Chimpanzee Adenovirus Vector Ebola Vaccine — Preliminary Report


ABSTRACT

BACKGROUND

The unprecedented 2014 epidemic of Ebola virus disease (EVD) has prompted an international response to accelerate the availability of a preventive vaccine. A replication-defective recombinant chimpanzee adenovirus type 3–vectored ebolavirus vaccine (cAd3-EBO), encoding the glycoprotein from Zaire and Sudan species that offers protection in the nonhuman primate model, was rapidly advanced into phase 1 clinical evaluation.

METHODS

We conducted a phase 1, dose-escalation, open-label trial of cAd3-EBO. Twenty healthy adults, in sequentially enrolled groups of 10 each, received vaccination intramuscularly in doses of $2 \times 10^{10}$ particle units or $2 \times 10^{11}$ particle units. Primary and secondary end points related to safety and immunogenicity were assessed throughout the first 4 weeks after vaccination.

RESULTS

In this small study, no safety concerns were identified; however, transient fever developed within 1 day after vaccination in two participants who had received the $2 \times 10^{11}$ particle-unit dose. Glycoprotein-specific antibodies were induced in all 20 participants; the titers were of greater magnitude in the group that received the $2 \times 10^{11}$ particle-unit dose than in the group that received the $2 \times 10^{10}$ particle-unit dose (geometric mean titer against the Zaire antigen, 2037 vs. 331; P=0.001). Glycoprotein-specific T-cell responses were more frequent among those who received the $2 \times 10^{11}$ particle-unit dose than among those who received the $2 \times 10^{10}$ particle-unit dose, with a CD4 response in 10 of 10 participants versus 3 of 10 participants (P=0.004) and a CD8 response in 7 of 10 participants versus 2 of 10 participants (P=0.07).

CONCLUSIONS

Reactogenicity and immune responses to cAd3-EBO vaccine were dose-dependent. At the $2 \times 10^{11}$ particle-unit dose, glycoprotein Zaire–specific antibody responses were in the range reported to be associated with vaccine-induced protective immunity in challenge studies involving nonhuman primates. Clinical trials assessing cAd3-EBO are ongoing. (Funded by the Intramural Research Program of the National Institutes of Health; VRC 207 ClinicalTrials.gov number, NCT02231866.)
In August 2014, the World Health Organization declared the epidemic of Ebola virus disease (EVD) in West Africa to be a public health emergency of international concern. This was the first time in more than 20 outbreaks since EVD was identified in 1976 that such a declaration had been made. The epidemic has accounted for more cases of EVD than all prior EVD outbreaks combined, with more than 15,000 cases and 5420 deaths reported since the epidemic was first recognized. The majority of cases have occurred in Guinea, Liberia, and Sierra Leone, with a small number of cases in other West African countries, Europe, and the United States. Whereas previous EVD outbreaks have been controlled by implementation of strategies for the identification of cases, isolation of case patients, and contact tracing, the scope and duration of the current epidemic illustrate the importance of establishing additional prevention tools such as an effective vaccine.

Ebola virus is a filovirus with a 19-kb, nonsegmented, negative-strand RNA genome that encodes seven viral proteins. The surface glycoprotein mediates viral entry into host cells and has been the primary antigenic target for vaccine development. We previously evaluated a series of gene-based approaches to developing an Ebola vaccine in Ebola challenge studies involving nonhuman primates, and three early-generation candidate Ebola vaccines were assessed in clinical trials between 2003 and 2009. Because of theoretical safety concerns involving wild-type Ebola glycoprotein cytotoxic effects in cell culture, initial antigen designs included a transmembrane-deleted version of glycoprotein and a full-length glycoprotein antigen containing a single amino acid mutation. No safety concerns were identified with these vaccines, but advanced development was not pursued because immunogenicity and subsequent preclinical efficacy results were deemed to be inadequate. Therefore, full-length wild-type glycoprotein delivered by DNA vaccination was clinically evaluated and shown to be immunogenic. These data supported the accelerated development of the chimpanzee adenovirus type 3 (cAd3) vaccine vector described here, which encodes wild-type glycoprotein antigens from the Zaire and Sudan species of ebolavirus.

