

VACCINES

Immunology of protection from Ebola virus infection

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A December 2014 meeting reviewed Ebola virus immunology relevant to vaccine development, including Ebola prevention, immunity, assay standardization, and regulatory considerations. Vaccinated humans appear to achieve immune responses comparable in magnitude with those associated with protection in nonhuman primates, suggesting that immunological data could be used to demonstrate vaccine efficacy.

The Ebola epidemic in West Africa has highlighted gaps in our understanding of both the pathogenesis and immunological response to this devastating disease. To bridge these gaps and inform future clinical, scientific, and regulatory decision-making related to vaccines against Ebola, a workshop entitled “Immunology of Protection from Ebola Virus Infection,” cosponsored by the U.S. Food and Drug Administration (FDA), the National Institutes of Allergy and Infectious Diseases (NIAID), the U.S. Department of Defense (DOD), the Centers for Disease Control and Prevention (CDC), and the Biomedical Advanced Research and Development Authority, was convened in December 2014 to discuss important aspects of Ebola virus and vaccine immunology (Table 1).

PREVENTION

To date, the most effective response to Ebola virus infection has been prevention: identifying and isolating patients to prevent spread of the disease. Indeed, as the result of enhanced surveillance put in place after the initial outbreak in Liberia, Sierra Leone, and Guinea, some countries (including Nigeria and Senegal) were able to rapidly isolate infected patients and prevent sustained transmission, leading to local control of the outbreak. However, these strategies met with varying degrees of success in the countries where the initial outbreaks occurred. In Liberia, after early high transmission levels, changes in isolation and burial prac-

tices reduced new infection rates. However, Sierra Leone and Guinea were still experiencing substantial levels of virus transmission as of December 2014 (1). Therefore, although primary preventive measures are considered critical to stopping Ebola virus transmission, a safe and effective vaccine is also needed to reduce Ebola-related mortality in outbreak settings. Even a partially effective vaccine could reduce the basic reproduction number (R_0 , which represents the average number of new cases that are generated from each existing case) from 2014 estimates of 1.38 to 2.02 (2) to below 1.0, which would allow control of the epidemic. Thus, the international community has been engaged in an unprecedented effort to facilitate the development of an Ebola vaccine. Vaccine developers, manufacturers, and regulators have worked to expeditiously initiate clinical trials of leading candidate vaccines, while at the same time assuring adequate product characterization and human subject protection (3).

IMMUNITY TO EBOLA VIRUS

Understanding of Ebola virus immunology is a key to vaccine development. Much of our current understanding of Ebola virus immunology comes from animal models, which include mice, guinea pigs, and non-human primates (NHPs, typically rhesus or

cynomolgus macaques). These models have limitations, including that typical human exposures to the Ebola virus may not be represented by the intramuscular injection of 1000 plaque-forming units (PFU) of virus generally used in NHP challenge/protection studies. Indeed, animals exposed in this way become ill more rapidly than do humans and die sooner after infection. Nonetheless, existing animal models, especially macaque models, do mimic human infections, and protective immunity in these models may be considered likely to predict human response to the challenge strain.

Humoral immunity plays an important role in protection from Ebola virus disease. However, data derived from passive transfer studies in NHPs show that some antibodies protect animals from subsequent challenge but do not neutralize the virus, whereas others neutralize virus but do not protect animals. Thus, the relative importance of antibodies that are neutralizing versus those that may confer protection through other mechanisms (for example, antibody-dependent cellular cytotoxicity, complement-mediated, or Fc-dependent mechanisms) is unclear. Consistent with these data, the most successful passive transfer regimens, including the use of the monoclonal antibody cocktail ZMapp (Mapp Biopharmaceutical), which both protects and treats NHPs exposed to Ebola virus, include combinations of antibodies that target different effector functions of humoral immunity (4). A sample bank that includes sera from protected and unprotected vaccinated NHPs could be used in studies designed to differentiate these mechanisms as well as further inform vaccine development strategies.

