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Phase 2 Placebo-Controlled Trial of Two Vaccines to Prevent Ebola in Liberia

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Abstract

BACKGROUND—The safety and efficacy of vaccines to prevent Ebola virus disease (EVD) were unknown when the incidence of EVD was peaking in Liberia.

METHODS—We initiated a randomized, placebo-controlled, phase 3 trial of the chimpanzee adenovirus 3 vaccine (ChAd3-EBO-Z) and the recombinant vesicular stomatitis virus vaccine (rVSVΔG-ZEBOV-GP) in Liberia. A phase 2 subtrial was embedded to evaluate safety and immunogenicity. Because the incidence of EVD declined in Liberia, the phase 2 component was expanded and the phase 3 component was eliminated.

RESULTS—A total of 1500 adults underwent randomization and were followed for 12 months. The median age of the participants was 30 years; 36.6% of the participants were women. During the week after the administration of vaccine or placebo, adverse events occurred significantly more often with the active vaccines than with placebo; these events included injection-site reactions (in 28.5% of the patients in the ChAd3-EBO-Z group and 30.9% of those in the rVSVΔG-ZEBOV-GP group, as compared with 6.8% of those in the placebo group), headache (in 25.1% and 31.9%, vs. 16.9%), muscle pain (in 22.3% and 26.9%, vs. 13.3%), feverishness (in 23.9% and 30.5%, vs. 9.0%), and fatigue (in 14.0% and 15.4%, vs. 8.8%) ($P<0.001$ for all comparisons); these differences were not seen at 1 month. Serious adverse events within 12 months after injection were seen in 40 participants (8.0%) in the ChAd3-EBO-Z group, in 47 (9.4%) in the rVSVΔG-ZEBOV-GP group, and in 59 (11.8%) in the placebo group. By 1 month, an antibody response developed in 70.8% of the participants in the ChAd3-EBO-Z group and in 83.7% of those in the rVSVΔG-ZEBOV-GP group, as compared with 2.8% of those in the placebo group ($P<0.001$ for both comparisons). At 12 months, antibody responses in participants in the ChAd3-EBO-Z group (63.5%) and in those in the rVSVΔG-ZEBOV-GP group (79.5%) remained significantly greater than in those in the placebo group (6.8%, $P<0.001$ for both comparisons).

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*A complete list of the members of the Partnership for Research on Ebola Virus in Liberia (PREVAIL) I study group is provided in the Supplementary Appendix, available at NEJM.org.

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

CONCLUSIONS—A randomized, placebo-controlled phase 2 trial of two vaccines that was rapidly initiated and completed in Liberia showed the capability of conducting rigorous research during an outbreak. By 1 month after vaccination, the vaccines had elicited immune responses that were largely maintained through 12 months. (Funded by the National Institutes of Allergy and Infectious Diseases and the Liberian Ministry of Health; PREVAIL I ClinicalTrials.gov number, NCT02344407.)

The Ebola Virus Disease (EVD) Outbreak that began in December 2013 in western Africa created new challenges for the design and implementation of protocols to test experimental vaccines and therapeutic agents. After a request for investigational interventions from the Liberian minister of health to the secretary of health and human services in the United States in October 2014, the National Institutes of Health (NIH) engaged in discussions with the Liberian Ministry of Health regarding possible studies. On the basis of those discussions and projections of a substantial number of new cases in the coming months,[1] planning for a vaccine trial commenced under the auspices of a U.S.–Liberian clinical research partnership currently called the Partnership for Research on Ebola Virus in Liberia (PREVAIL).

Preclinical data were available on two candidate Ebola virus (EBOV) vaccines, the chimpanzee adenovirus 3–based vaccine (ChAd3-EBO-Z) and the recombinant vesicular stomatitis virus–based vaccine (rVSVΔG-ZEBOV-GP), which were in phase 1 testing. In order to evaluate these vaccines rapidly, a randomized, placebo-controlled, phase 3 trial (PREVAIL I) was designed with the aim of preventing EVD; the trial included an embedded phase 2 subtrial to evaluate safety and immunogenicity. The phase 3 trial was not completed because of a declining number of EVD cases and, ultimately, the end of the epidemic. The results of the phase 2 subtrial are now reported.