The cAd3 Ebola vaccine (cAd3-EBO) was chosen for clinical development on the basis of a demonstration of significant efficacy in a nonhuman primate challenge model 5 weeks after a single injection and of partial efficacy at 10 months and low levels of preexisting antivector antibody in the human population. In addition, cAd3-EBO primes nonhuman primates for a boost with recombinant modified vaccinia Ankara (MVA) wild-type glycoprotein vaccine, resulting in more durable protection from challenge at 10 months.

Clinical development of the cAd3-EBO vaccine began in 2011; a Pre-Investigational New Drug Application (pre-IND) was submitted to the Food and Drug Administration (FDA) in 2013, and a phase 1 clinical trial was scheduled for the first quarter of 2015. However, in response to the emerging outbreak in May 2014, we accelerated the initiation of the cAd3-EBO phase 1 clinical trial, working closely with the FDA and condensing standard timelines. Here we report the first safety and immunogenicity results of the cAd3-EBO vaccine in healthy adults.

METHODS

STUDY DESIGN AND PARTICIPANTS

VRC 207 is a phase 1, dose-escalation, open-label, clinical trial designed to determine the safety, side-effect profile, and immunogenicity of an investigational recombinant cAd3 ebolavirus vaccine. Eligible participants were healthy adults, 18 to 50 years of age. Full details of the inclusion and exclusion criteria and study conduct can be found in the protocol, available with the full text of this article at NEJM.org. Participants were recruited from the Washington, D.C., metropolitan area. The trial was conducted at the National Institutes of Health (NIH) Clinical Center by investigators at the Vaccine Research Center (VRC) of the NIH National Institute of Allergy and Infectious Diseases (NIAID). The study was reviewed and approved by the institutional review board at the NIAID. The Department of Health and Human Services guidelines for the protection of human research subjects were followed. All participants provided written informed consent before enrollment. VRC developed the vaccine, and members of that center performed the study.

VACCINE

The cAd3 drug substances were manufactured at Advent, a subsidiary of Okainos (now GlaxoSmithKline), and the drug product (recombinant chimpanzee adenovirus type 3–vectored Ebola vaccine, VRC-EBOADC069-00-VP) was manufactured...
at the VRC Vaccine Pilot Plant, under contract with the Vaccine Clinical Materials Program, Leidos Biomedical Research. The vaccine is a sterile, aqueous, buffered solution that includes cAd3-EBO glycoprotein Zaire and cAd3-EBO glycoprotein Sudan drug substances, in a 1:1 ratio, in single-dose vials of 1×10^{11} particle units per milliliter of each drug substance (2×10^{11} particle units per milliliter total). Zaire and Sudan species were chosen because of the five species of ebolavirus, they are responsible for the majority of EVD outbreaks.\textsuperscript{2,18} VRC-DILADC065-00-VP was the formulation buffer in vaccine production and the diluent for the cAd3-EBO.

**STUDY PROCEDURES**

A single dose of vaccine was administered intramuscularly (in the deltoid muscle) by needle and syringe at a dose of 2×10^{10} particle units in group 1 and 2×10^{11} particle units in group 2. The dose-escalation plan specified that no more than one participant per day would be vaccinated for the first three participants in each group, with interim safety reviews required before additional vaccinations were performed in each group and before enrollment began in group 2. Safety monitoring included laboratory and clinical evaluations that were performed during protocol-specified study visits. Local and systemic reactogenicity and medication use for relief of symptoms were recorded by all participants for 7 days after vaccination through an electronic data-capture system (EMMES Corporation). Clinical assessments were performed, complete blood counts obtained, and levels of creatinine and alanine aminotransferase, prothrombin time, and activated partial-thromboplastin time (aPTT) measured at scheduled study visits during the first 4 weeks after vaccination. Adverse events were graded according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (modified from FDA Guidance, September 2007).\textsuperscript{19}

**Ebola Glycoprotein-Specific Antibody Responses**

Glycoprotein titers as assessed by enzyme-linked immunosorbent assay (ELISA) were measured as described previously.\textsuperscript{12} A positive response was considered to be a significant increase in titer, expressed as the 90% effective concentration (EC90; the concentration at which there is a 90% decrease in antigen binding) over the baseline value (P<0.05). Glycoprotein ELISA titers were measured against the vaccine-matched Sudan and Zaire (Mayinga) species at weeks 0, 2, and 4 and against the newly discovered Zaire species Guinea strain (Zaire–Guinea) at weeks 0 and 4.