The Ebola vaccines that are most advanced in development are based on generating immune responses against the structural glycoprotein (GP). Viral soluble glycoprotein (sGP), which is a nonstructural viral protein that shares features with GP and is secreted from infected cells, may influence

Table 1. Next steps to address gaps in understanding Ebola virus immunology in the context of regulatory evaluation.

Develop and curate an NHP sample bank that will allow different laboratories to analyze samples from NHPs that were protected versus unprotected from Ebola virus challenge.
Form a clinical assay working group to facilitate standardization of clinical assays among stakeholders.
Evaluate humoral responses as potential immune markers of protection in upcoming clinical trials.
Develop protocols to safely handle and store serum and/or PBMCs from trial participants who may have Ebola infection.
Collect and store samples from as many vaccinees as possible in areas of risk for Ebola exposure in order to aid in establishing an immune marker of protection.

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protective humoral immunity and complicate identification of protective epitopes (5). Nevertheless, GP-targeted approaches show promise in NHPs. NHPs immunized with 2×10^7 PFU of vesicular stomatitis virus (VSV)-vectored Ebola vaccines and subsequently challenged with 1000 PFU of Ebola Zaire demonstrated a correlation between survival and levels of total immunoglobulin G (IgG) specific to Ebola Zaire GP. Surviving and nonsurviving NHPs differed in their prechallenge anti-Ebola GP enzyme-linked immunosorbent assay (ELISA) titers, which averaged 1:12,805 and 1:64, respectively (6). Moreover, NHP studies using VSV-vectored vaccine reported protection from Ebola Zaire challenge in 4/4 animals, with antibody titer in the 1:100 to 1:1000 range (7). However, neutralizing antibody was not consistently detectable after immunization, suggesting that as in the passive transfer studies, neutralizing antibody may not predict protection for this particular vaccine.

There are also differences in responses to vaccine platforms, in particular for cell-mediated immunity (CMI). CMI may not predict protection by use of VSV-vectored vaccines because studies have shown that CMI was not detected before challenge of protected NHPs and no interferon- γ (IFN- γ) or tumor necrosis factor- α (TNF- α) response in CD8⁺ T cell intracellular cytokine staining studies could be detected after challenge (7). In addition, in vaccinated NHPs, CD8⁺ T cell depletion at the time of vaccination did not affect survival after challenge. Depletion of CD4⁺ T cells at time of immunization, but not at day 28, reduced survival after challenge. These data support a greater relative importance of humoral as compared with cellular response for this vaccine (8). Recent studies suggest that innate responses may aid the humoral immune response in VSV-vectored vaccine-induced protection (6, 9).

CMI may play a larger role in protecting NHPs immunized with adenovirus (Ad) type 5-vectored vaccines from Ebola virus challenge. In one study, 100% survival was observed at GP ELISA titers of $>1:3700$ and 85% survival at a titer of $>1:1500$ (10). This protection appeared not to be mediated solely through antibodies because animals depleted of CD8⁺ T cells were not protected, and passive transfer of hyperimmune sera failed to protect nonvaccinated animals from challenge (11). Further study of CD8⁺ T cell quality indicated that CD8⁺ T effector (IFN- γ - and TNF- α -positive) and CD8⁺

T memory [interleukin-2 (IL-2)-, IFN- γ -, and TNF- α -positive] cells may be most important in providing protection. However, use of this vaccine platform may be limited in populations with high incidence of natural immunity to related adenoviruses because immune responses induced after a first dose of Ad5-vectored vaccine reduced both humoral and CMI responses after a second dose of the same vaccine (12).