METHODS

TRIAL DESIGN AND PARTICIPANTS

In this randomized, double-blind trial, we evaluated the safety and immunogenicity of the ChAd3-EBO-Z vaccine and the rVSVΔG-ZEBOV-GP vaccine as compared with a saline placebo.[2] GlaxoSmithKline provided ChAd3-EBO-Z, and Merck provided rVSVΔG-ZEBOV-GP.

The phase 2 subtrial was powered to compare antibody responses to EBOV and the percentage of grade 3 or 4 adverse events 1 month after injection. (Details about the grading of toxic effects are provided in Section 3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Other safety measurements included injection-site reactions, targeted signs and symptoms (i.e., signs and symptoms that trial personnel asked participants specifically about), unsolicited reports of adverse events (i.e., adverse events that participants reported although they had not been asked specifically about them by trial personnel), and changes in complete blood counts and results of serum chemical tests.

Persons with a history of EVD, those with a temperature of more than 38°C, and women who were pregnant or breast-feeding were excluded from participation. Volunteers 18 years of age or older who consented to the requirements of the protocol (available at NEJM.org)

were randomly assigned in a 2:1:2:1 ratio to receive an intramuscular injection of the ChAd3-EBO-Z vaccine (2 ml, at a concentration of 1×10^{11} particle units per milliliter), 2 ml of placebo, the rVSVΔG-ZEBOV-GP vaccine (1 ml, at a concentration of 2×10^{7} plaque-forming units per milliliter), or 1 ml of placebo (Fig. S1 in the Supplementary Appendix; the high-level molecular structures of the vaccines are also described in Section 3 in the Supplementary Appendix). The 1:1:1 ratio for the analyses was obtained by combining the two placebo groups.

The trial investigators were unaware of the interim summary results throughout the trial. An independent data safety and monitoring board sponsored by the National Institute of Allergy and Infectious Diseases reviewed interim analyses that were focused on safety.

The trial protocol was approved by the National Research Ethics Board of Liberia, the institutional review board of the National Cancer Institute, the Liberian Medicines and Health Products Regulatory Authority, and the Food and Drug Administration. Written informed consent was obtained from all the participants during a private session after they attended information sessions during which the trial was explained to potential volunteers in small groups with the use of pictorial flip charts.

The trial was designed and the data analyzed by the senior authors and biostatisticians. Data were collected by the investigators and staff at Redemption Hospital and the Liberian Institute for Biomedical Research. The authors vouch for the accuracy and completeness of the analyses and data reported and also confirm adherence to the protocol. The initial draft of the manuscript was written by the first two authors and last two authors, and all the authors provided final approval to submit the manuscript for publication. Representatives of Merck and Glaxo-SmithKline participated in the review of the protocols and the manuscript and provided their approvals to both.

FOLLOW-UP

Follow-up visits occurred at week 1, month 1, and month 2 and then every 2 months thereafter through 12 months, with blood samples obtained at week 1 and at months 1, 6, and 12. In April 2015, the protocol was amended to include a follow-up visit at week 2 to look specifically for joint problems. This amendment was made after findings from a phase 1 study of the rVSVΔG-ZEBOV-GP vaccine showed that 22% of the participants reported arthritis.[3] This amendment applied to the participants who underwent randomization after April 14, 2015 (20% of all participants). Participants with medical conditions that were identified during follow-up were referred for counseling and medical care.

ANTIBODY RESPONSES TO EBOLA GLYCOPROTEIN

IgG antibody levels against the Ebola surface glycoprotein were measured in serum at baseline and at week 1 and months 1, 6, and 12 with the use of the Filovirus Animal Nonclinical Group (FANG) assay (Section 3 in the Supplementary Appendix). Antibody levels were also measured in plasma at days 3, 10, and 14 in 24 participants for whom rVSVΔG-ZEBOV-GP shedding was measured on those days.

A participant was considered to have a positive vaccine response at a follow-up visit if the $\log_{10}$ titer was increased by a factor of 4 or more from the baseline value (see Section 3 in the Supplementary Appendix) and if the participant had not had an elevated titer at baseline. All the laboratory measurements were performed in Liberia. At the time of the trial, there were no facilities in the country for measuring T-cell responses.

