists because of the striking clinical syndrome exhibited by patients (which culminates in a hemorrhagic diathesis in approximately 35% of infected individuals) [1], high case-fatality rate (50%–90%), and facile transmissibility of the virus among close contacts [2], including caregivers [3]. Heretofore, its limited geographic distribution (Central and East Africa) and modest overall burden of disease, manifested as occasional small outbreaks ultimately interrupted by institution of stringent infection

control methods, combined to make this an uncommon exotic tropical infectious disease [4]. After the 11 September 2001 attacks and subsequent anthrax bioterrorism episodes in the United States, there was concern in the United States and Europe over the potential use of certain pathogens as bioterrorism agents. Ebolavirus, with its high case-fatality rate and potential for enhanced transmissibility, is ranked by the Centers for Disease Control and Prevention as a category A bioterrorism agent (highest priority). This prompted virologists to study the pathogenesis of ebolavirus infection and vaccine developers to design strategies to generate vaccine candidates. During the next decade, impressive progress was made in Ebola vaccine research. However, the population targets for use of such vaccines were limited and included civilian populations in defined geographic areas, for whom reactive immunization would be performed following a deliberate release during a bioterrorism event, and laboratory scientists working with the virus.

## EBOLA STRIKES WEST AFRICA WITH A VENGEANCE

The current outbreak in West Africa has altered dogma on Ebola virus disease and

markedly changed perceptions about the need for an Ebola vaccine for civilian populations in Africa [5]. West Africa encompasses some of the world's least developed, resource-deprived countries, many also having experienced in recent years upheavals of civic society, including civil wars. Not surprisingly, the healthcare infrastructure in these impoverished countries is severely under-resourced and needs strengthening at all levels. In these settings, *Zaire ebolavirus* has penetrated crowded poor urban slums [5], as well as rural villages, and led to a massive outbreak with >5864 cases and 2811 deaths [6]. Healthcare workers have comprised approximately 10% of the deaths. Consequently, fear for their lives and concern for their families have led healthcare workers in some settings to be absent from their jobs at hospitals and health centers, while others have declined to care for patients with Ebolavirus disease. This represents a crisis with many dimensions, since patients with Ebola virus disease need intensive medical care from clinical staff who must administer it while practicing strict isolation techniques.

The West African epidemic has been relentless and has revealed that, in certain high-density impoverished populations,

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ebolavirus has the potential to spread much more easily than previously anticipated. The high frequency of severe disease and deaths among healthcare workers has identified a new highly focused target population. A well-tolerated, highly effective Ebola vaccine that can rapidly elicit protection following the administration of a single dose would constitute an important public health tool [7] that, at the very least, would protect healthcare workers and avoid interruptions in medical care [8]. Administration of multiple vaccine doses, each separated by an appropriate interval, or a more complicated heterologous prime-boost regimen, can achieve more-durable protection [9–11] but may not be needed for epidemic control.

## EBOLA VACCINE CANDIDATES

Since 2000, diverse Ebola vaccine development strategies have borne fruit. Candidates include vaccines based on live viral vectors (such as replication-competent and replication-defective human adenovirus [12–14], replication-defective chimpanzee adenovirus [15, 16], vesicular stomatitis virus [17], and modified vaccinia Ankara virus), DNA vaccines [18], and virus-like particle vaccines [19]. Vaccine candidates with characteristics rendering them particularly attractive as potential single-dose interventions to rapidly stimulate protective immune responses are certain live viral vector vaccines expressing the wild-type glycoprotein antigens of ebolavirus [14]. Their speed in eliciting protection following administration of a single dose makes them promising potential public health tools for reactive immunization of healthcare workers and family contacts and neighbors in outbreaks such as that in West Africa. It is hoped that they will interrupt virus transmission at key points, when transmission would otherwise be amplified. Interfering with transmission at amplification points to control epidemics is supported by both theoretical and practical observations [8].

## THE PATH TO LICENSURE FOR EBOLA VACCINES

It is straightforward to generate evidence documenting the safety, clinical acceptability, and immunogenicity of candidate Ebola vaccines to support a biologics license application. However, establishing that the vaccine is efficacious and identifying an immunologic correlate of protection represent more-daunting undertakings [20]. Ethical and practical issues make it difficult to perform a classical randomized, controlled field trial to assess the efficacy of an Ebola vaccine, as has been done for vaccines against many other infectious diseases. Large outbreaks of ebolavirus infection are unpredictable, so it is difficult beforehand to set up a field trial in expectation of a large epidemic that would yield enough cases to assess vaccine protection. Moreover, trying to undertake controlled efficacy trials during an epidemic of a highly lethal disease poses ethical issues. Accordingly, placebo-controlled challenges in a nonhuman primate model under good laboratory practices at a biosafety level 4 facility would appear to be one lynchpin source of efficacy data [20]. Although no human vaccine has heretofore been licensed on the basis of the so-called Animal Rule [21], an Ebola vaccine might set the precedent. Several nonhuman primate models elicit disease that closely resembles human Ebola virus disease [22], a key argument for the relevance of animal protection data. This strategy toward licensure should be accompanied by measurement of an immune response that correlates with protection in the animal model so that it can be carefully measured in humans and that a rational immunization schedule and likely duration of protection (based on the longevity of the immune response) can be assessed. While the wild-type glycoprotein has been unequivocally identified as a protective antigen [14], the search for an immunologic correlate has been problematic [20, 23]. Both serum antibodies and T cells have been implicated as contributing

