One Step Closer to an Ebola Virus Vaccine
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Despite cautious optimism from the apparent recent slowing of the spread of Ebola virus disease (EVD) in some parts of West Africa, the remaining pockets of intense transmission and the recent incursion of the virus into Mali remind us that the battle for control is still on. This is no time to be complacent. The scale of this outbreak, in which every few days about the same number of cases accrue as occurred during the entire 3-month outbreak in Gulu, Uganda, in 2000–2001 — previously the largest outbreak on record — has prompted us to pull out all the stops, albeit after a slow start. Vaccines constitute a key, but still theoretical, weapon in our armamentarium against EVD. For some years, a number of promising vaccine candidates have been identified, with many more in development. The two leading candidates are vectored vaccines in which the Ebola virus glycoprotein is presented in a replication-incompetent chimpanzee adenovirus 3 (cAd3) or a replication-competent vesicular stomatitis virus (VSV). Both vaccines have shown 100% protection in nonhuman primates at 4 to 5 weeks after single doses were administered and have now been rushed into phase 1 trials in hopes that the promise of a vaccine to help stem the crisis in Africa can be more than theoretical.

Ledgerwood and colleagues now present in the Journal the first results of the phase 1 VRC 207 trial, a nonrandomized, open-label trial of two dose levels of a cAd3-vectored bivalent vaccine against the two most virulent species of ebolavirus, Zaire and Sudan. They conclude that the vaccine was safe and immunogenic, inducing strong humoral and cell-mediated responses. Although the results of the trial are indeed promising, questions remain; both immunogenicity and reactogenicity were dose-dependent. The higher dose, which was required to generate the more vigorous immune response, was also associated with minor adverse effects in 70% of the participants, including one in whom a high fever (temperature, 39.9°C) developed, and with transient leukopenia in 20%. There were no major adverse effects, but the sample size (10 persons at each dose level) is too small to draw firm conclusions in this regard. Of particular concern is that the virus-specific CD8 T-cell response, which may be a key correlate of protection, was only 20% in the lower-dose group and 70% in the higher-dose group. Getting the dose right has relevance not only for ensuring individual protection and minimizing adverse effects, but also for stretching the vaccine supply to the maximum number of doses possible to combat the ongoing outbreak.

Interpretation of the findings of the study by Ledgerwood et al., as with all studies of filovirus vaccines, is hampered by a lack of knowledge regarding the specific correlates of immunity, although, as the authors point out, the immune responses observed in their study involving humans are consistent with those associated with protection in efficacy studies in nonhuman primates. The matter is further complicated by a lack of standardization of stock viruses and the fact that, to achieve 100% mortality in control animals, and thus interpretable results, in studies in nonhuman primates, an extremely high challenge dose of virus (1000 plaque-forming units) is used, which is probably orders of magnitude higher than the inoculum that typically infects a human. Until the correlates of immunity are better understood, it is impossible to say whether the immune response shown at the lower dose in the study by Ledgerwood et al., which caused fewer side effects, is “good enough.” Will similar results be observed in West Africa,
where malaria is holoendemic and has been associated with diminished immunogenicity with other vectored vaccines.\(^7\) At exactly what time point after vaccination is adequate immunity conferred? This is an important question, given the urgency of the situation in Africa. Will it be necessary to administer a booster with a modified vaccinia Ankara vaccine expressing the Ebola glycoprotein, which has been shown to increase the duration of immunity but would considerably complicate delivery?\(^8\) Results from ongoing phase 1 trials of a monovalent cAd3-EBO Zaire vaccine, which may be more immunogenic than a bivalent formation,\(^9\) as well as of the VSV-vectored vaccine, in various locations in the United States, Europe, and Africa (outside the epidemic area for EVD) are due soon and may help answer these important questions.

Perhaps one of the only silver linings of the EVD crisis that has shaken West Africa over the past year is that the event has pushed therapeutics and vaccines for EVD, which had previously been relatively stalled in development despite the promising results in nonhuman primates, into accelerated production and clinical trials. Assuming that the findings of Ledgerwood et al. are confirmed, especially in African populations, cAd3-EBO certainly warrants efficacy trials, but difficult decisions on the best dosage and trial design await. Can traditional phase 2 and 3 efficacy trials be performed in West Africa given the many ethical considerations, community expectations regarding the use of a placebo, and projected vaccine supply? Should the cAd3 and VSV vaccines be compared head-to-head? What should be the target population? And can it all be arranged in time for a human trial, or will we ultimately need to turn to the Food and Drug Administration Animal Rule?\(^10\) The road is still long and there are many challenges, but we are nevertheless one step closer to a solution.

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