STATISTICAL ANALYSIS

The two active vaccine groups were each compared with the pooled placebo group and analyzed according to the intention-to-treat principle. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and R software.[4] All P values are two-sided. P values for clinical events were based on Barnard's test, and those for injection-site reactions and symptoms on Fisher's exact test. Given the many comparisons with no adjustment for type I error, we recommend caution in interpreting P values between 0.05 and 0.01.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

After a community-based social mobilization strategy about the trial and about Ebola, volunteers were encouraged to visit the vaccination center at Redemption Hospital in Monrovia, Liberia. From February 2, 2015, to April 30, 2015, a total of 1500 volunteers who attended the vaccination center and consented to participate in the trial were enrolled (500 participants per group). In the last month of enrollment, recruitment efforts were focused on enrolling women. The groups were well balanced at baseline (Table 1). The median age of the participants was 30 years, and 36.6% of the participants were women. All the participants who underwent randomization received an injection of vaccine or placebo.

Overall, the median IgG antibody level against EBOV at baseline was 78 enzyme-linked immunosorbent assay units (EU) per milliliter (interquartile range, 47 to 139; 5th and 95th percentiles, 22 and 548). A total of 4.0% of the participants had antibody levels of more than 607 EU per milliliter, a level that denoted a positive antibody response at baseline (Section 3 in the Supplementary Appendix).

FOLLOW-UP

The rate of attendance at follow-up visits through 12 months was 98.3% and was similar among the three trial groups (Fig. S1 in the Supplementary Appendix). There were no cases of EVD (defined as a positive result on reverse-transcriptase–polymerase-chain-reaction assay for Ebola virus RNA) in the trial participants during the follow-up period.

SAFETY

Serious Adverse Events at 1 Month and 12 Months—Within 1 month after injection, the time period during which serious adverse events that are due to vaccination are likely to occur, 20 participants had a serious adverse event, including 6 participants (1.2%) in the ChAd3-EBO-Z group, 6 (1.2%) in the rVSVΔG-ZEBOV-GP group, and 8 (1.6%) in the placebo group (P = 0.68 for the comparison of each vaccine with placebo) (Table 2, and

Table S1 in the Supplementary Appendix). A total of 70% of the serious adverse events in the first 30 days after injection were attributed to malaria.

Over the 12 month follow-up period, a serious adverse event occurred in 40 participants (8.0%) in the ChAd3-EBO-Z group, in 47 (9.4%) in the rVSVΔG-ZEBOV-GP group, and in 59 (11.8%) in the placebo group (Table 2, and Table S2 in the Supplementary Appendix). Most of the serious adverse events were attributed to malaria (71% overall). Malaria developed in fewer participants in the ChAd3-EBO-Z group than in the placebo group (5.2% vs. 8.8%, P = 0.03); a similar finding was observed in participants in the rVSVΔG-ZEBOV-GP group (6.6%, vs. 8.8% in the placebo group; P = 0.25) (Table 2).

By 12 months, one death had occurred among participants in the ChAd3-EBO-Z group, five among those in the rVSVΔG-ZEBOV-GP group, and six among those in the placebo group (Table 2, and Table S3 in the Supplementary Appendix). None of the deaths were attributed to EVD.

In the small subgroup of participants who were positive for the human immunodeficiency virus (HIV), none who had received an active vaccine had a serious adverse event within 1 month after injection; one of the participants who had received placebo died from *Pneumocystis jiroveci* pneumonia (see Section 4 in the Supplementary Appendix). Over a period of 12 months, in this subgroup, at least one serious adverse event occurred in 4 of 25 participants (16%) in the ChAd3-EBO-Z group (one event was attributed to malaria, two were attributed to gastroenteritis, and one was a death from an unknown cause), in 1 of 22 (5%) in the rVSVΔG-ZEBOV-GP group (two events attributed to gastroenteritis and respiratory failure), and in 6 of 31 (19%) in the placebo group (five events attributed to malaria and one death, as cited above). Participants who received a diagnosis of HIV infection, syphilis, or another incidentally discovered health issue were referred to the local health care system for follow-up.

Injection-Site Reactions, Targeted and Unsolicited Symptoms, and Laboratory Variables—During the week after injection, injection-site reactions were reported in 28.5% of the participants in the ChAd3-EBO-Z group and 30.9% of those in the rVSVΔG-ZEBOV-GP group, as compared with 6.8% of those in the placebo group (P<0.001 for both comparisons) (Table 2).

