ORIGINAL ARTICLE

# Randomized Trial of Vaccines for Zaire Ebola Virus Disease

PREVAC Study Team*


## ABSTRACT

### BACKGROUND

Questions remain concerning the rapidity of immune responses and the durability and safety of vaccines used to prevent Zaire Ebola virus disease.

### METHODS

We conducted two randomized, placebo-controlled trials — one involving adults and one involving children — to evaluate the safety and immune responses of three vaccine regimens against Zaire Ebola virus disease: Ad26.ZEBOV followed by MVA-BN-Filo 56 days later (the Ad26–MVA group), rVSVΔG-ZEBOV-GP followed by placebo 56 days later (the rVSV group), and rVSVΔG-ZEBOV-GP followed by rVSVΔG-ZEBOV-GP 56 days later (the rVSV–booster group). The primary end point was antibody response at 12 months, defined as having both a 12-month antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4.

### RESULTS

A total of 1400 adults and 1401 children underwent randomization. Among both adults and children, the incidence of injection-site reactions and symptoms (e.g., feverishness and headache) was higher in the week after receipt of the primary and second or booster vaccinations than after receipt of placebo but not at later time points. These events were largely low-grade. At month 12, a total of 41% of adults (titer, 401 EU per milliliter) and 78% of children (titer, 828 EU per milliliter) had a response in the Ad26–MVA group; 76% (titer, 992 EU per milliliter) and 87% (titer, 1415 EU per milliliter), respectively, had a response in the rVSV group; 81% (titer, 1037 EU per milliliter) and 93% (titer, 1745 EU per milliliter), respectively, had a response in the rVSV–booster group; and 3% (titer, 93 EU per milliliter) and 4% (titer, 67 EU per milliliter), respectively, had a response in the placebo group ($P<0.001$ for all comparisons of vaccine with placebo). In both adults and children, antibody responses with vaccine differed from those with placebo beginning on day 14.

### CONCLUSIONS

No safety concerns were identified in this trial. With all three vaccine regimens, immune responses were seen from day 14 through month 12. (Funded by the National Institutes of Health and others; PREVAC ClinicalTrials.gov number, NCT02876328; EudraCT numbers, 2017-001798-18 and 2017-001798-18/3rd; and Pan African Clinical Trials Registry number, PACTR201712002760250.)


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Zaire ebola virus disease (EVD) outbreaks have high mortality and morbidity, place an enormous financial and logistic burden on public health systems of affected countries,[1,2] and can lead to worldwide disruption. The risk of reemergence of EVD is ever-present, as highlighted by the recurrences of EVD in the Democratic Republic of Congo and Guinea.[3,4]

Two vaccine strategies to prevent EVD — the recombinant vesicular stomatitis virus (rVSV)–based vaccine expressing the surface glycoprotein of *Zaire ebolavirus* (ZEBOV; the rVSVΔG-ZEBOV-GP vaccine) and the combination of an adenovirus type 26–vectored vaccine encoding the ZEBOV glycoprotein (Ad26.ZEBOV) followed by a booster dose of a modified vaccinia Ankara virus strain (MVA-BN-Filo)[5-15] — have received World Health Organization (WHO) prequalification status and were used during the most recent Ebola outbreaks. The rVSVΔG-ZEBOV-GP vaccine is designed as a one-dose vaccine and has been recommended for reactive ring vaccination use in persons at high risk for exposure during outbreaks; a ring strategy is used to identify contacts and contacts of contacts. The Ad26.ZEBOV–MVA-BN-Filo combination is a two-dose regimen, with the vaccines administered 56 days apart, that has recently been recommended for persons who are at some risk for EVD but are not considered to be at high risk.[16] We report here the results of two randomized, placebo-controlled trials, one involving adults and the other involving children, that were conducted under one protocol by the Partnership for Research on Ebola Vaccinations (PREVAC) consortium in western Africa to assess the safety of these vaccines, as well as the rapidity and durability of antibody responses to these vaccines.[17]

## METHODS

### TRIAL DESIGN AND PARTICIPANTS

The PREVAC protocol, which describes the design and methods of separate comparisons of the three vaccine regimens with placebo, separately in adults and children (two separate trials undertaken, conducted concurrently), has been published previously.[18] The protocol (version 4.0), statistical analysis plan, and descriptions of earlier versions of the protocol are provided with the full text of this article at NEJM.org.

Eligible adults 18 years of age or older and children 1 to 17 years of age, all without a history of EVD, who were not pregnant or breastfeeding, were enrolled at six sites in four West African countries. The full inclusion and exclusion criteria are provided in the protocol. Enrollment was staggered according to age group, starting with adults and with adolescents 12 to 17 years of age, followed by children 5 to 11 years of age, and finally children 1 to 4 years of age.

Participants were randomly assigned to receive the Ad26.ZEBOV vaccine (0.5 ml; $5\times10^{10}$ viral particles), followed by the MVA-BN-Filo vaccine (0.5 ml; $1\times10^{8}$ infectious units) 56 days later (the Ad26–MVA group); the rVSVΔG-ZEBOV-GP vaccine (1.0 ml; $9.4\times10^{7}$ plaque-forming units), followed by placebo 56 days later (the rVSV group); the rVSVΔG-ZEBOV-GP vaccine, followed by a booster dose of the same vaccine 56 days later (the rVSV–booster group); or saline placebo. Two placebos were required in the trial owing to different fill volumes for the vaccines; the placebo groups were pooled for analysis (Section S3.1 in the Supplementary Appendix, available at NEJM.org).[18]

An independent data and safety monitoring committee provided trial oversight. The trial protocol was approved by the Food and Drug Administration and by ethics committees of the sponsors.

The authors vouch for the accuracy and completeness of the analyses and data reported. Representatives of Merck Sharp and Dohme and Janssen (which provided the vaccines) and of the funding organizations participated in the preparation of the protocol and of the manuscript.

### FOLLOW-UP

Follow-up visits occurred on days 7, 14, and 28 after the first dose of vaccine or placebo. The second or booster dose of vaccine or placebo was administered on day 56, with further follow-up visits at day 63 and during months 3, 6, and 12. Antibody response was assessed at each follow-up visit, injection-site reactions and symptoms (e.g., feverishness and headache) were assessed through month 6, and data on serious adverse events were collected through month 12.