**Ebola Glycoprotein-Specific T-Cell Responses**

Vaccine-induced T-cell responses were evaluated by means of a qualified intracellular cytokine staining assay as described previously.\textsuperscript{15} Cryopreserved peripheral-blood mononuclear cells obtained at weeks 0, 2, and 4 were stimulated with overlapping peptide pools matching the vaccine inserts for glycoprotein Sudan and Zaire and were quantified to determine the proportion of total and memory CD4 and CD8 T cells producing interleukin-2, interferon-γ, or tumor necrosis factor (TNF). Participants were considered to have had a positive response if they had a positive CD4 or CD8 response to either peptide pool (measured by interleukin-2, interferon-γ, or TNF) at week 2 or week 4. To assess vaccine-induced glycoprotein-specific memory T-cell responses, memory CD4 and CD8 T-cells were identified on the basis of CD45RA and CD28 expression, and their cytokine expression was quantified.

**cAd3 and Ad5 Serologic Assessment**

An adenovirus serum neutralization assay was performed to assess neutralizing antibody titers in order to determine baseline and vaccine-induced (week 4) neutralization of cAd3 and human Ad5. Reciprocal antibody titers are reported as the inhibitory concentration 90% (IC90; the titer at which 90% of infectivity is inhibited). The assay was performed according to previously described methods.\textsuperscript{20}

**STATISTICAL ANALYSIS**

Positive response rates with respect to the development of Ebola-specific antibodies and T-cell responses and adenovirus neutralization were calculated along with exact 95% confidence intervals. The antibody response (EC90) as assessed by ELISA was reported as the geometric mean titer with the 95% confidence interval. Fisher’s exact test was used for between-group comparisons of positive response rates, Student’s t-test for comparisons of the magnitude of the antibody response after log transformation, and the Wilcoxon test for comparisons of the magnitude of T-cell responses. The association of adenovirus neutralization with antibodies and T-cell responses was evaluated with the use of the
Spearman rank-correlation method. T-cell data from intracellular cytokine staining assays were analyzed and displayed with the use of SPICE, version 5.3. Other analyses were performed with the use of the R statistical package, version 3.1.1.

RESULTS

STUDY POPULATION
A total of 20 participants were enrolled and vaccinated from September 2 through September 23, 2014 (Fig. 1). The study population comprised 11 women and 9 men; the mean age was 37 years (range, 25 to 50) (Table 1).

VACCINE SAFETY
Information on local and systemic reactogenicity was solicited from participants at each scheduled visit. When present, reactogenicity was usually mild to moderate. There was evidence of a dose effect with respect to the use of medication for symptom relief (e.g., acetaminophen or nonsteroidal antiinflammatory drugs) and lowering of body temperature (Table 1 in the Supplementary Appendix, available at NEJM.org). Fever was not reported after vaccination in the group that received the $2 \times 10^{10}$ particle-unit dose; 2 of 10 vaccine recipients in the group that received the $2 \times 10^{11}$ particle-unit dose reported fever: one case of grade 1 fever (temperature of 38.1°C) and one of grade 3 fever (temperature of 39.9°C). Fever developed 8 to 24 hours after vaccination, responded to antipyretic medication, and resolved within 1 day. There were no serious adverse events.

Asymptomatic prolonged aPTT was observed 2 weeks after vaccination in one recipient of the $2 \times 10^{10}$ particle-unit dose (aPTT, 70.5 seconds; grade 4) and two recipients of the $2 \times 10^{11}$ particle-unit dose (aPTT, 48.4 seconds and 58.4 seconds; grade 2 and grade 4, respectively). Further evaluation (Table 2 in the Supplementary Appendix) showed that all three instances of prolonged aPTT were consistent with the induction of an antiphospholipid antibody, which causes an in vitro effect in the laboratory assay for aPTT and does not indicate a coagulopathy. Asymptomatic neutropenia or leukopenia of grade 1 or 2 was observed 3 to 4 days after vaccination in one recipient of the $2 \times 10^{10}$ particle-unit dose and in three recipients of the $2 \times 10^{11}$ particle-unit dose.