A chimpanzee adenovirus 3 (ChAd3)-vectored vaccine avoids this limitation and provided 100% protection in NHPs at a dose of 10^{10} virus particle units (VPU), a dose at which stronger cellular immune responses became apparent (13). Alternatively, studies showed that boosting responses to Ad-vectored (such as Ad5, Ad26, or ChAd3) in various combinations with a different Ad-vector (12) or with modified vaccinia virus Ankara (MVA)-vectored vaccines (13, 14) can yield greatly improved immune responses and durability of protection. Both higher immune responses and greater survival were observed when an 8-week interval was used as compared with a 2-week interval for both adenovirus- and MVA-vectored vaccine boosts. In NHPs immunized with Ad26- or MVA-vectored vaccines and boosted with heterologous Ad26-, Ad35-, or MVA-vectored vaccines, ELISA titers above $\sim 1:5000$ were associated with protection, but these titers also were associated with greater CMI responses by means of enzyme-linked immunosorbent spot (ELISPOT), which also appeared to be a marker of increased protection among NHPs with lower ELISA titers (14). Thus, for adenovirus-vectored vaccines, in contrast to VSV-vectored vaccines, CMI response may be an immune correlate of risk of infection.

These studies are now being complemented by data from human trials. Preliminary data derived from phase 1 studies of a VSV-vectored vaccine expressing Ebola glycoprotein showed median GP ELISA antibody responses of $\sim 1:2000$ at day 28 at a vaccine dose of 10^6 PFU (15). Data from subjects who received higher doses in these studies are pending. Because this is a replicating virus, the dose-response curve may not be as steep as for a nonreplicating virus, suggesting that lower doses could also be considered. Studies to evaluate immune responses to lower doses of the VSV-vectored vaccine have begun.

Recently published results of an NIAID-sponsored phase 1 study of a bivalent ChAd3-vectored vaccine expressing

Ebola glycoproteins showed that the strongest immune response was induced at the highest (2×10^{11} VPU) dose of vaccine (16). Immune responses measured by ELISA at this dose (mean titer 1:2037 at day 28) were roughly comparable with those induced by using 10^{10} VPU of the ChAd3-vectored vaccine in previous NHP studies. Whereas CD8⁺ T cell responses were comparable at both 10^{10} and 10^{11} VPU of the ChAd3-vectored vaccine, 10^{11} VPU was required for consistent CD4⁺ T cell responses. Additional studies—including of ChAd3-vectored vaccine boosting of individuals previously primed with an Ebola DNA vaccine—are under way or planned. Preliminary data from a study conducted at the Jenner Institute of Oxford University also showed that antibody or CMI responses induced by up to 5×10^{10} VPU of monovalent ChAd3-vectored vaccine were not comparable with those observed in NHPs protected from challenge (17). However, preliminary data show that boosting of these responses with a multivalent MVA-vectored vaccine at an interval of 3 to 10 weeks (mean of 6 weeks) could yield further improvement of both humoral and CMI responses (18).

ASSAY STANDARDIZATION

With the increasing availability of human data to complement the NHP studies, it is critical to develop standardized assays that can be used to compare immune responses across vaccines, across studies, and across species. Issues to be considered when developing GP standards for ELISA assays include selection of the GP virus strain, ideal GP conformation, and GP stability. Antibody standards could be derived from sera from vaccinated individuals, convalescent individuals (who present potential safety issues because of the possibility of the presence of Ebola virus), and/or animals protected from challenge. Use of assays in a regulatory setting will require qualification or validation, depending on the stage of clinical development. Validated assays are generally required when used to support licensure. CMI assays present additional challenges, including determination of appropriate peptide pools to be used, and logistical issues in collecting, storing, and shipping peripheral blood mononuclear cells (PBMCs) in an epidemic setting. Standardization efforts addressing these challenges are ongoing. For example, the U.S. government-sponsored Filovirus Animal Nonclinical Working Group (FANG) has made substantial progress toward standardizing reagents and

models for Ebola virus challenge experiments (19); the UK's National Institute of Biological Standards and Control is planning to develop an antibody standard for World Health Organization (WHO) use (20); and Battelle is developing a transferable GP-ELISA assay that includes standard operating procedures, a training module, and a technology transfer package with a proficiency panel and tracking system (21).