### ANTIBODY RESPONSES TO EBOLA GLYCOPROTEIN

Serum concentrations of IgG binding antibodies against the Ebola virus surface glycoprotein were measured at baseline and at each follow-

up visit with the Filovirus Animal Nonclinical Group (FANG) enzyme-linked immunosorbent assay (ELISA) (Section S3.6.1 and the protocol). The primary immunogenicity end point was an antibody response at month 12, with response defined as an antibody concentration of at least 200 ELISA units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4. As in other studies, including the Partnership for Research on Ebola Virus in Liberia (PREVAIL) I trial,[9] an increase from baseline in the antibody concentration by at least a factor of 4 was used to define antibody response. An antibody concentration of at least 200 EU per milliliter and an increase from baseline by at least a factor of 2 were included because it was considered a possible correlate of protection.[19] As a secondary objective, we compared the rVSVΔG-ZEBOV-GP and Ad26.ZEBOV–MVA-BN-Filo regimens, separately, with placebo in an analysis of immediacy of response at day 14.

The protocol also specified primary objectives in support of regulatory submissions by Merck Sharp and Dohme and Janssen. These objectives stated that the time point of the antibody comparison with placebo for the rVSVΔG-ZEBOV-GP vaccine (Merck Sharp and Dohme) would be day 28 and the time point for the Ad26.ZEBOV–MVA-BN-Filo regimen (Janssen) would be month 3.

Antibody concentrations were determined in two laboratories: the Liberian Institute for Biomedical Research in Charlesville, Liberia, and the National Institute of Allergy and Infectious Diseases (NIAID) Integrated Research Facility in Frederick, Maryland. Specimens that were obtained from participants who had undergone randomization in Guinea and Sierra Leone were analyzed at the Liberian Institute for Biomedical Research laboratory, and those from participants who had undergone randomization in Liberia and Mali were analyzed at the NIAID Integrated Research Facility.

### STATISTICAL ANALYSIS

Sample sizes for comparing each vaccine regimen with placebo with regard to antibody response and serious adverse events, separately among adults and children, exceeded those required. A larger-than-required sample size was specified because if a correlate of protection was identified after the start of the trial, the plan was to compare the active vaccines with one another (Sections S3.2 and S4). For the comparisons before the second injection in the rVSV group (which was placebo) and the rVSV–booster group, data from the two groups were pooled.

Data from adults and children were analyzed as two separate trials, with the use of identical statistical analyses. The trial involving children also included additional, prespecified analyses (see below).

Each active vaccine was compared with the pooled placebo group in the analysis of antibody response at month 12 with the use of logistic regression with trial site as a covariate. Odds ratios with 95% confidence intervals were used to compare percentages of participants with an antibody response between each vaccine regimen and placebo at each follow-up visit. Additional analyses to further characterize the antibody response are described in the Supplementary Appendix.

After $\log_{10}$ transformation, the mean antibody concentrations were compared between the vaccine groups and the placebo group at each follow-up visit, with the use of analysis of covariance with the baseline $\log_{10}$ level and site as covariates. Geometric mean concentrations after back-transformation are reported. Geometric mean ratios (for each vaccine vs. placebo) and 95% confidence intervals are also reported.

Subgroup analyses for antibody response were performed according to laboratory and according to country within laboratory. In addition, in the trial involving children, we performed prespecified subgroup analyses according to age group.

For each of the two trials, one involving children and one involving adults, we used a two-sided significance level of 0.0167 (Bonferroni method) to control the type I error for the three comparisons of each vaccine group with the placebo group for the primary analysis at month 12. Because the statistical analysis plan did not include a provision for correcting for multiplicity across outcomes, results for secondary outcomes are reported as point estimates with 95% confidence intervals. The widths of these confidence intervals have not been adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects for secondary outcomes. Statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

## RESULTS

### CHARACTERISTICS OF THE PARTICIPANTS

From April through December 2018, a total of 1400 adults and 1401 children were enrolled in the two trials (Figs. S1 and S2). The characteristics of the participants in the randomized groups were balanced at baseline (Table 1).

In the trial involving adults, the median age was 27 years (interquartile range, 20 to 38), and 45% of the participants were women. At baseline, 15% of the adults had an antibody concentration of at least 200 EU per milliliter. The percentage of participants with an antibody concentration of at least 200 EU per milliliter at baseline was higher in Guinea (13%), Liberia (21%), and Sierra Leone (21%) than in Mali (5%) (Table S1).

In the trial involving children, one third of the participants were enrolled in each of the three age groups: 1 to 4 years, 5 to 11 years, and 12 to 17 years; 46% of the children were female. At baseline, 12% of the children had an antibody concentration of at least 200 EU per milliliter. As was observed with the adults, among children 12 to 17 years and 5 to 11 years of age, the percentage of participants with an antibody concentration of at least 200 EU per milliliter was lower in Mali than other countries; this relationship was not seen among participants 1 to 4 years of age.

### ADHERENCE TO BOOSTER VACCINATION AND COMPLETENESS OF PRIMARY ANTIBODY OUTCOME

The second injection was administered to 92 to 96% of the adults and to 97 to 99% of the children (Table S2). The primary end point was assessed in more than 90% of the adults and children (Table S3).

### SAFETY

#### *Injection-Site Reactions and Symptoms in Adults*

Most injection-site reactions and symptoms were reported by participants in the 7 days after vaccination, were more frequent in the active-vaccine groups than in the placebo group, and were largely of grade 1 severity (Table 2 and Table S4). Through day 7, the incidence of injection-site reaction was 9% in the Ad26–MVA group, 22% in the pooled rVSV groups, and 5% in the placebo group. The percentages of participants who reported symptoms through day 7 were 50%, 66%, and 44%, respectively. By day 14, the frequency of injection-site reactions and symptoms were similar in the Ad26–MVA group, the pooled rVSV groups, and the placebo group (Table 2). Similar trends were observed after the second or booster vaccinations (Table 2 and Table S5). By month 3, the percentage of participants reporting injection-site reactions and symptoms was similar in the vaccine groups and the placebo group (Table 2).