Ebola-Specific Antibody Responses
At 4 weeks after vaccination, vaccine-induced anti-glycoprotein antibodies to Zaire species were detected in 90% of the participants in group 1 and in 100% of the participants in group 2, anti-glycoprotein antibodies to Sudan species were detected in 70% and 80% of the participants, respectively, and anti-glycoprotein antibodies to Zaire–Guinea were detected in 90% and 90% of the participants, respectively. Anti-glycoprotein antibody responses (by ELISA) to at least one species or strain were detected in all 20 participants. The EC90 geometric mean titer against the Zaire antigen was higher at week 4 than at week 2 in both groups (331 vs. 106 in group 1 and 2037 vs. 376 in group 2; P = 0.001 and P < 0.001, respectively) (Table 2 and Fig. 2). The EC90 geometric mean titer against the Sudan antigen was also higher at week 4 than at week 2 (279 vs. 161 in group 1 and 936 vs. 400 in group 2), and the difference between weeks 2 and 4 reached significance in group 2 (P = 0.004) (Table 2 and Fig. 2). The EC90 geometric mean titer against the Zaire–Guinea glycoprotein antigen was higher in group 2 than in group 1 at week 4 (623 vs. 177, P = 0.02).
Ebola-Specific T-Cell Responses
Vaccine-induced CD4 and CD8 T-cell responses, as determined by expression of cytokines (interferon-γ, interleukin-2, and TNF) in response to stimulation with Zaire or Sudan glycoprotein peptides, were assessed by means of intracellular cytokine staining at weeks 2 and 4, and the expression of the cytokines (as a percentage of total CD4 and CD8 T cells) was compared with the baseline expression in all participants. Glycoprotein-specific CD8 responses to at least one antigen (Zaire or Sudan) developed by week 4 in 20% of the participants in group 1 and 70% of those in group 2 (P = 0.07); glycoprotein-specific CD4 responses to at least one antigen (Zaire or Sudan) developed by week 4 in 30% of the participants in group 1 and 100% of those in group 2 (P = 0.004) (Table 2). Glycoprotein-specific memory CD4 and CD8 T-cell responses were greater in magnitude at week 4 than at week 2 and greater in group 2 than in group 1 (Fig. 3). The majority of the memory CD4 and CD8 glycoprotein-specific T-cell responses were polyfunctional, expressing two or three cytokines (Fig. 3); the vaccine elicited high proportions of CD8 cells coproducing interferon-γ and TNF, which are known to be associated with protection in nonhuman primates.16

Table 1. Characteristics of the Participants at Enrollment.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1, 2x10^10 Particle Units (N = 10)</th>
<th>Group 2, 2x10^11 Particle Units (N = 10)</th>
<th>Overall (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (30)</td>
<td>6 (60)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (70)</td>
<td>4 (40)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>33.9±6.7</td>
<td>40.7±7.5</td>
<td>37.3±7.8</td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (30)</td>
<td>0</td>
<td>3 (15)</td>
</tr>
<tr>
<td>White</td>
<td>6 (60)</td>
<td>8 (80)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>0</td>
<td>1 (10)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Hispanic or Latino ethnic group — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Body-mass index‡</td>
<td>26.8±5.5</td>
<td>27.0±3.5</td>
<td>26.9±4.5</td>
</tr>
<tr>
<td>College or higher educational level — no. (%)</td>
<td>10 (100)</td>
<td>10 (100)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>cAd3 IC90 antibody titer &gt;200 — no. (%)§</td>
<td>5 (50)</td>
<td>3 (30)</td>
<td>8 (40)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. The abbreviation cAd3 denotes chimpanzee adenovirus type 3.
† Race and ethnic group were self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. This calculation was performed on the basis of weight and height measured at the time of screening.
§ The inhibitory concentration 90% (IC90) is the titer at which 90% of infectivity is inhibited.

