ORIGINAL ARTICLE

A Recombinant Vesicular Stomatitis Virus Ebola Vaccine — Preliminary Report

J.A. Regules, J.H. Beigel, K.M. Paolino, J. Voell, A.R. Castellano, P. Muñoz, J.E. Moon, R.C. Ruck, J.W. Bennett, P.S. Twomey, R.L. Gutiérrez, S.A. Remich, H.R. Hack, M.L. Wisniewski, M.D. Josleyn, S.A. Kwilas, N. Van Deusen, O. Tshiani Mbaya, Y. Zhou, D.A. Stanley, R.L. Bliss, D. Cebrik, K.S. Smith, M. Shi, J.E. Ledgerwood, B.S. Graham, N.J. Sullivan, L.L. Jagodzinski, S.A. Peel, J.B. Alimonti, J.W. Hooper, P.M. Silvera, B.K. Martin, T.P. Monath, W.J. Ramsey, C.J. Link, H.C. Lane, N.L. Michael, R.T. Davey, Jr., and S.J. Thomas, for the rVSVΔG-ZEBOV-GP Study Group*

ABSTRACT

BACKGROUND

The current Ebola virus disease (EVD) outbreak has resulted in more than 24,000 cases and 10,000 deaths. We present a preliminary report from two phase 1 trials of an attenuated, replication-competent, recombinant vesicular stomatitis virus (rVSV)–based vaccine candidate to prevent EVD.

METHODS

We conducted two phase 1, placebo-controlled, double-blind, dose-escalation trials of an rVSV-based vaccine candidate expressing the glycoprotein of a Zaire strain of Ebola virus (ZEBOV). A total of 26 adults at each site (52 participants in all) were consecutively enrolled into groups of 13 each. Three volunteers in each group received an intramuscular injection of placebo, and 10 received an intramuscular injection of the rVSV-ZEBOV vaccine at a dose of either 3 million plaque-forming units (PFU) or 20 million PFU. Safety and immunogenicity were assessed for the 28 days after vaccination.

RESULTS

The most common adverse events were injection-site pain, myalgia, and fatigue; no events resulted in withdrawal from the study. Transient VSV viremia was noted in all the vaccine recipients. By day 28, all the vaccine recipients had seroconversion as assessed by an enzyme-linked immunosorbent assay (ELISA) against the glycoprotein of the ZEBOV-Kikwit strain. At day 28, geometric mean titers of antibodies against ZEBOV glycoprotein were higher in the group receiving 20 million PFU than in the group receiving 3 million PFU, as assessed by ELISA (geometric mean antibody titer, 4079 vs. 1300; $P<0.001$) and by pseudovirion neutralization assay (geometric mean antibody titer, 441 vs. 223; $P=0.07$).

CONCLUSIONS

No safety concerns were identified after a single administration of the rVSV-ZEBOV vaccine candidate, and anti-Ebola immune responses were identified in all the volunteers. VSV viremia was detected but was of limited duration. These preliminary results support the further development of the vaccine dose of 20 million PFU. (Funded by the National Institutes of Health and others; rVSVΔG-ZEBOV-GP ClinicalTrials.gov numbers, NCT02269423 and NCT02280408.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Regules at the Walter Reed Army Institute of Research, 503 Robert Grant Ave., Silver Spring, MD 20910, or at jason.a.regules.mil@mail.mil.

Drs. Regules and Beigel and Drs. Davey and Thomas contributed equally to this article.