#### *Serious Adverse Events and Deaths through 12 Months in Adults*

Serious adverse events were reported in 14 of 396 adults (4%) in the Ad26–MVA group, 6 of 395 (2%) in the rVSV group, 1 of 197 (1%) in the rVSV–booster group, and 5 of 412 (1%) in the pooled placebo group (Table 2 and Table S6). Overall, 6 adults died: 2 in the Ad26–MVA group (from septic shock and myocardial infarction, in 1 participant each), 3 in the rVSV group (from sepsis, HIV infection, and appendicitis, in 1 each), and 1 in the placebo group (from malaria). None of the deaths were judged by the site investigator to be related to the vaccine or placebo.

#### *Injection-Site Reactions and Symptoms in Children*

As in adults, most injection-site reactions and symptoms that were reported in children occurred in the week after the first injection (through day 7), were more frequent in the vaccine groups than in the placebo group, and were largely of grade 1 severity (Table 2 and Table S7). Through day 7, the incidence of injection-site reaction was 15% in the Ad26–MVA group, 21% in the pooled rVSV groups, and 5% in the placebo group. Symptoms through day 7 were reported in 48%, 60%, and 43% of the participants, respectively. Through day 14, the incidences of injection-site reactions and symptoms were similar in the Ad26–MVA group, the pooled rVSV groups, and the placebo group. Similar trends were observed after the second injection (Table 2 and Table S8). By month 3, the incidence of symptoms was similar in the vaccine groups and the placebo group. Differences between the vaccine groups and the placebo group were similar in each age group (Tables S9 through S13).

#### *Serious Adverse Events and Deaths through 12 Months in Children*

Serious adverse events were reported in 5 of 403 children (1%) in the Ad26–MVA group, in 9 of 407 (2%) in the rVSV group, in 3 of 202 (1%) in

**Table 1. Characteristics of the Participants at Baseline.***

| Characteristic | Ad26–MVA Group | rVSV Group | rVSV–Booster Group | Placebo Group | Total |
|---|---|---|---|---|---|
| **Adults** | | | | | |
| No. of participants | 396 | 395 | 197 | 412 | 1400 |
| Age | | | | | |
| Median (IQR) — yr | 27 (21–40) | 27 (20–39) | 26 (20–35) | 27 (20–38) | 27 (20–38) |
| Distribution — no. (%) | | | | | |
| 18–29 yr | 227 (57) | 213 (54) | 119 (60) | 238 (58) | 797 (57) |
| 30–39 yr | 67 (17) | 89 (23) | 41 (21) | 84 (20) | 281 (20) |
| ≥40 yr | 102 (26) | 93 (24) | 37 (19) | 90 (22) | 322 (23) |
| Female sex — no. (%) | 171 (43) | 182 (46) | 87 (44) | 187 (45) | 627 (45) |
| Country — no. (%) | | | | | |
| Guinea | 121 (31) | 130 (33) | 66 (34) | 135 (33) | 452 (32) |
| Liberia | 73 (18) | 70 (18) | 35 (18) | 81 (20) | 259 (18) |
| Mali | 81 (20) | 84 (21) | 41 (21) | 86 (21) | 292 (21) |
| Sierra Leone | 121 (31) | 111 (28) | 55 (28) | 110 (27) | 397 (28) |
| HIV-positive status — no. (%) | 6 (2) | 13 (3) | 2 (1) | 4 (1) | 25 (2) |
| Ebola IgG concentration† | | | | | |
| ≥200 EU/ml — no./total no. (%) | 50/394 (13) | 58/388 (15) | 32/197 (16) | 68/409 (17) | 208/1388 (15) |
| <66.96 EU/ml — no./total no. (%) | 142/394 (36) | 144/388 (37) | 66/197 (34) | 146/409 (36) | 498/1388 (36) |
| Median (IQR) — EU/ml | 94 (43–149) | 92 (45–145) | 94 (46–143) | 96 (47–156) | 95 (46–148) |
| Geometric mean — EU/ml | 85 | 87 | 91 | 90 | 88 |
| **Children** | | | | | |
| No. of participants | 403 | 407 | 202 | 389 | 1401 |
| Age | | | | | |
| Median (IQR) — yr | 8 (4–13) | 9 (4–12) | 8 (3–13) | 8 (4–13) | 8 (4–13) |
| Distribution — no. (%) | | | | | |
| 1–4 yr | 137 (34) | 123 (30) | 71 (35) | 136 (35) | 467 (33) |
| 5–11 yr | 127 (32) | 146 (36) | 65 (32) | 129 (33) | 467 (33) |
| 12–17 yr | 139 (34) | 138 (34) | 66 (33) | 124 (32) | 467 (33) |
| Female sex — no. (%) | 186 (46) | 185 (45) | 85 (42) | 182 (47) | 638 (46) |
| Country — no. (%) | | | | | |
| Guinea | 163 (40) | 156 (38) | 77 (38) | 150 (39) | 546 (39) |
| Liberia | 64 (16) | 66 (16) | 33 (16) | 55 (14) | 218 (16) |
| Mali | 95 (24) | 94 (23) | 46 (23) | 91 (23) | 326 (23) |
| Sierra Leone | 81 (20) | 91 (22) | 46 (23) | 93 (24) | 311 (22) |
| Ebola IgG concentration† | | | | | |
| ≥200 EU/ml — no./total no. (%) | 43/398 (11) | 47/401 (12) | 19/200 (10) | 54/386 (14) | 163/1385 (12) |
| <66.96 EU/ml — no./total no. (%) | 198/398 (50) | 187/401 (47) | 97/200 (48) | 188/386 (49) | 670/1385 (48) |
| Median (IQR) — EU/ml | 67 (29–127) | 74 (33–122) | 69 (33–122) | 71 (33–141) | 70 (32–128) |
| Geometric mean — EU/ml | 63 | 67 | 67 | 70 | 66 |

* Two randomized, placebo-controlled trials — one involving adults and one involving children — evaluated the safety and immune responses of three vaccine regimens against Ebola virus disease: the Ad26.ZEBOV vaccine followed by the MVA-BN-Filo vaccine 56 days later (the Ad26–MVA group), the rVSVΔG-ZEBOV-GP vaccine followed by placebo 56 days later (the rVSV group), and the rVSVΔG-ZEBOV-GP vaccine followed by a booster dose of the same vaccine 56 days later (the rVSV–booster group). Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, and IQR interquartile range.