cAd3 and Ad5 Serologic Assessment
Background immunity may affect the response to virus-vectored vaccines. We assessed cAd3 neutralizing antibody titers in all participants at baseline and 4 weeks after vaccination and compared them with antibody and T-cell responses (Fig. 1 in the Supplementary Appendix). At baseline, reciprocal titers of anti-cAd3 neutralizing activity ranged from undetectable (<12) to 911. After vaccination, cAd3 antibody titers increased by a factor of at least 1.9 in all participants (Table 3 in the Supplementary Appendix). As assessed with the use of the Spearman rank-correlation method, preexisting antibodies to cAd3 did not significantly correlate with glycoprotein-specific antibody responses at week 4 for Zaire species (correlation, −0.277; P = 0.24) or Sudan species (correlation, −0.333; P = 0.15). In addition, preexisting antibodies to cAd3 did not significantly correlate with the magnitude of vaccine-induced memory CD4 T-cell response (correlation, −0.232; P = 0.33). There was a moderate association between the titer of preexisting antibodies to cAd3 and the memory CD8 T-cell response (correlation, −0.511; P = 0.02) (Fig. 1 in the Supplementary Appendix).

Owing to the genetic relatedness of Ad5 to Given the importance of understanding the efficacy of vaccine-induced T-cell responses, it is crucial to consider the role of background immunity in shaping the immune response. This study highlights the potential impact of pre-existing antibodies on vaccine efficacy, particularly in the context of cross-species immunity and the need for vaccine titration to optimize protective outcomes.
cAd3, anti-Ad5 neutralizing antibody titers were also assessed in all participants at baseline and 4 weeks after vaccination. At baseline, reciprocal titers of anti-Ad5 neutralizing activity ranged from undetectable (<12) to higher than 8748 (Table 3 in the Supplementary Appendix). As assessed with the use of the Spearman rank-correlation method, preexisting antibodies to Ad5 did not significantly correlate with glycoprotein-specific antibody responses at week 4 for Zaire species (correlation, 0.194; P = 0.41) or Sudan species (correlation, 0.162; P = 0.50) or with vaccine-induced glycoprotein-specific memory T-cell responses for CD4 (correlation, −0.014; P = 0.95) or CD8 (correlation, −0.144; P = 0.55).

These initial clinical data for the Ebola virus vaccine (cAd3-EBO) support the safety and immunogenicity of a single vaccination. The rates and severity of local and systemic side effects, including fever at higher dose levels, were similar to those observed in previous studies of other adenovirus vectors.14,22 In future studies, a fever developing more than 1 day after vaccination or lasting longer than 1 day may require evaluation to determine additional causes. Vector-induced antiphospholipid antibodies were detected in 3 of 20 participants. This phenomenon was transient and has been reported previously with adenovirus vectors and licensed vaccines.14,23,24 The antiphospholipid antibodies induced by vaccination bind the phospholipid reagent in the in vitro aPTT assay but do not have a clinical effect because phospholipids are not limited in vivo. The presence of these antibodies has not been shown previously to be associated with a clinical risk of coagulopathy or a hypercoagulable state. The observation of asymptomatic, mild-to-moderate neutropenia or leukopenia on day 3 to 4 after vaccination is consistent with margination (the relative adherence of leukocytes to endothelial cells temporarily preventing detection of the leukocytes in the bloodstream) related to vaccine-induced innate immune responses.