Targeted symptoms (one or more) were reported more often in each vaccine group than in the placebo group at week 1 (P<0.001 for both comparisons). At month 1, the percentage of participants who reported targeted symptoms did not differ significantly between either vaccine group and the placebo group (Table 2). Three participants in each vaccine group had a grade 2 symptom at week 1. All the remaining symptoms at week 1 and all the targeted symptoms that were reported at month 1 were of grade 1. The most commonly reported symptoms were headache, muscle pain, feverishness, and fatigue (Fig. 1). The percentage of participants who reported joint pain and other joint problems did not differ significantly between either vaccine group and the placebo group at 1 week, 2 weeks, or 1 month (Fig. 1). Specific unsolicited symptoms that were reported are summarized in the Supplementary Appendix. There was no pattern to the unsolicited symptoms that were reported for each

vaccine. There were no clinically significant laboratory changes in any of the groups. Details are provided in Section 4 and Tables S4 through S8 in the Supplementary Appendix.

MEASUREMENT OF RVSVΔG-ZEBOV-GP ON RT-PCR

A total of 24 participants participated in a substudy to measure plasma levels of rVSVΔG-ZEBOV-GP RNA by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays on days 3, 10, and 14. RNA was detected in the plasma of 2 of 8 participants who had been assigned to receive rVSVΔG-ZEBOV-GP and in none of those who had been assigned to receive ChAd3-EBO-Z or placebo. One participant had rVSVΔG-ZEBOV-GP RNA on day 3 but not on days 10 and 14, whereas the results in the second participant were positive on days 3 and 10 but not on day 14.

ANTIBODY RESPONSES TO EBOV GLYCOPROTEIN

Antibody responses to the two vaccines were greatest at month 1 and then declined at 6 months and 12 months (Table 3 and Fig. 2). As compared with the placebo group, in which the rate of antibody response was 2.8%, the rate of antibody response at month 1 was 70.8% in the ChAd3-EBO-Z group and 83.7% in the rVSVΔG-ZEBOV-GP group ($P<0.001$ for both comparisons). Findings were similar in subgroups that were defined according to age at baseline, sex, and previous contact with a person who had EVD; the percentage of participants with an antibody response to each vaccine was lower among participants with HIV infection than among those without HIV infection (Tables S9 and S10 in the Supplementary Appendix).

At 12 months, the rate of antibody response was 63.5% in the ChAd3-EBO-Z group and 79.5% in the rVSVΔG-ZEBOV-GP group, as compared with 6.8% in the placebo group ($P<0.001$ for both comparisons). Analyses that included all the participants regardless of the antibody titer at baseline and analyses that included participants with a titer level of 200 EU or less per milliliter at baseline and in which a response was defined as an increase in the titer from baseline by a factor of 4 showed similar results (Tables S11 and S12 in the Supplementary Appendix). In a small subsample, IgG antibody titers at days 3, 10, and 14 were similar in each active vaccine group (Table S13 in the Supplementary Appendix).

Log_{10}-transformed antibody titers are summarized in Table 3, and in Figure S3 in the Supplementary Appendix. In each vaccine group, the geometric mean titer levels differed significantly from those in the placebo group at each follow-up time point. At week 1, the differences were small, but by month 1, antibody titers had increased substantially in the two vaccine groups. The geometric mean titer was 621 EU per milliliter in the ChAd3-EBO-Z group and 1000 EU per milliliter in the rVSVΔG-ZEBOV-GP group, as compared with 75 EU per milliliter in the placebo group ($P<0.001$ for both comparisons). The differences in the geometric mean titer at month 6 and month 12 between each vaccine group and the placebo group were also significant ($P<0.001$ for all comparisons). Additional descriptive statistics regarding the changes in antibody titer levels are provided in Figures S2 and S4 in the Supplementary Appendix.

DISCUSSION

The data from this randomized, double-blind, placebo-controlled trial of ChAd3-EBO-Z and rVSVΔG-ZEBOV-GP show that by 1 month after injection the two vaccines, as compared with placebo, elicited an immune response (antibodies to the EBOV surface glycoprotein) that was largely maintained through 12 months. No safety concerns were identified.

In the two vaccine groups, side effects were generally not severe, were time-limited, and were similar to reports from phase 1 studies that used various doses of the two vaccines.[3,5–9] The incidence of joint problems did not differ significantly among the three groups. We did not see the frank arthritis that was reported in another study (conducted in Geneva) and that has been thought to be due to the direct replication of rVSVΔG-ZEBOV-GP in the joints.[5] Reasons for this difference in the occurrence of arthritis among the participants enrolled in Geneva and the Liberian participants in our trial are not clear.

An unexpected finding was that the percentage of participants in whom malaria developed by 12 months was lower in each active vaccine group than in the placebo group, significantly so for those who received ChAd3-EBO-Z. Such heterologous or off-target effects of vaccines to enhance immunity in an antigen-nonspecific manner have been observed with some childhood vaccinations, and the presence of malaria has recently been reported to be associated with an improved outcome in patients with EVD,[10] a finding that suggests possible cross-reactive immunity.[11,12] To determine whether this finding is possibly a result of trained immunity[13] or a chance finding (as stated in the Methods section, P values of <0.05 but not <0.01 should be interpreted cautiously), future studies are needed.

The two vaccines elicited the production of antibodies to the EBOV surface glycoprotein. Responses at 1 week were modest with the two vaccines. By 1 month, the immune response was much greater in participants who received either vaccine than in those who received placebo, and this response was largely maintained through 12 months. Immune response did not vary according to age, sex, or previous contact with a person who had EVD. The immune response in participants with HIV infection was smaller than in those without HIV infection in the two vaccine groups, but only 78 enrolled participants (5.2%) had HIV infection. To establish the efficacy and safety of these vaccines in this subgroup, future studies will need to enroll more participants with HIV infection and others with immune dysfunction. It is possible that booster vaccinations may need to be considered in such persons.

The immune response that was observed with the two vaccines increased by 14 days after injection in a sample of 24 participants who were selected for frequent measurements. This response pattern is consistent with limited data from phase 1 studies.[6,7] The clinical significance of these changes is difficult to assess because of the lack of an identified correlate of protective immunity, the lack of licensed assays to measure antibodies against EBOV, and the lack of reference standards for measuring antibodies against EBOV infection. Given that time may be of the essence in responding to an outbreak of Ebola, the rapidity of an immune response as well as magnitude and durability of an immune response are all desirable characteristics of an EBOV vaccine.

The results of the ring vaccination trial that was conducted in Guinea highlight the importance of a vaccine that provides a rapid immune response.[14,15] Although the rVSVΔG-ZEBOV-GP vaccine was reported to provide protection from EVD in an analysis that included events that occurred 10 or more days after randomization, 41 of 64 events that were reported in the analysis cohort occurred before the 10-day cutoff, with 20 in the group assigned to immediate vaccination and 21 in the group assigned to delayed vaccination. Thus, the rapidity of the immune response is an important consideration for the vaccines that were used in a ring vaccination strategy and would be useful to assess in future research efforts.

Our trial has some limitations. First, the trial did not include children. The demonstration of safety and efficacy of these vaccines in children is a priority, since 16% of the persons with EVD in the current epidemic were children.[16] Second, as previously noted, the lack of an identified laboratory correlate of protective immunity makes it difficult to assess the clinical significance of any long-term antibody changes. Finally, we could not establish whether either vaccine was effective in preventing EVD since the number of cases of EVD declined drastically in Liberia owing to a concerted public health effort that succeeded in ending the outbreak in Liberia before the PREVAIL I trial could be expanded to its phase 3 component. Even though the trial began in early February 2015, once an infrastructure for the trial had been established and the vaccines became available, too much time had elapsed. This situation emphasizes the importance of completing phase 1 studies before outbreaks occur and of being prepared to initiate phase 2 and phase 3 trials as soon as such outbreaks occur.

Placebo controls were an important strength of this trial for the evaluation of safety outcomes. At the time that this trial was designed and implemented, there were no completed and published phase 1 studies. Thus, it was critical that this trial be able to assess safety objectively. Whether studies are conducted in the context of an outbreak or otherwise does not change the principles of science and the potential biases in studies that lack adequate controls. One might argue that rigorous study designs that provide a rapid and reliable answer are even more important in the context of an emergency. The randomized, placebo-controlled trial was acceptable to participants and Liberian officials, enrollment was accomplished at a single site in 3 months, and the completeness of follow-up was 98.3% at 12 months.

The inclusion of two vaccines that had advanced through phase 1 by January 2015 was also a strength of the trial. The opportunity to collaborate with the respective companies and the use of a common placebo group were efficient and responsible approaches, given the urgency of the public health need.

In conclusion, the results observed with the ChAd3-EBO-Z and rVSVΔG-ZEBOV-GP vaccines in this trial extended our knowledge of their safety and immunogenicity. The results point to further research to be conducted in order to be better prepared for future outbreaks of EVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

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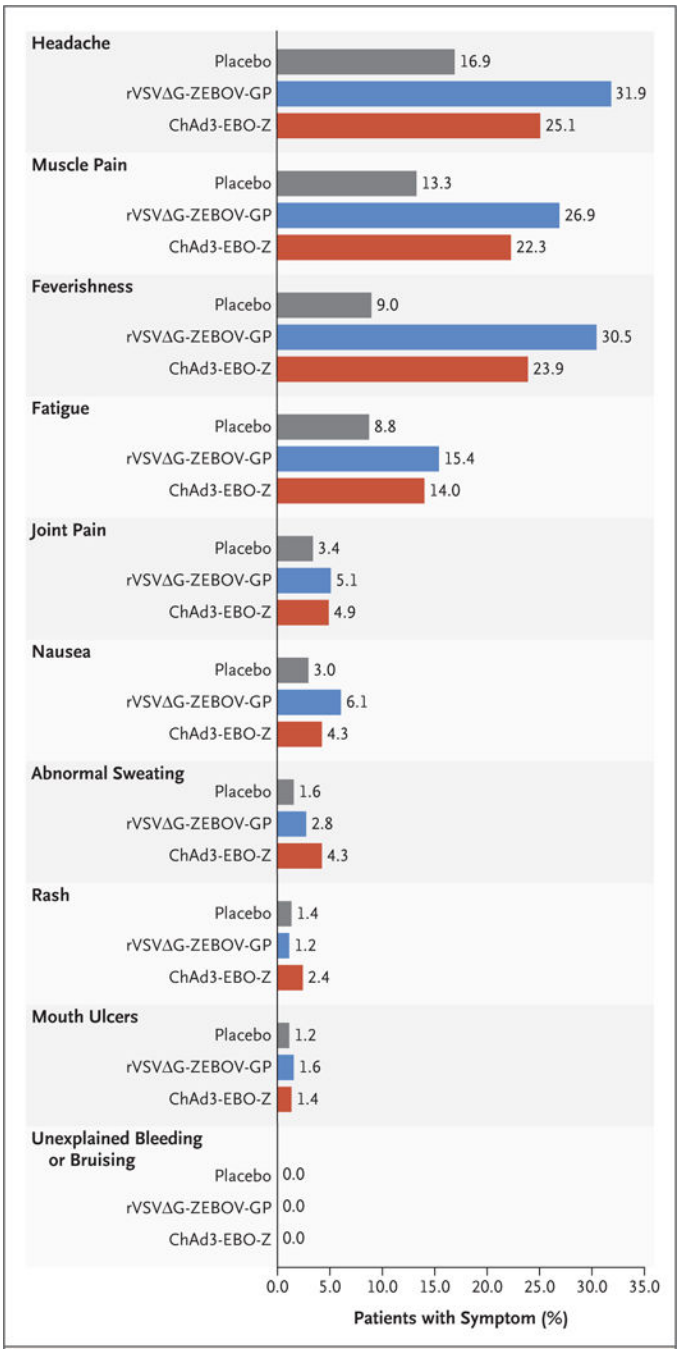

Figure 1. Targeted Symptoms Reported at Week 1

Shown are the percentages of participants who reported the indicated symptom at the week 1 visit in the placebo group, in the group that received the recombinant vesicular stomatitis virus–based vaccine (rVSVΔG-ZEBOV-GP), and in the group that received the chimpanzee adenovirus 3–based vaccine (ChAd3-EBO-Z). Symptoms are ordered according to the frequency with which they were reported by participants in the placebo group. Symptoms were prespecified in a checklist (i.e., targeted) at the week 1 visit.