† An Ebola IgG concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter was considered to indicate positivity. The assay developer's lower limit of quantification was 66.96 EU per milliliter. The median concentration and geometric mean concentration were assessed among participants with a result.

**Table 2. Injection-Site Reactions, Targeted Symptoms, and Serious Adverse Events.***

| Event | Ad26–MVA Group | Pooled rVSV Groups | rVSV Group | rVSV–Booster Group | Placebo Group |
|---|---|---|---|---|---|
| | *number of participants with event/total number (percent)* | | | | |
| **Adults** | | | | | |
| Injection-site reaction after first injection | | | | | |
| At 0–7 days | 36/396 (9)† | 133/592 (22)‡ | — | — | 21/412 (5) |
| At 14 days | 2/387 (1) | 1/579 (<1) | — | — | 0/404 |
| Symptoms after first injection | | | | | |
| At 0–7 days | 198/396 (50) | 390/592 (66)‡ | — | — | 182/412 (44) |
| At 14 days | 92/387 (24) | 133/579 (23) | — | — | 100/404 (25) |
| Injection-site reaction after second injection | | | | | |
| At 56–63 days | 49/380 (13)‡ | — | 12/365 (3) | 20/187 (11)† | 20/392 (5) |
| At 3 mo | 0/369 | — | 1/356 (<1) | 1/187 (1) | 0/385 |
| Symptoms after second injection | | | | | |
| At 56–63 days | 124/382 (32) | — | 127/373 (34) | 76/188 (40) | 127/398 (32) |
| At 3 mo | 122/373 (33) | — | 95/371 (26) | 53/188 (28) | 102/393 (26) |
| Serious adverse event or death§ | 14/396 (4) | — | 6/395 (2) | 1/197 (1) | 5/412 (1) |
| Death | 2/396 (1) | — | 3/395 (1) | 0/197 | 1/412 (<1) |
| **Children** | | | | | |
| Injection-site reaction after first injection | | | | | |
| At 0–7 days | 59/403 (15)‡ | 126/609 (21)‡ | — | — | 19/389 (5) |
| At 14 days | 1/397 (<1) | 1/603 (<1) | — | — | 0/380 |
| Symptoms after first injection | | | | | |
| At 0–7 days | 195/403 (48) | 363/609 (60)‡ | — | — | 166/389 (43) |
| At 14 days | 64/397 (16) | 93/603 (15) | — | — | 70/380 (18) |
| Injection-site reaction after second injection | | | | | |
| At 56–63 days | 55/398 (14)‡ | — | 26/396 (7) | 23/198 (12)‡ | 16/381 (4) |
| At 3 mo | 0/392 | — | 0/392 | 0/197 | 0/378 |
| Symptoms after second injection | | | | | |
| At 56–63 days | 127/399 (32) | — | 112/400 (28) | 64/198 (32) | 106/383 (28) |
| At 3 mo | 85/393 (22) | — | 93/396 (23) | 41/198 (21) | 90/380 (24) |
| Serious adverse event or death¶ | 5/403 (1) | — | 9/407 (2) | 3/202 (1) | 8/389 (2) |
| Death | 0/403 | — | 3/407 (1) | 0/202 | 2/389 (1) |

* Data for the rVSV group and the rVSV–booster group were pooled for the assessment after receipt of the primary dose because all the participants in these groups had received one dose of the rVSVΔG-ZEBOV-GP vaccine. The second injection was administered on day 56. Targeted symptoms included feverishness and headache. Serious adverse events and deaths were assessed in adults and children through month 12.

† P=0.016 for the comparison of vaccine with placebo, which was below the P-value threshold of less than 0.0167.

‡ P<0.001 for the comparison of vaccine with placebo.

§ Of the 26 adults with a serious adverse event, 12 events were attributed to appendicitis, all in women. There was no evidence of a difference in the incidence of appendicitis between the vaccine groups and the placebo group.

¶ Four of the serious adverse events in children were attributed to appendicitis.

the rVSV–booster group, and in 8 of 389 (2%) in the placebo group (Table 2 and Table S14). Overall, 5 children died: 3 children in the rVSV group (from sudden unexplained death, drowning, and fever of unknown origin, in 1 participant each) and 2 in the placebo group (from cardiopulmonary failure after malaria and from suspected meningitis, in 1 participant each). None of the deaths were judged by the site investigator to be related to the vaccine or placebo.

#### ANTIBODY RESPONSES

Among adults at month 12, the percentages of participants with an antibody response and the geometric mean concentrations were 41% and 401 EU per milliliter in the Ad26–MVA group, 76% and 992 EU per milliliter in the rVSV group, 81% and 1037 EU per milliliter in the rVSV–booster group, and 3% and 93 EU per milliliter in the placebo group ($P<0.001$ for all comparisons of vaccine with placebo) (Table 3). In both the Ad26–MVA and rVSV–booster groups, the percentages of participants with an antibody response and the geometric mean concentrations were greatest 7 days after receipt of the second or booster vaccination (day 63) and at month 3. By month 12, the percentage of participants with a response and the geometric mean concentrations had decreased to the levels that had been observed before the receipt of the second or booster vaccination (Table 3 and Fig. 1A).

Among children at month 12, the percentages of participants with a response and the geometric mean concentrations were 78% and 828 EU per milliliter in the Ad26–MVA group, 87% and 1415 EU per milliliter in the rVSV group, 93% and 1745 EU per milliliter in the rVSV–booster group, and 4% and 67 EU per milliliter in the placebo group ($P<0.001$ for all comparisons of vaccine with placebo) (Table 3 and Tables S17 and S18). In each of the vaccine groups, the percentages of participants with a response and the geometric mean concentrations at month 12 were greater among children than among adults. Among children, as was observed among adults, both the Ad26–MVA and rVSV–booster groups had their greatest percentage of participants with a response and highest geometric mean concentrations at visits shortly after the second or booster vaccination (day 63) and at month 3. By month 12, the percentage of participants with a response and the geometric mean concentrations had decreased to the levels observed immediately before the receipt of the second or booster vaccination (Table 3 and Fig. 1B).

These results were similar in an analysis that excluded participants with a baseline (prevaccination) antibody concentration of at least 200 EU per milliliter, since these persons may have had an asymptomatic infection in a previous outbreak (Table S19). Results were also similar to those in the primary analysis when we imputed the assay developer's lower limit of quantification (66.96 EU per milliliter) for baseline and follow-up antibody concentrations below that level (Table S20). To facilitate consideration in the context of previous studies, we determined antibody responses for a range of differences in the factor increase (Table 4) and follow-up antibody levels above a specific level (Tables S21 and S22).

Subgroup analyses according to laboratory and country are provided in the Figures S3 through S8 and Tables S23 and S24. Although there were differences in the geometric mean concentrations among the countries and laboratories, all the differences in response between the vaccine group and the placebo group were large and followed a similar pattern of geometric mean concentrations over follow-up among both the adults and children, regardless of country or laboratory.

## DISCUSSION

These two trials provide immunogenicity and safety data for three Zaire Ebola vaccine regimens in adults and in children 1 year of age or older. By day 14 after the first injection, an antibody response was observed with both vaccines (i.e., Ad26.ZEBOV and rVSV). The peak percentage of participants with a response in each group was observed at month 3 (28 days after the receipt of the second dose) in the Ad26–MVA group among both adults and children, at day 28 in the rVSV group among both adults and children, and at day 63 among adults and at month 3 among children in the rVSV–booster group.

There is no universally agreed-on correlate of protective immunity to EVD, and in this trial we were unable to assess protection from disease given that there were no incident cases of EVD.

**Table 3. Geometric Mean Concentrations and Antibody Response According to Follow-up Visit.***

| Variable | Ad26–MVA Group | Pooled rVSV Groups | rVSV Group | rVSV–Booster Group | Placebo Group |
|---|---|---|---|---|---|
| **Adults** | | | | | |
| At 7 days | | | | | |
| No. of participants | 379 | 560 | — | — | 396 |
| Geometric mean concentration (EU/ml) | 87 | 91 | — | — | 79 |
| Percentage of participants with response | 2 | 2 | — | — | 1 |
| At 14 days | | | | | |
| No. of participants | 375 | 561 | — | — | 386 |
| Geometric mean concentration (EU/ml) | 244 | 428 | — | — | 89 |
| Percentage of participants with response | 22 | 44 | — | — | 1 |
| At 28 days | | | | | |
| No. of participants | 374 | 553 | — | — | 381 |
| Geometric mean concentration (EU/ml) | 355 | 1218 | — | — | 87 |
| Percentage of participants with response | 36 | 80 | — | — | 1 |
| At 56 days | | | | | |
| No. of participants | 369 | 541 | — | — | 364 |
| Geometric mean concentration (EU/ml) | 387 | 1193 | — | — | 96 |
| Percentage of participants with response | 41 | 84 | — | — | 2 |
| At 63 days | | | | | |
| No. of participants | 362 | — | 355 | 182 | 354 |
| Geometric mean concentration (EU/ml) | 2726 | — | 1243 | 4819 | 96 |
| Percentage of participants with response | 82 | — | 85 | 98 | 2 |
| At 3 mo | | | | | |
| No. of participants | 359 | — | 360 | 184 | 360 |
| Geometric mean concentration (EU/ml) | 3328 | — | 1084 | 3294 | 91 |
| Percentage of participants with response | 94 | — | 81 | 96 | 2 |
| At 6 mo | | | | | |
| No. of participants | 365 | — | 368 | 184 | 359 |
| Geometric mean concentration (EU/ml) | 666 | — | 973 | 1221 | 103 |
| Percentage of participants with response | 69 | — | 80 | 87 | 4 |
| At 12 mo | | | | | |
| No. of participants | 374 | — | 371 | 185 | 377 |
| Geometric mean concentration (EU/ml) | 401 | — | 992 | 1037 | 93 |
| Percentage of participants with response† | 41 | — | 76 | 81 | 3 |
| **Children** | | | | | |
| At 7 days | | | | | |
| No. of participants | 379 | 571 | — | — | 365 |
| Geometric mean concentration (EU/ml) | 74 | 69 | — | — | 61 |
| Percentage of participants with response | 2 | 1 | — | — | 1 |
| At 14 days | | | | | |
| No. of participants | 382 | 586 | — | — | 372 |
| Geometric mean concentration (EU/ml) | 377 | 440 | — | — | 64 |
| Percentage of participants with response | 48 | 58 | — | — | 1 |

**Table 3. (Continued.)**

| Variable | Ad26–MVA Group | Pooled rVSV Groups | rVSV Group | rVSV–Booster Group | Placebo Group |
|---|---|---|---|---|---|
| At 28 days | | | | | |
| No. of participants | 389 | 580 | — | — | 369 |
| Geometric mean concentration (EU/ml) | 572 | 1688 | — | — | 62 |
| Percentage of participants with response | 66 | 90 | — | — | 1 |
| At 56 days | | | | | |
| No. of participants | 389 | 584 | — | — | 362 |
| Geometric mean concentration (EU/ml) | 679 | 1561 | — | — | 68 |
| Percentage of participants with response | 73 | 91 | — | — | 2 |
| At 63 days | | | | | |
| No. of participants | 382 | — | 392 | 186 | 356 |
| Geometric mean concentration (EU/ml) | 10,605 | — | 1560 | 9750 | 69 |
| Percentage of participants with response | 97 | — | 92 | 99 | 3 |
| At 3 mo | | | | | |
| No. of participants | 380 | — | 388 | 194 | 362 |
| Geometric mean concentration (EU/ml) | 9406 | — | 1351 | 5103 | 63 |
| Percentage of participants with response | 98 | — | 90 | 99 | 1 |
| At 6 mo | | | | | |
| No. of participants | 381 | — | 388 | 191 | 344 |
| Geometric mean concentration (EU/ml) | 1254 | — | 1153 | 1963 | 66 |
| Percentage of participants with response | 88 | — | 86 | 95 | 4 |
| At 12 mo | | | | | |
| No. of participants | 381 | — | 385 | 189 | 364 |
| Geometric mean concentration (EU/ml) | 828 | — | 1415 | 1745 | 67 |
| Percentage of participants with response† | 78 | — | 87 | 93 | 4 |