*A complete list of members of the rVSVΔG-ZEBOV-GP Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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The current Ebola virus disease (EVD) outbreak has resulted in more than 24,000 cases and 10,000 reported deaths as of March 25, 2015.[1] Although the primary strategy to stop the transmission of human Ebola virus remains the identification and isolation of contacts and the use of appropriate personal protective equipment, the development and deployment of a safe and efficacious vaccine would provide an important public health tool that could be used to interrupt transmission within outbreaks and prevent subsequent occurrences. Numerous Ebola virus vaccine candidates are in preclinical development, and some have proceeded to human trials.[2-4]

An Ebola virus vaccine candidate based on an attenuated, replication-competent, recombinant vesicular stomatitis virus (rVSV) has shown great promise in preclinical studies. The vaccine candidate (rVSV-ZEBOV) is genetically engineered to replace the VSV glycoprotein with the glycoprotein from a Zaire strain of Ebola virus (ZEBOV). Vaccination induces replication of viral particles similar to VSV but expressing the ZEBOV surface glycoprotein. ZEBOV glycoprotein is responsible for receptor binding and membrane fusion between ZEBOV and host target cells.[5]

Preclinical testing of rVSV-ZEBOV supports its potential for clinical benefit in human populations. Live viral vaccines have the ability to elicit rapid and durable immune responses.[6] The rVSV-ZEBOV vaccine has been shown to be attenuated in normal and immunocompromised nonhuman primates in safety and immunogenicity studies.[7,8] Multiple studies in cynomolgus macaques have shown that a single administration of the vaccine confers a high level of protection against lethal challenge, including challenge through the aerosol route.[9,10] Various methods of vaccine delivery (oral, intranasal, or intramuscular) have shown retention of protective efficacy in animal models.[11] Furthermore, preclinical data suggest that the rVSV platform could support a pan-filovirus (ZEBOV, *Sudan ebolavirus*, and Marburg virus) vaccine candidate in single or multiple doses.[12] Studies of postexposure prophylaxis in various animal models, including nonhuman primates, indicate that the rVSV platform may also be able to protect against *Sudan ebolavirus* or ZEBOV disease when it is administered 30 minutes to 24 hours after infection, and this approach has recently been used 43 hours after a possible exposure in a patient.[13-15]

On the basis of this favorable preclinical experience, we conducted a phase 1, double-blind, placebo-controlled, dose-escalation study of rVSV-ZEBOV at two locations in the United States: the Walter Reed Army Institute of Research (WRAIR), in Silver Spring, Maryland, and the National Institutes of Health (NIH) Clinical Center, in Bethesda, Maryland. The WRAIR evaluated a single-dose strategy, whereas the NIH evaluated a homologous prime-boost regimen administered at study days 0 and 28. Initial safety and humoral-immunogenicity data through day 28 after vaccination, generated by the same laboratories for both trials, are presented here for the two vaccine dose levels (3 million plaque-forming units [PFU] and 20 million PFU) that were under consideration for the anticipated phase 2 and 3 trials in affected countries in West Africa. On the basis of the data presented here and additional clinical and preclinical data, the rVSV-ZEBOV vaccine (at the dose of 20 million PFU) was selected for inclusion in the Partnership for Research on Ebola Vaccines in Liberia trial (ClinicalTrials.gov number, NCT02344407), a recently initiated phase 3 efficacy study in Guinea (sponsored by the World Health Organization, the Ministry of Health of Guinea, Médecins sans Frontières, Epicentre, and the Norwegian Institute of Public Health), and the soon-to-be-initiated phase 3 Sierra Leone Trial to Introduce a Vaccine against Ebola (sponsored by the U.S. Centers for Disease Control and Prevention and the Ministry of Health of Sierra Leone).

METHODS

VACCINE

The rVSV-ZEBOV vaccine candidate is a live attenuated recombinant virus consisting of the vesicular stomatitis virus strain Indiana (rVSV), with the glycoprotein of the ZEBOV Kikwit 1995 strain replacing the gene for the VSV envelope glycoprotein. The resultant rVSV construct contains surface ZEBOV glycoprotein that exhibits a narrower host-cell tropism in vitro and considerable attenuation of replication, as compared with wild-type VSV.[16]

The vaccine was developed by the Public Health Agency of Canada, licensed to BioProtection Systems (NewLink Genetics), and most recently sublicensed to Merck, which is responsible for ongoing research and development. The study sponsor, BioProtection Systems, was involved in

discussions of the study design and in the study monitoring and statistical analysis; it also provided the vaccine candidate. The vaccine, which was manufactured according to current Good Manufacturing Practices, was formulated with recombinant human serum albumin and tris(hydroxymethyl)aminomethane buffer and was dispensed in a vial containing 100 million PFU per milliliter. Normal saline was used as a diluent to formulate the doses of 3 million PFU or 20 million PFU.

VOLUNTEERS AND STUDY DESIGN

Both trials are phase 1, double-blind, placebo-controlled, dose-escalation trials with staggered enrollment. The trials are designed to assess the safety, reactogenicity, and immunogenicity of rVSV-ZEBOV across three dose levels: 3 million PFU, 20 million PFU, and 100 million PFU. A total of 52 healthy adult men and women from the Washington, D.C.–Baltimore metropolitan area were recruited according to protocols that were approved by the institutional review board at each site. Written informed consent was obtained from all the volunteers before enrollment. Exclusion criteria were active involvement in clinical care of patients; substantial contact with immunocompromised populations, children 5 years of age or younger, or animals at risk for VSV infection; and a history of or predisposition to exposure to filoviruses or VSV. Pregnant or lactating women and persons found to have the human immunodeficiency virus, hepatitis B or C virus infection, or clinically significant metabolic or hematologic abnormalities at screening were excluded.

STUDY PROCEDURES

A total of 26 adults at each site were consecutively enrolled into groups of 13 each. In each group, 3 volunteers were randomly assigned in a blinded manner to receive the control (saline placebo), and 10 were assigned to receive the rVSV-ZEBOV vaccine at a dose of either 3 million PFU or 20 million PFU. Each participant received a 1-ml injection in the deltoid muscle. After the intramuscular injection on day 0, volunteers were assessed on days 1, 3, 7, 14, and 28. Data on solicited adverse events related to injection-site and systemic reactogenicity, unsolicited adverse events, changes in medical status, and concomitant medication use were collected for 14 days after injection. Blood samples were obtained to assess safety and immunologic end points. All the volunteers had safety laboratory evaluations at baseline and on day 7 and day 28 after vaccination. In addition, the WRAIR site evaluated these laboratory variables on days 1 and 3 after injection. Grading of adverse events was based on Food and Drug Administration toxicity grading.[17] Positivity for vaccine ZEBOV-glycoprotein nucleic acid sequences was assessed in plasma, saliva, and urine. At the WRAIR, samples were obtained before the injection and on days 1, 3, 7, and 14 after the injection. At the NIH site, specimens were obtained on days 3 and 7. Further details are available in the trial protocols, available with the full text of this article at NEJM.org.

rVSV-ZEBOV SURVEILLANCE BY RT-PCR

A reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay was used to measure potential rVSV virus in the plasma, saliva, and urine, through amplification of the Ebola Zaire glycoprotein gene insert of the vaccine. The assay was performed at the WRAIR. Details are provided in the Supplementary Appendix, available at NEJM.org.

MEASUREMENT OF ANTIBODY RESPONSES TO EBOLA GLYCOPROTEIN

Three assessments for antibody response were performed: an enzyme-linked immunosorbent assay (ELISA) against the heterologous Zaire-Mayinga strain glycoprotein, an ELISA against the homologous Zaire-Kikwit strain glycoprotein, and a pseudovirion neutralization assay (PsVNA) against the homologous Zaire-Kikwit strain glycoprotein. The ELISA against the Zaire-Mayinga strain glycoprotein was performed at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases with the use of methods described previously.[18] The ELISA against the Zaire-Kikwit strain glycoprotein and the PsVNA were performed at the U.S. Army Medical Research Institute of Infectious Diseases (see the Methods section in the Supplementary Appendix).