The relative contributions of antibodies and CD8 T cells to the protection of humans from EVD is unknown; however, both are thought to be important.25 The vaccine-induced immune responses reported here are similar to those that are known to be associated with protection in efficacy studies of cAd3 and other adenovirus-vectored Ebola vaccines in nonhuman primates.12,16,26 The vaccine-induced glycoprotein Zaire–specific antibody titer at week 4 in group 2 was a geometric mean titer of 2037, which was similar to reciprocal titers of 967 to 6600 in nonhuman primates protected by a 2×10^{10} particle-unit dose of cAd3-EBO.16 The ELISA-binding antibody observed here is considered to be an indicator of “vaccine take” and is similar to that seen in protected nonhuman primates, as assessed with the use of the same assay, standards, and controls; nonetheless, the antibody level is not thought to represent a mechanistic

### Table 2. Geometric Mean Antibody Titers and Positive T-Cell Responses.*

<table>
<thead>
<tr>
<th>Vaccine Group</th>
<th>Geometric Mean Antibody Titer (95% CI)</th>
<th>Percentage of Participants with Positive Response (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zaire Glycoprotein ELISA</td>
<td>Sudan Glycoprotein ELISA</td>
</tr>
<tr>
<td><strong>Group 1:</strong> 2×10^{10} dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>week 2‡</td>
<td>106 (49–228)</td>
<td>331 (158–695)</td>
</tr>
<tr>
<td>week 4‡</td>
<td>2037 (1007–4118)</td>
<td>400 (132–1212)</td>
</tr>
<tr>
<td><strong>Group 2:</strong> 2×10^{11} dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>week 2‡</td>
<td>376 (139–1023)</td>
<td>2037 (1007–4118)</td>
</tr>
</tbody>
</table>

* Each vaccine group included 10 participants. Geometric mean titers were assessed with the use of glycoprotein enzyme-linked immunosorbent assays (ELISAs) at week 2 and week 4; positive responses with respect to glycoprotein ELISA and total glycoprotein-specific T-cells through week 4 were assessed with the use of intracellular cytokine staining assays.
† CD4 and CD8 response rates were higher in group 2 than in group 1 (P = 0.004 for CD4, and P = 0.07 for CD8).
‡ Zaire glycoprotein ELISA titers were significantly higher in group 2 than in group 1 at week 2 (P = 0.03) and week 4 (P = 0.001). Zaire glycoprotein ELISA titers were significantly higher at week 4 than at week 2 in both group 1 (P = 0.001) and group 2 (P < 0.001).
§ Sudan glycoprotein ELISA titers were significantly higher in group 2 than in group 1 at week 4 (P = 0.01). Sudan glycoprotein ELISA titers were significantly higher at week 4 than at week 2 in group 2 only (P = 0.004).
The bivalent vaccine reported here is composed of two glycoprotein constructs (Zaire and Sudan), but since the Zaire species of ebolavirus is responsible for the 2014 epidemic, a monovalent cAd3-EBOZ Zaire vaccine (cAd3-EBOZ) has also been prepared. This has been done to increase the manufacturing capacity and is supported by preclinical data in nonhuman primates that showed the efficacy of the monovalent cAd3-EBOZ. This vaccine is currently being evaluated in the United States, United Kingdom, Mali, Uganda, and Switzerland in expanded phase 1/1B clinical trials and should provide the basis for dose selection and efficacy evaluation of cAd3-EBOZ in the current epidemic. In addition, an MVA-EBO booster vaccine will be evaluated in upcoming clinical trials on the basis of improved immunogenicity and durable protection achieved by administration of a booster...
Figure 3. Vaccine-Induced Memory CD4 and CD8 T-Cell Responses, According to Dose, at Baseline, Week 2, and Week 4. Panels A through D show the individual responses for increases from baseline to week 2 and week 4 in glycoprotein Zaire–specific and glycoprotein Sudan–specific CD4 and CD8 memory T cells. A Wilcoxon test was used to calculate the P values for the comparison of the magnitude of the T-cell response. Horizontal lines indicate medians, and shaded areas interquartile ranges. The proportions, at week 4, of glycoprotein–specific CD4 and CD8 T cells (i.e., cells secreting at least one cytokine) that make any given combination of the three cytokines are shown in Panel E. The proportion of vaccine–specific CD8 T cells capable of simultaneously secreting interferon-γ (IFN+) and tumor necrosis factor (TNF+) is labeled; this level of cells with this functional profile was shown to be associated with protection in a preclinical nonhuman primate model.
vaccine in cAd3-EBO-primed nonhuman primates.16

The findings and conclusions in this report are those of the authors and do not necessarily reflect the views of the funding agency or collaborators.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES