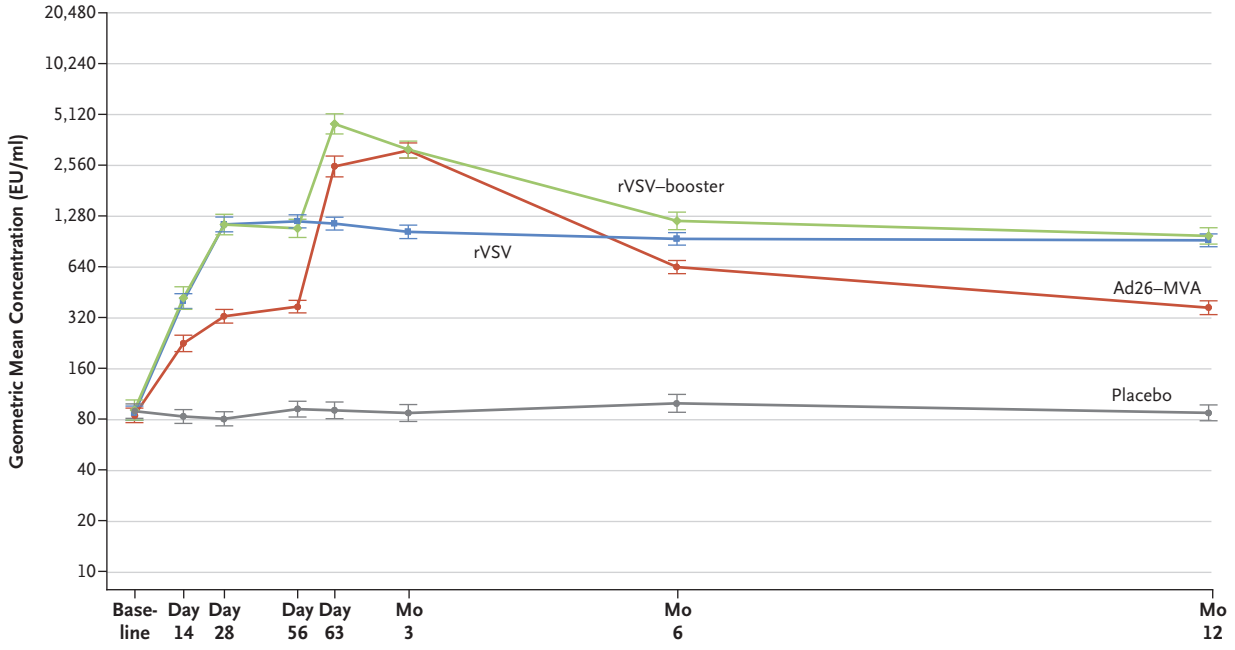
* The geometric mean concentration was based on a $\log_{10}$ concentration with baseline $\log_{10}$ titer and trial site as covariates. A response was defined as an antibody concentration of at least 200 EU per milliliter and an increase from baseline in the antibody concentration by a factor of at least 4. The 95% confidence intervals for the geometric mean ratios and odds ratios for the comparisons of vaccine groups with the placebo group are provided in Tables S15 and S16. Data for the rVSV group and the rVSV–booster group are pooled up to the day 56 assessment because until that time point, participants in both groups had received one dose of the rVSVΔG-ZEBOV-GP vaccine.

† $P<0.001$ for the comparison of each vaccine group with the placebo group at month 12.

However, it has been shown that levels of glycoprotein-binding antibodies strongly correlate with neutralizing antibody titers in nonhuman primates and humans.[20-22] Moreover, the use of results from a clinical trial of a single dose of rVSVΔG-ZEBOV-GP, the threshold of 200 EU per milliliter, and an increase from baseline in the antibody concentration by a factor of 2 or more seem to be a reasonable correlate of protection for that vaccine.[19] Consequently, an analysis that is based on immunogenicity data such as the one reported here is useful in the evaluation of vaccination strategies against EVD.

Geometric mean concentrations of antibodies to the Ebola surface glycoprotein were above the threshold of 200 EU per milliliter for at least 12 months in the majority of participants.[19] One of the challenges in this field of study is that considerable variability exists in the measurements of antibody levels. As described in the Supplementary Appendix, variability in the results was seen over time and as a function of test laboratory. However, the findings that pooled the results across laboratory and country were qualitatively similar to those for each laboratory and country considered separately.

