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How the current West African Ebola epidemic is altering views on the need for vaccines and is galvanizing a global effort to field test leading candidates

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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, Ebolavirus disease has fascinated infectious disease clinicians, virologists and epidemiologists because of the striking clinical syndrome exhibited by patients (that culminates in a hemorrhagic diathesis in ~ 35%) [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 disease burden manifested as occasional small outbreaks ultimately interrupted by instituting stringent infection control methods combined to make this an uncommon exotic tropical infectious disease [4]. After the September 2001 attacks on the World Trade Center and ensuing anthrax bioterror episodes, there was concern in the USA and Europe over the potential use of certain pathogens as bioterror agents. Ebolavirus, with its high case fatality and potential for enhanced transmissibility, was ranked as a Category A pathogen of high concern as a potential bioterror agent. This prompted virologists to study the pathogenesis of Ebolavirus infection and vaccine developers to design strategies to generate vaccine candidates. During the ensuing decade impressive progress was made in Ebola vaccine research. However, the population targets for use of such vaccines were limited, and included biodefense reactive immunization of civilian populations in defined geographic areas following a deliberate bioterror release, and protection of laboratory scientists working with the virus.

Ebola strikes West Africa with a vengeance

The current outbreak in West Africa has altered dogma on Ebolavirus 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 health care infrastructure in these impoverished countries is severely under-resourced and needs strengthening at all levels. In these settings an Ebolavirus

Zaire species variant has penetrated crowded poor urban slums [5], as well as rural villages, and led to a massive outbreak with more than 3069 cases and 1552 deaths (WHO, August 28, 2014). 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 Ebola patients. This represents a crisis with many dimensions, since Ebola patients 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 Ebola has the potential in certain high density impoverished populations 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 [6], at the least to protect healthcare workers and avoid interruptions in medical care [7]. Multiple spaced vaccine doses or a more complicated heterologous prime-boost regimen may achieve more durable protection [8, 9], but may not be needed for epidemic control.

Ebola vaccine candidates

Since 2000, diverse Ebola vaccine development strategies have borne fruit. Candidates include viral live vector vaccines (replication competent and replication-defective human adenovirus [10-12], replication-defective chimpanzee adenovirus [13, 14], vesicular stomatitis virus [15], modified vaccinia Ankara virus, DNA vaccines [16] and virus-like particles [17], among others. 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 [12]. 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 in West Africa. It is hoped that they will interrupt virus transmission at key points where it is otherwise amplified. Interfering with transmission at amplification points to control epidemics is supported by both theoretical and practical observations [7].

The path to licensure for Ebola vaccines.

It is straight forward 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 [18]. 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 Ebola outbreaks 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 non-human primate model under Good Laboratory Practices at BSL-4 containment would appear to be one lynchpin source of efficacy data [18]. Although no human vaccine has heretofore been licensed based on the “Animal Rule” [19], an Ebola vaccine might set the precedent. Several non-human primate models elicit disease that closely resembles human Ebola disease [20], a key argument for the relevance of animal protection data. This strategy towards 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 a rational immunization schedule and likely duration of protection (based on longevity of the immune response) can be assessed. While the wild type glycoprotein has been unequivocally identified as a protective antigen [12], the search for an immunologic correlate has been problematic [18, 21]. Both serum antibodies and T cells

have been implicated as contributing to protection [21]. For licensed vaccines for which a mechanistic immunologic correlate of protection has been identified, it has almost always been a serum antibody [22]. A serum antibody correlate of protection based on experimental challenges of non-human primates would facilitate clinical development and the path to licensure but modern techniques make a cell-mediated immunity correlate also feasible [23].

Administration of a pre-licensure candidate Ebola vaccine to high risk contacts (including healthcare workers) in large Phase 2 clinical trials in an extensive outbreak such as is 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, i.e., a “before versus after vaccine use” 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 collaborators performed demonstration mass immunizations with his live vaccine strains in populations where polio epidemics were raging, and documented a precipitous fall in cases following mass administrations [24].

Once sufficient pre-licensure 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 Ebolavirus disease cases that received vaccine versus the proportion of healthy controls vaccinated [25-27]. Case/control studies can also be undertaken post-licensure to assess effectiveness under real-life outbreak conditions. Whether pre- or post-licensure, these studies assume that persons who get the vaccine are comparable in risk of exposure to 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 Ebolavirus 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 pre-clinical arena into clinical trials in sub-Saharan Africa [28]. Two related vaccines developed at NIH's Vaccine Research Center, including a monovalent non-replicating chimpanzee type 3 adenovirus live vector expressing expressing Ebolavirus Zaire glycoprotein, and a bivalent vaccine consisting of the Zaire vaccine plus the same vector expressing Sudan virus glycoprotein (~ 1:1 mix) are headed for Phase 1 and 2 studies in Africa. Monovalent vaccine will be tested in Mali and The Gambia in West Africa mainly among healthcare worker volunteers who would be responsible for caring for Ebola patients, should they occur (Mali shares a long border with Ebola-affected Guinea). Bivalent vaccine will be tested in Uganda and Mali.

Summary comment.

The Ebola epidemic spreading in three of the world's least developed countries in West Africa, with high case fatality and with health workers accounting for ~ 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 single-dose Ebola vaccines may serve as future adjunct control measures, clinical trials of promising vaccines are commencing in Africa.

Reference List

(1) Feldmann H, Geisbert TW. Ebola haemorrhagic fever. Lancet **2011 Mar 5**; 377 (9768) :849-62.