Potential sequence differences between assay strain and circulating wild-type strains and vaccine strains are critical concerns in developing neutralizing assays, as are the risks of using live Ebola virus strains. One way to address these challenges is to use high-throughput assays that can be performed in biological safety level 2 laboratories that use viral pseudotypes or pseudovirions, which also can be readily adapted to changes in virus strain. In these assays, serum is tested for the ability to neutralize either pseudotyped VSV virus derived from cells cotransfected with VSV and Ebola-GP or VSV pseudovirions that coexpress green fluorescent protein (GFP) and Ebola-GP. The pseudotype assay will be used to evaluate sera for the presence of neutralizing antibodies from volunteers enrolled in current phase 1 trials. Additional studies will be needed to determine whether these assays measure similar or different aspects of Ebola-neutralizing immunity or whether (given that neutralizing responses appear not to predict protection in NHPs) these assays provide advantages over ELISA. The potential for responses to non-Ebola virus components to influence assay results may also impede application of these VSV-based assays to evaluation of VSV-vectored vaccines.

GP-based ELISAs are preferred for evaluating sera from volunteers enrolled in phase 2 or phase 3 trials. However, because an immune marker predicting protection from Ebola virus disease has not yet been established (and may differ between vaccines), various immune assays may need to be considered, including assays that have not yet been developed. A clinical assay working group may facilitate continued discussions to identify best practices and approaches with regard to standardization of assays to evaluate immune responses to Ebola virus vaccines.

REGULATORY CONSIDERATIONS

A vaccine can be licensed only if it is shown to be safe, pure, and potent and if the manufacturing facility meets standards designed

to assure that the product continues to be safe, pure, and potent (22). There are three regulatory pathways by which an Ebola vaccine could be licensed: “traditional” approval—in which clinical evidence either directly shows protection against disease or shows (using reliable and validated assays) an immunologic response based on a marker scientifically well established to predict protection; accelerated approval (23)—in which meaningful benefit is shown to patients over existing treatments based on adequate, well-controlled clinical trials with a surrogate end point (such as immune response) that is likely to predict clinical benefit; and approval by the “animal rule” (24), which allows adequate studies in animals to provide evidence of substantial effectiveness when human efficacy studies are not ethical or feasible. Approval under the Accelerated Approval and Animal Rule provisions require post licensure studies in order to verify the product's clinical benefit. Notably, demonstration of safety is required for all regulatory pathways described, and immunogenicity data can support product approval with any of these three regulatory pathways.

Immunogenicity data from Ebola vaccines are becoming available from phase 1 studies in the United States, Europe, and Africa. Although human and NHP responses have not yet been compared in validated assays, these data suggest that vaccines are able to induce immune responses in humans at levels associated with protection in NHPs—an important conclusion that suggests the feasibility of considering vaccine approval on the basis of immunogenicity data via accelerated approval or animal rule pathways.

A number of phase 3 clinical studies are planned in this area using Ebola infection or disease end points, including a randomized controlled trial sponsored by NIAID in Liberia and a study sponsored by CDC in other African countries. However, successful control of infection in affected countries may make performing definitive clinical trials operationally challenging, and variability of supportive care (25) may muddy interpretation of mortality or clinical morbidity results from vaccine trials. In the event a prime-boost regimen is needed to achieve adequate and durable immune responses, consideration will need to be given to optimizing the dosing interval in humans.

Declining Ebola virus infection incidence or a shift in disease away from urban centers to small, geographically dispersed

foci may limit the ability of these studies to definitively assess vaccine efficacy. Yet even if efficacy cannot be established, cases of Ebola virus infection in immunized individuals from whom serum is available could be used to help to identify one or more immune markers of protection that could potentially support licensure of these or other Ebola vaccines. Suggestive evidence for immune markers predictive of Ebola virus infection could be based on studies of samples (serum and, if feasible, PBMCs) from individuals who become infected and those who remain uninfected with Ebola virus, and thus, collection and storage (although not necessarily initial testing) of as many such samples as possible from planned clinical trials could facilitate development of such immune markers. Indeed, despite acknowledged logistical difficulties, thousands of serology samples were collected and tested in other developing country vaccine trials (26), supporting the feasibility and value of collecting such samples. In addition, collection of samples from vaccinated individuals who present with suspected Ebola virus infection could provide important information regarding levels of immune response that are not protective. Of course, very low Ebola virus infection rates could also interfere with identifying an immune marker of protection. One consideration in collecting such samples will be the development of procedures to assure that they can be safely stored and tested, given the potential for some of them to contain live Ebola virus (27).