STATISTICAL ANALYSIS

Statistical analyses were performed with the use of SAS for Windows software, version 9.3. For each serologic variable, data were summarized by assessment day and included the geometric mean titer and 95% confidence interval, the median value, and minimum and maximum values. Analysis-of-variance models were performed for

each variable for comparison of observed geometric mean titers among dose levels. Comparisons between day 14 and day 28 used paired t-tests according to dose level. All calculations and comparisons of geometric mean titers were performed on the $\log_{10}$ scale.

A positive response for the Kikwit strain ELISA was defined as a titer of 50 or more, with titers of less than 50 assigned values of 25 for calculation. A positive response for the PsVNA was defined as a titer of 20 or more, with titers of less than 20 assigned values of 10 for calculation. Seroconversion on these assays was defined as an increase in the titer by a factor of 4 over the baseline value. Baseline values were subtracted from the postvaccination values for determination of the Mayinga strain ELISA titers, as described previously.[3,4] The preliminary results presented here are from an interim database from these two ongoing trials.

RESULTS

STUDY PARTICIPANTS

A total of 52 volunteers (36 men [69%] and 16 women [31%]), with a mean age of 34 years (range, 20 to 61), were enrolled in a consecutive manner; injections were administered between October 10 and November 20, 2014. A total of 40 volunteers were randomly assigned to receive rVSV-ZEBOV, and 12 volunteers were randomly assigned to receive saline placebo. All the volunteers completed the planned follow-up visits during the 28-day postvaccination period (Fig. S1 in the Supplementary Appendix). Additional details regarding the demographic characteristics of the volunteers are provided in Table 1.

Figure 1 (facing page). Frequency of Solicited Adverse Events According to Cohort and Grade.

Cohort 1 received a dose of 3 million plaque-forming units (PFU) of the vaccine, and Cohort 2 received a dose of 20 million PFU. All adverse events were graded for relatedness to the vaccine and severity. Adverse events that were judged by the investigating physicians not to be related to the vaccine are not presented. Unsolicited adverse events and laboratory adverse events are shown in the Supplementary Appendix. Grading of adverse events was based on Food and Drug Administration toxicity grading.[17]