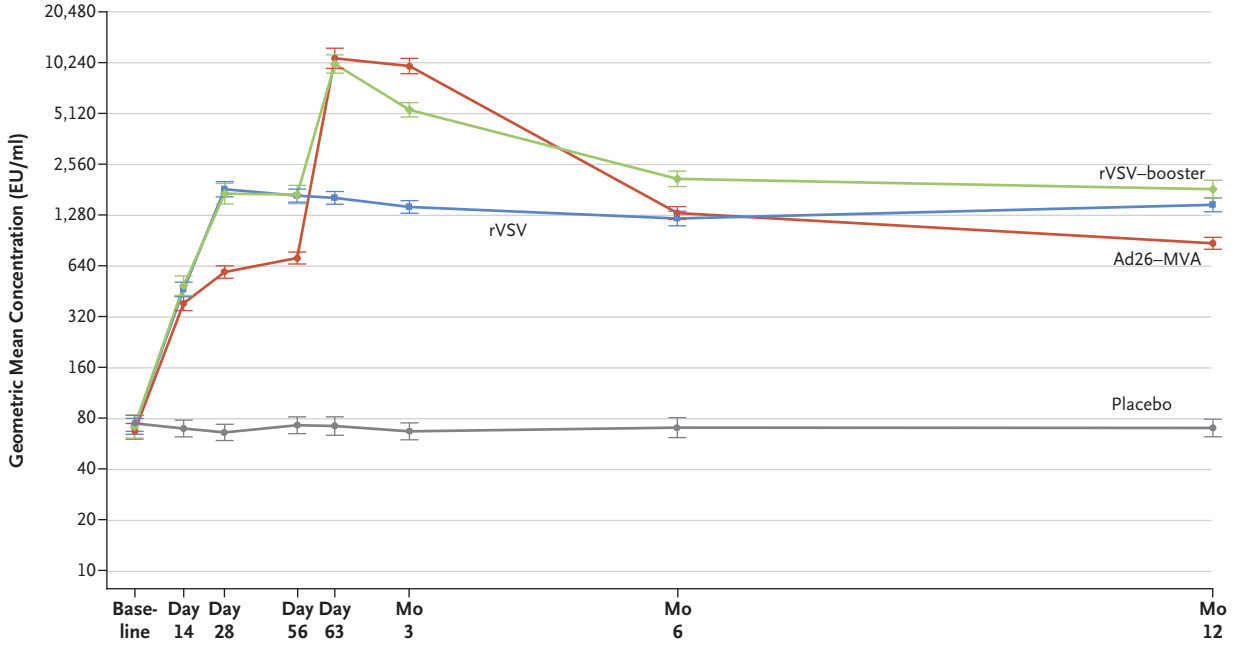
**A Adults**




**No. of Participants**

| | Base-line | Day 14 | Day 28 | Day 56 | Day 63 | Mo 3 | Mo 6 | Mo 12 |
|---|---|---|---|---|---|---|---|---|
| rVSV–booster | 197 | 187 | 188 | 184 | 182 | 184 | 184 | 185 |
| rVSV | 388 | 381 | 372 | 364 | 361 | 367 | 375 | 378 |
| Ad26–MVA | 394 | 377 | 376 | 371 | 364 | 361 | 367 | 376 |
| Placebo | 409 | 388 | 384 | 366 | 356 | 363 | 361 | 379 |

**B Children**




**No. of Participants**

| | Base-line | Day 14 | Day 28 | Day 56 | Day 63 | Mo 3 | Mo 6 | Mo 12 |
|---|---|---|---|---|---|---|---|---|
| rVSV–booster | 200 | 195 | 191 | 195 | 188 | 196 | 193 | 191 |
| rVSV | 401 | 398 | 396 | 397 | 398 | 393 | 392 | 391 |
| Ad26–MVA | 398 | 386 | 393 | 394 | 386 | 384 | 386 | 386 |
| Placebo | 386 | 374 | 372 | 364 | 359 | 364 | 346 | 367 |

**Figure 1 (facing page). Antibody Response in Adults and Children (Geometric Mean Concentrations), According to Trial Visit.**

The geometric mean concentration was based on a $\log_{10}$ concentration with baseline $\log_{10}$ titer and trial site as covariates. Antibody response was defined as an antibody concentration of at least 200 enzyme-linked immunosorbent assay units (EU) per milliliter and an increase from baseline in the antibody concentration by at least a factor of 4. Geometric mean concentrations are shown. I bars indicate 95% confidence intervals.

Given that vaccines against EVD have typically been administered during an outbreak to populations at risk for infection, it was important to investigate the early kinetics of the antibody response. In this regard, both the rVSVΔG-ZEBOV-GP and Ad26.ZEBOV vaccinations led to an increase in geometric mean antibody concentrations beginning at day 14.

The use of primary immunization followed by booster immunization is standard practice for several vaccines. Data on rVSV booster immunizations for Ebola are limited. In this trial, the effect of a second injection of rVSVΔG-ZEBOV-GP at 56 days provided only a transient increase in antibody concentrations, a finding that is in line with responses that have been observed with other live-attenuated vaccines.[23] Additional trials (e.g., ClinicalTrials.gov number, NCT02788227) are under way to determine the effect of a booster given at a later time.

We observed higher antibody concentrations with the Ad26–MVA and rVSV vaccines in children than we did in adults. These data are consistent with findings from studies with a variety of different vaccines, including Ad26.ZEBOV–MVA-BN-Filo and rVSVΔG-ZEBOV-GP,[13,14,24] and probably reflect the more complete immunologic repertoire in children than in adults.[25] Differences in response may also be observed on the basis of host genetic and environmental factors. It has also been shown that the kinetic features of antibodies in children who are vaccinated with rVSVΔG-ZEBOV-GP may differ from those in adults.[24]

No safety concerns were identified in either the adults or children. Side effects were generally mild to moderate in intensity, were time-limited, and were similar to those in previous studies.[11,13,14,20,24,26] Our results regarding the safety of these vaccines have implications for the use of Ebola vaccines in children. Although the Ad26–MVA regimen has received marketing authorization for persons 1 year of age or older from the European Medicines Agency, the licensing of the rVSVΔG-ZEBOV-GP vaccine has thus far been limited to adults.

The PREVAC protocol and our trial findings have several strengths. First, sample sizes were determined to provide reasonable power to analyze antibody and safety results in both adults and children. Second, good follow-up rates were achieved by means of continuous community engagement and ongoing trust building throughout the clinical trial process. Third, we evaluated the two EVD vaccines that have been recommended by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) as compared with a common placebo group, separately in adults and children. Finally, this research was conducted through an international consortium that includes research and academic institutions from the United States, Europe, and western Africa with strong collaborative partnerships.

These two trials have some limitations. We were unable to assess protection from disease or determine a correlate of protection. Although the FANG ELISA, conducted by the Liberian Institute for Biomedical Research and the NIAID Integrated Research Facility, was performed with standard quality controls and has been used to measure antibody responses to the Ebola surface glycoprotein in a previous trial in Liberia,[9] it has not been validated for regulatory submissions. As described in the Supplementary Appendix, variability in the measurements of antibody levels to Ebola virus surface glycoprotein was seen both over time and between the two laboratories. Immunologic correlates of protection have not been established for Ebola vaccines in humans; thus, it is not possible to compare the degree of protection provided by each vaccine because the vaccines generate immune responses by means of different platforms and potentially different mechanisms. Although it has been shown that glycoprotein-specific binding antibodies strongly correlate with neutralizing antibody titers in nonhuman primates and in humans,[9,20-22] any potential binding antibody threshold above which humans would have a high probability of protection is unknown.