LOOKING AHEAD

A randomized, double-blind, placebo-controlled phase 2/3 study has been initiated by NIAID in Liberia in order to assess the efficacy of both the VSV- and ChAd3-vectored Ebola vaccines. The CDC has announced plans for a study to test the VSV-vectored vaccine in Sierra Leone, and the WHO recently began an efficacy study based on ring vaccination of Ebola contacts in Guinea, also using the VSV-vectored vaccine (28). Recent success in reducing the number of Ebola cases in West Africa will reduce the statistical power of these studies to demonstrate vaccine efficacy, potentially increasing the importance of considering the use of immunogenicity-based approaches to demonstration of efficacy in support of vaccine licensure. Thus, immunogenicity evaluations from these and other studies may take on increasing importance in facilitating the rapid approval of an effective vaccine.

REFERENCES

1. J. Agua-Agum, A. Ariyaratnam, B. Aylward, I. M. Blake, R. Brennan, A. Cori, C. A. Donnelly, I. Dorigatti, C. Dye, T. Eckmanns, N. M. Ferguson, P. Formenty, C. Fraser, E. Garcia, T. Garske, W. Hinsley, D. Holmes, S. Hugonnet, S. Iyengar, T. Jombart, R. Krishnan, S. Meijers, H. L. Mills, Y. Mohamed, G. Nedjati-Gilani, E. Newton, P. Nouvellet, L. Pelletier, D. Perkins, S. Riley, M. Sagrado, J. Schnitzler, D. Schumacher, A. Shah, M. D. Van Kerkhove, O. Varsaneux, N. Wijekoon Kannangarage, WHO Ebola Response Team, West African Ebola epidemic after one year—Slowing but not yet under control. *N. Engl. J. Med.* **372**, 584–587 (2015).
2. WHO Ebola Response Team, Ebola virus disease in West Africa—The first 9 months of the epidemic and forward projections. *N. Engl. J. Med.* **371**, 1481–1495 (2014).
3. C. L. Cooper, S. Bavari, A race for an Ebola vaccine: Promises and obstacles. *Trends Microbiol.* **23**, 65–66 (2015).
4. C. D. Murin, M. L. Fusco, Z. A. Bornholdt, X. Qiu, G. G. Olinger, L. Zeitlin, G. P. Kobinger, A. B. Ward, E. O. Saphire, Structures of protective antibodies reveal sites of vulnerability on Ebola virus. *Proc. Natl. Acad. Sci. U.S.A.* **111**, 17182–17187 (2014).
5. M. A. de La Vega, G. Wong, G. P. Kobinger, X. Qiu, The multiple roles of sGP in Ebola pathogenesis. *Viral Immunol.* **28**, 3–9 (2015).
6. G. Wong, J. S. Richardson, S. Pillet, A. Patel, X. Qiu, J. Alimonti, J. Hogan, Y. Zhang, A. Takada, H. Feldmann, G. P. Kobinger, Immune parameters correlate with protection against ebola virus infection in rodents and nonhuman primates. *Sci. Transl. Med.* **4**, 158ra146 (2012).
7. S. M. Jones, H. Feldmann, U. Ströher, J. B. Geisbert, L. Fernando, A. Grolla, H. D. Klenk, N. J. Sullivan, V. E. Volchkov, E. A. Fritz, K. M. Daddario, L. E. Hensley, P. B. Jahrling, T. W. Geisbert, Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. *Nat. Med.* **11**, 786–790 (2005).
8. A. Marzi, F. Engelmann, F. Feldmann, K. Habertur, W. L. Shupert, D. Brining, D. P. Scott, T. W. Geisbert, Y. Kawaoka, M. G. Katze, H. Feldmann, I. Messaoudi, Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. *Proc. Natl. Acad. Sci. U.S.A.* **110**, 1893–1898 (2013).
9. K. J. Williams, X. Qiu, L. Fernando, S. M. Jones, J. B. Alimonti, VSVΔG/EBOV GP-induced innate protection enhances natural killer cell activity to increase survival in a lethal mouse adapted Ebola virus infection. *Viral Immunol.* **28**, 51–61 (2015).
10. N. J. Sullivan, J. E. Martin, B. S. Graham, G. J. Nabel, Correlates of protective immunity for Ebola vaccines: Implications for regulatory approval by the animal rule. *Nat. Rev. Microbiol.* **7**, 393–400 (2009).
11. N. J. Sullivan, L. Hensley, C. Asiedu, T. W. Geisbert, D. Stanley, J. Johnson, A. Honko, G. Olinger, M. Bailey, J. B. Geisbert, K. A. Reimann, S. Bao, S. Rao, M. Roederer, P. B. Jahrling, R. A. Koup, G. J. Nabel, CD8⁺ cellular immunity mediates rAd5 vaccine protection against Ebola virus infection of nonhuman primates. *Nat. Med.* **17**, 1128–1131 (2011).
12. T. W. Geisbert, M. Bailey, L. Hensley, C. Asiedu, J. Geisbert, D. Stanley, A. Honko, J. Johnson, S. Mulangu, M. G. Pau, J. Custers, J. Vellinga, J. Hendriks, P. Jahrling, M. Roederer, J. Goudsmit, R. Koup, N. J. Sullivan, Recombinant adenovirus serotype 26 (Ad26) and Ad35 vaccine vectors bypass immunity to Ad5 and protect nonhuman primates against ebolavirus challenge. *J. Virol.* **85**, 4222–4233 (2011).
13. D. A. Stanley, A. N. Honko, C. Asiedu, J. C. Trefry, A. W. Lau-Kilby, J. C. Johnson, L. Hensley, V. Ammendola, A. Abbate, F. Grazioli, K. E. Foulds, C. Cheng, L. Wang, M. M. Donaldson, S. Colloca, A. Folgori, M. Roederer, G. J. Nabel, J. Mascola, A. Nicosia, R. Cortese, R. A. Koup, N. J. Sullivan, Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nat. Med.* **20**, 1126–1129 (2014).
14. B. Callendret, Human adenovirus and MVA-vectored vaccines, Immunology of Protection from Ebola Virus Infection, 12-12-2014; available at <http://videocast.nih.gov/summary.asp?Live=15350&bhcp=1> (2014).
15. J. Ramsey, rVSV ZEBOV Vaccine (BPSC1001), Immunology of Protection from Ebola Virus Infection, 12-12-2014; available at <http://videocast.nih.gov/summary.asp?Live=15350&bhcp=1> (2014).
16. J. E. Ledgerwood, A. D. DeZure, D. A. Stanley, L. Novik, M. E. Enama, N. M. Berkowitz, Z. Hu, G. Joshi, A. Ploquin, S. Sitar, I. J. Gordon, S. A. Plummer, L. A. Holman, C. S. Hendel, G. Yamshchikov, F. Roman, A. Nicosia, S. Colloca, R. Cortese, R. T. Bailer, R. M. Schwartz, M. Roederer, J. R. Mascola, R. A. Koup, N. J. Sullivan, B. S. Graham, the VRC 207 Study Team, Chimpanzee adenovirus vector Ebola vaccine—Preliminary report. *N. Engl. J. Med.* **10.1056/NEJMoa1410863** (2014).
17. T. Rampling, K. Ewer, G. Bowyer, D. Wright, E. B. Imoukhuede, R. Payne, F. Hartnell, M. Gibani, C. Bliss, A. Minhinick, M. Wilkie, N. Venkatraman, I. Poulton, N. Lella, R. Roberts, K. Sierra-Davidson, V. Krähling, E. Berrie, F. Roman, I. De Ryck, A. Nicosia, N. J. Sullivan, D. A. Stanley, J. E. Ledgerwood, R. M. Schwartz, L. Siani, S. Colloca, A. Folgori, S. Di Marco, R. Cortese, S. Becker, B. S. Graham, R. A. Koup, M. M. Levine, V. Moorthy, A. J. Pollard, S. J. Draper, W. R. Ballou, A. Lawrie, S. C. Gilbert, A. V. S. Hill, A monovalent chimpanzee adenovirus Ebola vaccine—Preliminary report. *N. Engl. J. Med.* (2015). **10.1056/NEJMoa1411627**
18. A. V. Hill, Chimpanzee Adenovirus 3 EBO Z with MVA Boost, Immunology of Protection from Ebola Virus Infection, 12-12-2014; available at <http://videocast.nih.gov/summary.asp?Live=15350&bhcp=1> (2014).
19. R. Hirschberg, L. A. Ward, N. Kilgore, R. Kurnat, H. Schiltz, M. T. Albrecht, G. W. Christopher, E. Nuzum, Challenges, progress, and opportunities: Proceedings of the filovirus medical countermeasures workshop. *Viruses* **6**, 2673–2697 (2014).
20. M. Page, Requirement for Assay Reference Standards, Immunology of Protection from Ebola Virus Infection, 12-12-2014; available at <http://videocast.nih.gov/summary.asp?Live=15350&bhcp=1> (2014).
21. C. Sabourin, Assays to Measure Ebola Humoral and Cellular Responses in Humans, Immunology of Protection from Ebola Virus Infection, 12-12-2014; available at <http://videocast.nih.gov/summary.asp?Live=15350&bhcp=1> (2014).
22. Public Health Service Act, Section 351. 42 USC 262 (1944).
23. Code of Federal Regulations. 21 CFR 601, Subpart E (2014).
24. Code of Federal Regulations. 21 CFR 601, Subpart H (2014).
25. R. A. Fowler, T. Fletcher, W. A. Fischer 2nd, F. Lamontagne, S. Jacob, D. Brett-Major, J. V. Lawler, F. A. Jacquerioz, C. Houlihan, T. O'Dempsey, M. Ferri, T. Adachi, M. C. Lamah, E. I. Bah, T. Mayet, J. Schieffelin, S. L. McLellan, M. Senga, Y. Kato, C. Clement, S. Mardel, R. C. Vallenar Bejar De Villar, N. Shindo, D. Bausch, Caring for critically ill patients with ebola virus disease. Perspectives from West Africa. *Am. J. Respir. Crit. Care Med.* **190**, 733–737 (2014).
26. S. Rerks-Ngarm, P. Pitisuttithum, S. Nitayaphan, J. Kaewkungwal, J. Chiu, R. Paris, N. Premrsi, C. Namwat, M. de Souza, E. Adams, M. Benenson, S. Gurunathan, J. Tagtagia, J. G. McNeil, D. P. Francis, D. Stablein, D. L. Birx, S. Chunsuttiwat, C. Khamboonruang, P. Thongcharoen, M. L. Robb, N. L. Michael, P. Kunasol, J. H. Kim, MOPH-TAVEG Investigators, Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N. Engl. J. Med.* **361**, 2209–2220 (2009).
27. P. C. Iwen, P. W. Smith, A. L. Hewlett, C. J. Kratochvil, S. J. Lisco, J. N. Sullivan, S. G. Gibbs, J. J. Lowe, P. D. Fey, V. L. Herrera, A. R. Sambol, J. L. Wisecarver, S. H. Hinrichs, Safety considerations in the laboratory testing of specimens suspected or known to contain Ebola virus. *Am. J. Clin. Pathol.* **143**, 4–5 (2015).
28. M. Enserink, High hopes for Guinean vaccine trial. *Science* **347**, 219–220 (2015).

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