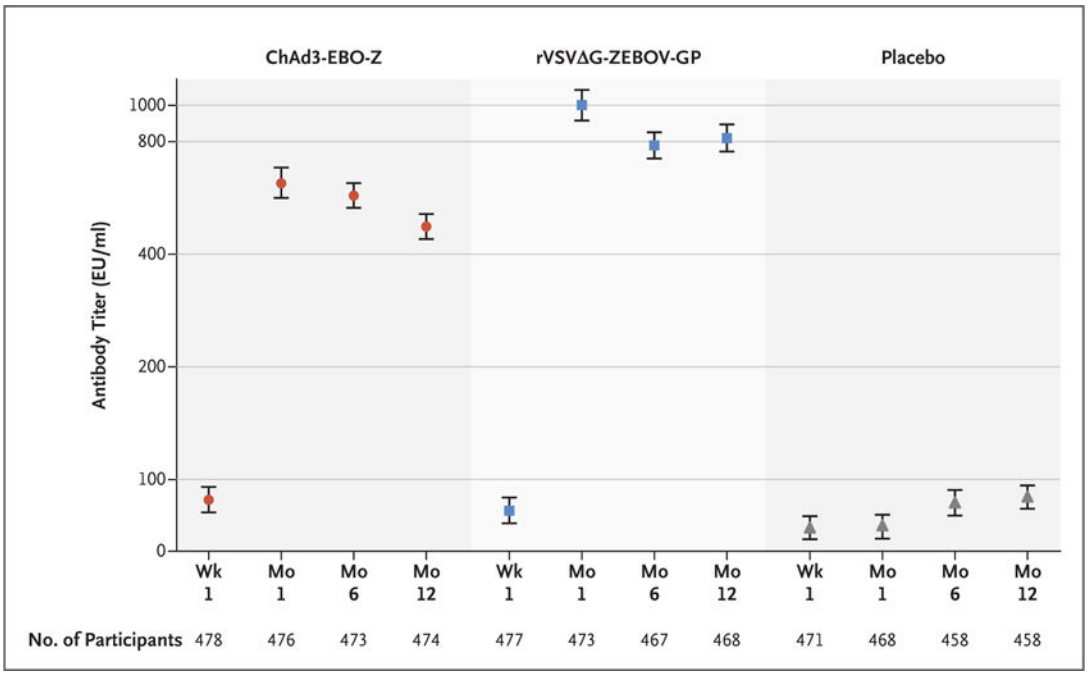

Figure 2. Geometric Mean Titers after Randomization

Shown are the geometric mean IgG antibody titers against the Ebola virus surface glycoprotein among participants who did not have an elevated level (>607 enzyme-linked immunosorbent assay units [EU] per milliliter) at baseline. I bars indicate 95% confidence intervals. Titers were measured at week 1, month 1, month 6, and month 12 in serum in the ChAd3-EBO-Z group, the rVSVΔG-ZEBOV-GP group, and the placebo group. Antibody titers had a skewed distribution and were $\log_{10}$-transformed. Geometric means were determined by back-transforming the transformed means and confidence intervals to the original scale. P values for the comparison of each active vaccine group with the placebo group were significant at a level of less than 0.001 at each visit, except at week 1, at which time the P value was 0.004 for the comparison of rVSVΔG-ZEBOV-GP with placebo.

Table 1

Characteristics of the Participants at Baseline.*

Characteristic	ChAd3-EBO-Z (N = 500)	rVSVΔG-ZEBOV-GP (N = 500)	Placebo (N = 500)	Total (N = 500)
Age (yr)				
Median	30	29	30	30
Interquartile range	25–38	24–36	24–39	24–38
Female sex (%)	37.0	37.4	35.4	36.6
Body-mass index†				
Median	21.4	22.0	21.7	21.7
Interquartile range	20.1–23.9	20.0–24.4	20.0–24.2	20.0–24.2
Contact in past month with person who had Ebola virus disease (%)	0.2	1.0	1.0	0.7
Work involves possible contact with person with Ebola virus disease (%)	4.4	5.0	4.4	4.6
HIV-positive status (%)	5.0	4.4	6.2	5.2
Syphilis (%)	6.0	4.4	5.0	5.1
Ebola IgG titer (EU/ml)				
Median	75	81	79	78
Interquartile range	44–135	49–141	50–148	47–139
Positive antibody response (%)‡	3.2	3.6	5.2	4.0

*There were no significant differences at baseline among the group that received the chimpanzee adenovirus 3–based vaccine (ChAd3-EBO-Z), the group that received the recombinant vesicular stomatitis virus–based vaccine (rVSVΔG-ZEBOV-GP), and the placebo group. EU denotes enzyme-linked immunosorbent assay unit, and HIV human immunodeficiency virus.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡A positive antibody response was defined as an IgG antibody titer against the Ebola virus surface glycoprotein of more than 607 EU per milliliter.

Table 2

Clinical Events, Injection-Site Reactions, and Targeted Symptoms.*

Event	ChAd3-EBO-Z (N = 500)	rVSVΔG-ZEBOV-GP (N = 500)	Placebo (N = 500)	P Value	
				ChAd3-EBO-Z vs. Placebo	rVSVΔG-ZEBOV-GP vs. Placebo
Serious adverse event in first 30 days — no. (%)	6 (1.2)	6 (1.2)	8 (1.6)	0.68	0.68
Death in first 30 days — no. (%)	0	0	1 (0.2)	0.53	0.53
Serious adverse event within 1 yr — no. (%)	40 (8.0)	47 (9.4)	59 (11.8)	0.05	0.25
Malaria within 1 yr — no. (%)	26 (5.2)	33 (6.6)	44 (8.8)	0.03	0.25
Other serious adverse event within 1 yr — no. (%)	16 (3.2)	16 (3.2)	19 (3.8)	0.68	0.68
Death within 1 yr — no. (%)	1 (0.2)	5 (1.0)	6 (1.2)	0.07	0.84
Injection-site reaction					
At 30 min after injection — no. (%)	36 (7.2)	32 (6.4)	23 (4.6)	0.11	0.27
At 1 wk — no./total no. (%)	141/494 (28.5)	153/495 (30.9)	34/498 (6.8)	<0.001	<0.001
At 1 mo — no./total no. (%)	4/492 (0.8)	8/491 (1.6)	5/494 (1.0)	1.00	0.42
Symptom of any grade — no./total no. (%)					
At 1 wk	272/494 (55.1)	288/495 (58.2)	174/498 (34.9)	<0.001	<0.001
At 1 mo	116/492 (23.6)	141/491 (28.7)	142/494 (28.7)	0.07	1.00

*Symptoms were prespecified in a checklist (i.e., targeted) at the week 1 visit. The P values for clinical events were based on Barnard's test, and those for injection-site reactions and symptoms were based on Fisher's exact test.

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Table 3

Antibody Response during Follow-up among Participants without an Elevated Antibody Level at Trial Entry.*

Variable	ChAd3-EBO-Z	rVSVΔG-ZEBOV-GP	Placebo	P Value	
				ChAd3-EBO-Z vs. Placebo	rVSVΔG-ZEBOV-GP vs. Placebo
At 1 wk					
No. of participants	478	477	471		
Geometric mean titer (95% CI) — EU/ml	88 (82–95)	83 (76–89)	74 (69–80)	<0.001	0.004
Participants with response (95% CI) — %	3.6 (1.9–5.2)	2.5 (1.1–3.9)	1.5 (0.4–2.6)	0.06	0.36
At 1 mo					
No. of participants	476	473	468		
Geometric mean titer (95% CI) — EU/ml	621 (565–682)	1000 (910–1099)	75 (69–80)	<0.001	<0.001
001 Participants with response (95% CI) — %	70.8 (66.7–74.9)	83.7 (80.4–87.1)	2.8 (1.3–4.3)	<0.001	<0.001
At 6 mo					
No. of participants	473	467	458		
Geometric mean titer (95% CI) — EU/ml	574 (532–619)	781 (721–847)	87 (80–94)	<0.001	<0.001
Participants with response (95% CI) — %	71.5 (67.4–75.5)	78.4 (74.6–82.1)	5.7 (3.6–7.8)	<0.001	<0.001
At 12 mo					
No. of participants	474	468	458		
Geometric mean titer (95% CI) — EU/ml	474 (439–512)	818 (752–889)	90 (83–96)	<0.001	<0.001
Participants with response (95% CI) — %	63.5 (59.2–67.8)	79.5 (75.8–83.1)	6.8 (4.5–9.1)	<0.001	<0.001

*Response was defined as a $\log_{10}$ titer that was increased by a factor of 4 or more from the baseline value among participants without an elevated antibody level at baseline. The P values for group comparisons of the geometric mean titer were based on the $\log_{10}$ titer values at the specified visit, with the baseline $\log_{10}$ titer as a covariate in analysis of covariance. The P values for the group comparisons of the percentage of participants with a response were based on Fisher's exact test. CI denotes confidence interval.