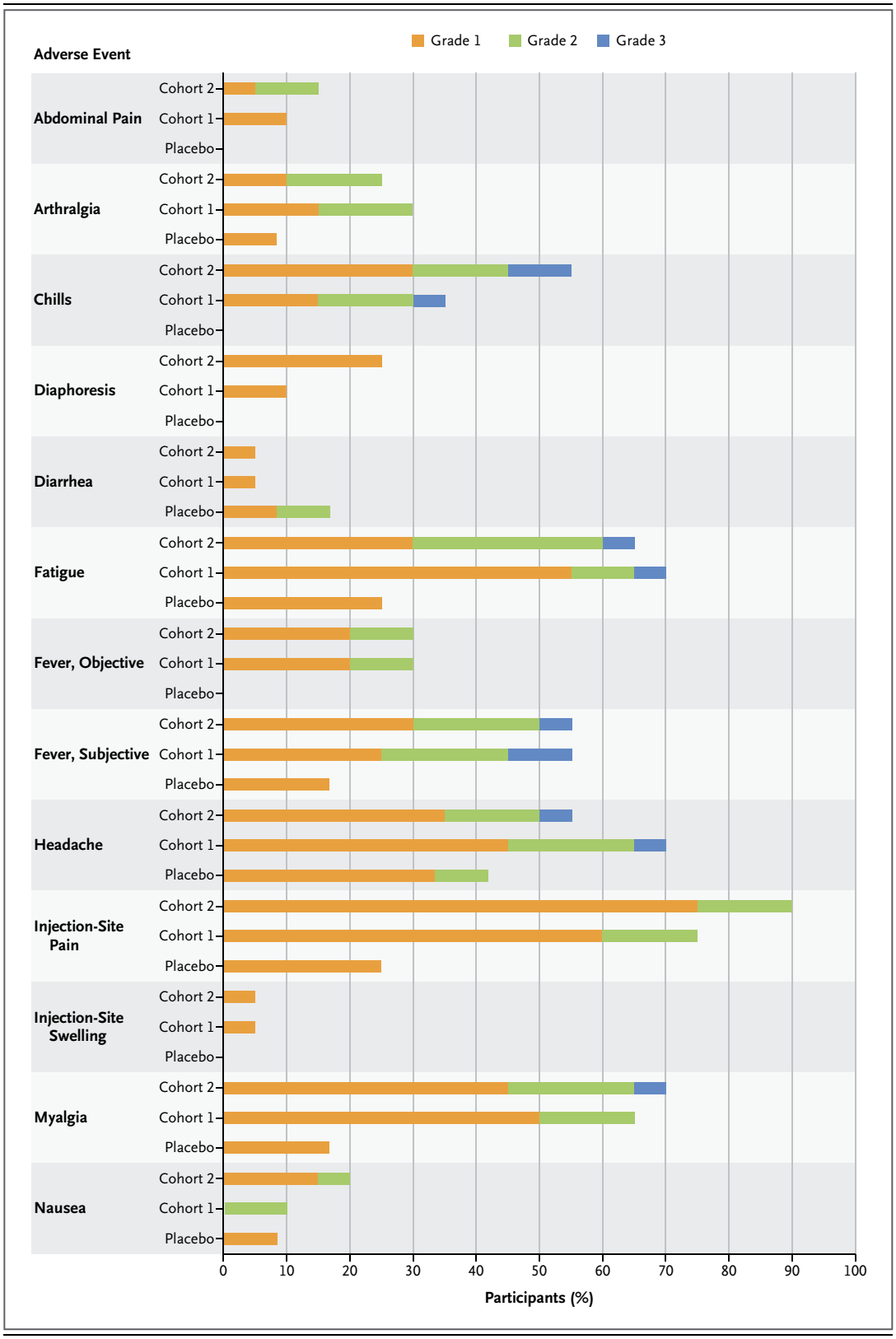
SAFETY

There were no deaths, serious adverse events, or adverse events resulting in withdrawal from the study. There was no association between vaccine dose and the frequency or severity of adverse events (Fig. 1, and Fig. S2 and S3 and Table S4 in the Supplementary Appendix). Mild-to-moderate injection-site pain was observed in the majority

Table 1. Characteristics of the Participants at Enrollment.*

Characteristic	Vaccine, 3 Million PFU (N=20)	Vaccine, 20 Million PFU (N=20)	Placebo (N=12)	Overall (N=52)
Sex — no. (%)				
Male	13 (65)	16 (80)	7 (58)	36 (69)
Female	7 (35)	4 (20)	5 (42)	16 (31)
Age — yr	36.9 ±11.8	34.7±12.1	29.9 ±6.8	34.4 ±11.1
Race — no. (%)†				
Asian	4 (20)	3 (15)	2 (17)	9 (17)
Black	5 (25)	7 (35)	3 (25)	15 (29)
White	10 (50)	10 (50)	7 (58)	27 (52)
Multirace	1 (5)	0	0	1 (2)
Hispanic ethnic group — no. (%)†	1 (5)	3 (15)	0	4 (8)
Body-mass index‡	26.5 ±4.7	26.5 ±5.3	29±7.4	28±5.7

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline. PFU denotes plaque-forming units.
† 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.



of participants. Systemic reactogenicity was transient and, in the majority of volunteers, mild to moderate in severity. Objective fever was noted in 12 of the 40 vaccinees: 8 (20%) had grade 1 fever (temperature range, 38.0 to 38.4°C), and 4 (10%) had grade 2 fever (temperature range, 38.5 to 38.9°C). Fever onset and frequency did not appear to be dose-dependent (Fig. 1, and Fig. S2 in the Supplementary Appendix); fever typically developed 12 to 24 hours after vaccination and resolved by the end of postvaccination day 1. One volunteer who received a dose of 3 million PFU had grade 1 fever 7 days after vaccination that resolved within 24 hours without development of other symptoms.