to protection [23]. For licensed vaccines for which a mechanistic immunologic correlate of protection has been identified, the correlate has almost always been a serum antibody [24]. A serum antibody correlate of protection based on experimental challenges of nonhuman primates would facilitate clinical development of a vaccine and the path to the vaccine's licensure, but modern techniques make a cell-mediated immunity correlate also feasible [25].

Administration of a prelicensure candidate Ebola vaccine to high-risk contacts (including healthcare workers) in large phase 2 clinical trials in an extensive outbreak such as the one ongoing in West Africa can assess immunogenicity following vaccine administration under field conditions and can provide hints that the vaccine is protective. If the experimental vaccine is highly protective in humans, one would expect rates of disease and fatalities to fall off precipitously in vaccinated high risk contacts compared to what was observed prior to vaccine use, ie, a “before versus after” comparison. The best example of such information constituting evidence of vaccine efficacy was with the Sabin live oral poliovirus vaccine strains, which were not subjected to large-scale, randomized, controlled field trials to assess their efficacy in preventing paralytic poliomyelitis. Rather, Sabin and his collaborators performed demonstration mass immunizations with his live vaccine strains in populations in which polio epidemics were raging. They documented a precipitous fall in circulating wild type polioviruses and cases of paralytic disease [26].

Once sufficient prelicensure safety data are accrued, in future outbreaks the Ebola vaccine could be offered as part of a reactive vaccination clinical trial in which consenting subjects would be given vaccine. Case-control studies could assess the proportion of individuals with Ebola virus disease who received vaccine versus the proportion of healthy controls who were vaccinated [27–29]. Case-control studies can also be undertaken after

licensure to assess vaccine effectiveness under real-life outbreak conditions. Whether performed before or after licensure, these studies assume that the risk of exposure among persons who receive the vaccine is comparable to the risk among those who do not, which may not be true.

## A GLOBAL CONSORTIUM OF PARTNERS MOBILIZES TO ACCELERATE THE TESTING OF EBOLA VACCINE CANDIDATES IN CLINICAL TRIALS DURING THE WEST AFRICAN OUTBREAK

Concerned over the relentless progression of Ebola virus disease in West Africa and aware of promising candidate Ebola vaccines, in early August 2014 the WHO encouraged an array of partners to undertake a historically rapid progression to move Ebola vaccines from the preclinical arena into clinical trials in sub-Saharan Africa [30]. Two related vaccines developed at the National Institutes of Health's Vaccine Research Center—a vaccine containing monovalent nonreplicating chimpanzee type 3 adenovirus live vector expressing *Zaire ebolavirus* glycoprotein and a bivalent vaccine consisting of the *Zaire ebolavirus* vaccine plus the same vector expressing Sudan virus glycoprotein (approximately 1:1 mix)—are headed for phase 1 and 2 studies in Africa. Monovalent vaccine will be tested in Mali and Gambia in West Africa, mainly among healthcare worker volunteers who would be responsible for treating cases of Ebola virus disease, should they occur (Mali shares a long border with Ebola-affected Guinea). Bivalent vaccine will be tested in Uganda and Mali.

### SUMMARY

The Ebola epidemic spreading in 3 of the world's least developed countries in West Africa, with high case-fatality rates and with health workers accounting for approximately 10% of the deaths, is a public health crisis that may be a harbinger of

similar epidemics occurring wherever poverty is extreme, civil society is in turmoil, and health services are rudimentary. Since delivery of single-dose Ebola vaccines may serve as a future adjunct control measure, clinical trials of promising vaccines are commencing in Africa.

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**Potential conflicts of interest.** M. M. L. serves as a member of the Scientific Advisory Working Group to the Vaccine Research Center (VRC) of the National Institute of Allergy and Infectious Diseases (NIAID), which has developed two candidate Ebola vaccines slated for clinical trials in West Africa. M. M. L. is also a member of the VRC Board of Scientific Counselors. A. V. H. has a patent on a different chimpanzee adenovirus vaccine vector pending, and a patent on a chimpanzee adenovirus vaccine for malaria issued. He has pioneered the use of chimpanzee adenovirus vectors as vaccines and has been involved in many clinical trials of this technology.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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