(2) Dowell SF, Mukunu R, Ksiazek TG, Khan AS, Rollin PE, Peters CJ. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. Commission de Lutte contre les Epidemies a Kikwit. J Infect Dis **1999 Feb**; 179 Suppl 1:S87-91.:S87-S91.

(3) Ftika L, Maltezou HC. Viral haemorrhagic fevers in healthcare settings. J Hosp Infect **2013 Mar**; 83 (3) :185-92.

(4) Leroy EM, Gonzalez JP, Baize S. Ebola and Marburg haemorrhagic fever viruses: major scientific advances, but a relatively minor public health threat for Africa. Clin Microbiol Infect **2011 Jul**; 17 (7) :964-76.

(5) Baize S, Pannetier D, Oestereich L, et al. Emergence of Zaire Ebola Virus Disease in Guinea - Preliminary Report. N Engl J Med **2014 Apr 16**.

(6) Hoenen T, Groseth A, Feldmann H. Current ebola vaccines. Expert Opin Biol Ther **2012 Jul**; 12 (7) :859-72.

(7) Kerstiens B, Matthys F. Interventions to control virus transmission during an outbreak of Ebola hemorrhagic fever: experience from Kikwit, Democratic Republic of the Congo, 1995. J Infect Dis **1999 Feb**; 179 Suppl 1:S263-7.:S263-S267.

(8) Fausther-Bovendo H, Mulangu S, Sullivan NJ. Ebolavirus vaccines for humans and apes. Curr Opin Virol **2012 Jun**; 2 (3) :324-9.

(9) Richardson JS, Dekker JD, Croyle MA, Kobinger GP. Recent advances in Ebolavirus vaccine development. Hum Vaccin **2010 Jun**; 6 (6) :439-49.

(10) Sullivan NJ, Geisbert TW, Geisbert JB, et al. Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates. Nature **2003 Aug 7**; 424 (6949) :681-4.

(11) Swenson DL, Wang D, Luo M, et al. Vaccine to confer to nonhuman primates complete protection against multistrain Ebola and Marburg virus infections. Clin Vaccine Immunol **2008 Mar**; 15 (3) :460-7.

(12) Sullivan NJ, Geisbert TW, Geisbert JB, et al. Immune protection of nonhuman primates against Ebola virus with single low-dose adenovirus vectors encoding modified GPs. Plos Med **2006 Jun**; 3 (6) :e177.

(13) Kobinger GP, Feldmann H, Zhi Y, et al. Chimpanzee adenovirus vaccine protects against Zaire Ebola virus. Virology **2006 Mar 15**; 346 (2) :394-401.

(14) Ledgerwood JE, Costner P, Desai N, et al. A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults. Vaccine **2010 Dec 16**; 29 (2) :304-13.

(15) Jones SM, Feldmann H, Stroher U, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. Nat Med **2005 Jul**; 11 (7) :786-90.

(16) Martin JE, Sullivan NJ, Enama ME, et al. A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. Clin Vaccine Immunol **2006 Nov**; 13 (11) :1267-77.

(17) Warfield KL, Aman MJ. Advances in virus-like particle vaccines for filoviruses. J Infect Dis **2011 Nov**; 204 Suppl 3:S1053-9. doi: 10.1093/infdis/jir346.:S1053-S1059.

(18) Sullivan NJ, Martin JE, Graham BS, Nabel GJ. Correlates of protective immunity for Ebola vaccines: implications for regulatory approval by the animal rule. Nat Rev Microbiol **2009 May**; 7 (5) :393-400.

(19) Burns DL. Licensure of vaccines using the Animal Rule. Curr Opin Virol **2012 Jun**; 2 (3) :353-6.

(20) Geisbert TW, Hensley LE, Larsen T, et al. Pathogenesis of Ebola hemorrhagic fever in cynomolgus macaques: evidence that dendritic cells are early and sustained targets of infection. Am J Pathol **2003 Dec**; 163 (6):2347-70.

(21) Sullivan NJ, Hensley L, Asiedu C, et al. CD8+ cellular immunity mediates rAd5 vaccine protection against Ebola virus infection of nonhuman primates. Nat Med **2011 Aug 21**; 17 (9):1128-31.

(22) Plotkin SA. Correlates of protection induced by vaccination. Clin Vaccine Immunol **2010 Jul**; 17 (7):1055-65.

(23) Plotkin SA. Complex correlates of protection after vaccination. Clin Infect Dis **2013 May**; 56 (10):1458-65.

(24) Sabin AB, Ramos-Alvarez M, Alvarez-Amezquita J, et al. Live, orally given poliovirus vaccine: effects of rapid immunization on population under conditions of massive enteric infection with other viruses. JAMA **1960**; 173:1521-6.

(25) Orenstein WA, Bernier RH, Dondero TJ, et al. Field evaluation of vaccine efficacy. Bull World Health Organ **1985**; 63 (6):1055-68.

(26) Lucas ME, Deen JL, von SL, et al. Effectiveness of mass oral cholera vaccination in Beira, Mozambique. N Engl J Med **2005 Feb 24**; 352 (8):757-67.

(27) Luquero FJ, Grout L, Ciglenecki I, et al. Use of Vibrio cholerae vaccine in an outbreak in Guinea. N Engl J Med **2014 May 29**; 370 (22):2111-20.

(28) http://www.wellcome.ac.uk/News/Media-office/Press-releases/2014/WTP057225.htm#.U_9OWtTjJ5g.mailto