Data from these two trials add to evidence on immunogenicity and safety of the Ad26.ZEBOV–MVA-BN-Filo combination and the rVSVΔG-ZEBOV-GP vaccine against EVD in adults and children.

**Table 4. Distribution of Increase in Antibody Concentration from Baseline.***

| Variable | Ad26–MVA Group | Pooled rVSV Groups | rVSV Group | rVSV–Booster Group | Placebo Group |
|---|---|---|---|---|---|
| **Adults** | | | | | |
| Response at 28 days | | | | | |
| No. of participants | 374 | 553 | 365 | 188 | 381 |
| Factor increase — % of participants (cumulative %) | | | | — | |
| ≥8.0× | 22 (22) | 60 (60) | — | — | 1 (1) |
| 4.0–7.9× | 14 (36) | 20 (80) | — | — | <1 (1) |
| 3.0–3.9× | 6 (42) | 6 (87) | — | — | <1 (1) |
| 2.5–2.9× | 6 (49) | 3 (90) | — | — | 0 (1) |
| 2.0–2.4× | 5 (54) | 3 (93) | — | — | <1 (2) |
| 1.0–1.9× | 12 (66) | 4 (97) | — | — | 5 (7) |
| Response at 3 mo | | | | | |
| No. of participants | 359 | — | 360 | 184 | 360 |
| Factor increase — % of participants (cumulative %) | | | | | |
| ≥8.0× | 86 (86) | — | 60 (60) | 89 (89) | 1 (1) |
| 4.0–7.9× | 8 (94) | — | 21 (81) | 7 (96) | 1 (2) |
| 3.0–3.9× | 2 (96) | — | 5 (86) | 2 (98) | 1 (3) |
| 2.5–2.9× | <1 (96) | — | 3 (89) | 1 (98) | 1 (4) |
| 2.0–2.4× | 1 (97) | — | 3 (92) | 0 (98) | 1 (6) |
| 1.0–1.9× | 1 (99) | | 4 (96) | 1 (99) | 7 (13) |
| Response at 12 mo | | | | | |
| No. of participants | 374 | — | 371 | 185 | 377 |
| Factor increase — % of participants (cumulative %) | | | | | |
| ≥8.0× | 24 (24) | — | 57 (57) | 58 (58) | 2 (2) |
| 4.0–7.9× | 17 (41) | — | 18 (76) | 23 (81) | 1 (3) |
| 3.0–3.9× | 9 (50) | — | 7 (83) | 6 (88) | 1 (3) |
| 2.5–2.9× | 8 (57) | — | 4 (87) | 3 (91) | 1 (4) |
| 2.0–2.4× | 4 (62) | — | 3 (89) | 3 (94) | 2 (6) |
| 1.0–1.9× | 12 (74) | — | 6 (95) | 2 (95) | 7 (13) |
| **Children** | | | | | |
| Response at 28 days | | | | | |
| No. of participants | 389 | 580 | 391 | 189 | 369 |
| Factor increase — % of participants (cumulative %) | | | | — | |
| ≥8.0× | 50 (50) | 80 (80) | — | — | 1 (1) |
| 4.0–7.9× | 15 (66) | 10 (90) | — | — | <1 (1) |
| 3.0–3.9× | 8 (74) | 1 (91) | — | — | <1 (1) |
| 2.5–2.9× | 4 (77) | 1 (92) | — | — | 0 (1) |
| 2.0–2.4× | 6 (83) | 1 (93) | — | — | 1 (2) |
| 1.0–1.9× | 6 (89) | 2 (95) | — | — | 4 (6) |

**Table 4. (Continued.)**

| Variable | Ad26–MVA Group | Pooled rVSV Groups | rVSV Group | rVSV–Booster Group | Placebo Group |
|---|---|---|---|---|---|
| Response at 3 mo | | | | | |
| No. of participants | 380 | — | 388 | 194 | 362 |
| Factor increase — % of participants (cumulative %) | | | | | |
| ≥8.0× | 96 (96) | — | 77 (77) | 96 (96) | 1 (1) |
| 4.0–7.9× | 2 (98) | — | 13 (90) | 3 (99) | <1 (1) |
| 3.0–3.9× | 1 (99) | — | 2 (92) | 0 (99) | 1 (2) |
| 2.5–2.9× | <1 (99) | — | 1 (93) | 1 (99) | 1 (2) |
| 2.0–2.4× | <1 (99) | — | 1 (94) | 0 (99) | 0 (2) |
| 1.0–1.9× | <1 (99) | — | 1 (96) | 1 (100) | 6 (8) |
| Response at 12 mo | | | | | |
| No. of participants | 381 | — | 385 | 189 | 364 |
| Factor increase — % of participants (cumulative %) | | | | | |
| ≥8.0× | 61 (61) | — | 75 (75) | 80 (80) | 1 (1) |
| 4.0–7.9× | 17 (78) | — | 12 (87) | 13 (93) | 2 (4) |
| 3.0–3.9× | 7 (85) | — | 4 (91) | 3 (95) | 1 (4) |
| 2.5–2.9× | 4 (89) | — | 1 (92) | 0 (95) | 1 (5) |
| 2.0–2.4× | 2 (91) | — | 1 (93) | 1 (96) | 1 (6) |
| 1.0–1.9× | 5 (96) | — | 2 (95) | 2 (97) | 3 (9) |

* Numbers of participants indicate participants who had a result at baseline and an antibody concentration of at least 200 EU per milliliter at the specified time point. Data for the rVSV group and the rVSV–booster group are pooled through day 28 because at that time point, participants in both groups had received one dose of the rVSVΔG-ZEBOV-GP vaccine. Cumulative percentages (i.e., the percentages of all the participants with any factor increase ≥1.0) may not total as expected because of rounding.

Immune responses were elicited by 14 days after injection for these vaccine regimens and were maintained for 12 months. No safety concerns were identified, including in children as young as 1 year of age. Children had higher immune responses than adults.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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## APPENDIX

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