Other commonly reported systemic symptoms were headache, myalgia, and fatigue, with typical onset 12 to 24 hours after vaccination. In the group receiving a dose of 20 million PFU, unilateral conjunctivitis developed in one volunteer 1 day after vaccination, and a single oral ulcer developed in one volunteer 4 days after vaccination. PCR analysis of swabs of the affected areas was negative for the Ebola glycoprotein gene insert in both cases, and both conditions resolved without complication. Cervical lymphadenopathy developed in two volunteers shortly after vaccination (on days 1 and 5); one of the two volunteers also reported the oral ulcer. All conditions resolved without complications. A complete list of solicited and unsolicited adverse events is provided in Table S4 in the Supplementary Appendix.

Safety laboratory values were generally unremarkable. Transient mild-to-moderate lymphopenia, which was noted in 13 of the 20 participants who were evaluated on day 1, improved by day 3 after vaccination. Mild-to-moderate neutropenia, which was noted by day 3 after vaccination in 6 of 20 participants, improved within 2 to 4 days. An asymptomatic grade 2 thrombocytopenia, associated with grade 1 lymphopenia, was noted on day 1 after vaccination in one volunteer who received a dose of 20 million PFU; the condition resolved by day 7.

After a report from another ongoing study of rVSV-ZEBOV of the onset of arthritis in the second week after injection, volunteers were specifically queried about the development of new arthralgia, arthritis, or rash during the second week or later after vaccination. One participant reported arthralgia that began on day 11 concurrent with the onset of menses, though she noted previous occurrences of arthralgia with menses onset. No cases of arthritis were diagnosed.

rVSV-ZEBOV on PCR Assay

PCR results are shown in Table 2. All the vaccinated volunteers had detectable vaccine viremia at the first visit after vaccination (day 1 at the WRAIR and day 3 at the NIH). Six of the 40 vaccinated volunteers (15%) had viremia on day 7 af-

Table 2. Vaccine Virus Detection by Means of Qualitative Reverse-Transcriptase–Polymerase-Chain-Reaction Assay.*

Type of Specimen	Day 1	Day 3	Day 7	Day 14
	no. of positive samples/no. of samples tested (%)			
Blood				
Vaccine, 3 million PFU	10/10 (100)	20/20 (100)	1/20 (5)	0/10
Vaccine, 20 million PFU	10/10 (100)	20/20 (100)	5/20 (25%)	0/10
Total	20/20 (100)	40/40 (100)	6/40 (15)	0/20
Urine				
Vaccine, 3 million PFU	0/10	1/10 (10)	1/10 (10)	0/10
Vaccine, 20 million PFU	0/10	0/7	0/20	0/10
Total	0/20	1/17 (6)	1/30 (3)	0/20
Saliva				
Vaccine, 3 million PFU	0/10	2/20 (10)	0/20	0/10
Vaccine, 20 million PFU	0/10	0/19	5/20 (25)	1/10 (10)
Total	0/20	2/39 (5)	5/40 (12)	1/20 (5)

* Data for days 1 and 14 are from the Walter Reed Army Institute of Research only.

ter vaccination. Viremia was undetectable by day 14 in all vaccinees tested at that time point (20 volunteers at the WRAIR). In the group that received a dose of 3 million PFU, there were two positive saliva samples and one positive urine sample on day 3 and one positive urine sample on day 7. In the group that received a dose of 20 million PFU, there were five positive saliva samples on day 7 and one positive sample on day 14. Two subsequent saliva samples were PCR-negative in the single volunteer who had a positive PCR saliva sample on day 14. Cycle-threshold values for the positive urine sample on day 7 and saliva sample on day 14 were near the lower limit of detection for the assay.

ELISA FOR EBOLA GLYCOPROTEIN

ELISA results for antibodies directed against the homologous Zaire-Kikwit and heterologous Zaire-Mayinga strains are shown in Figure 2 and

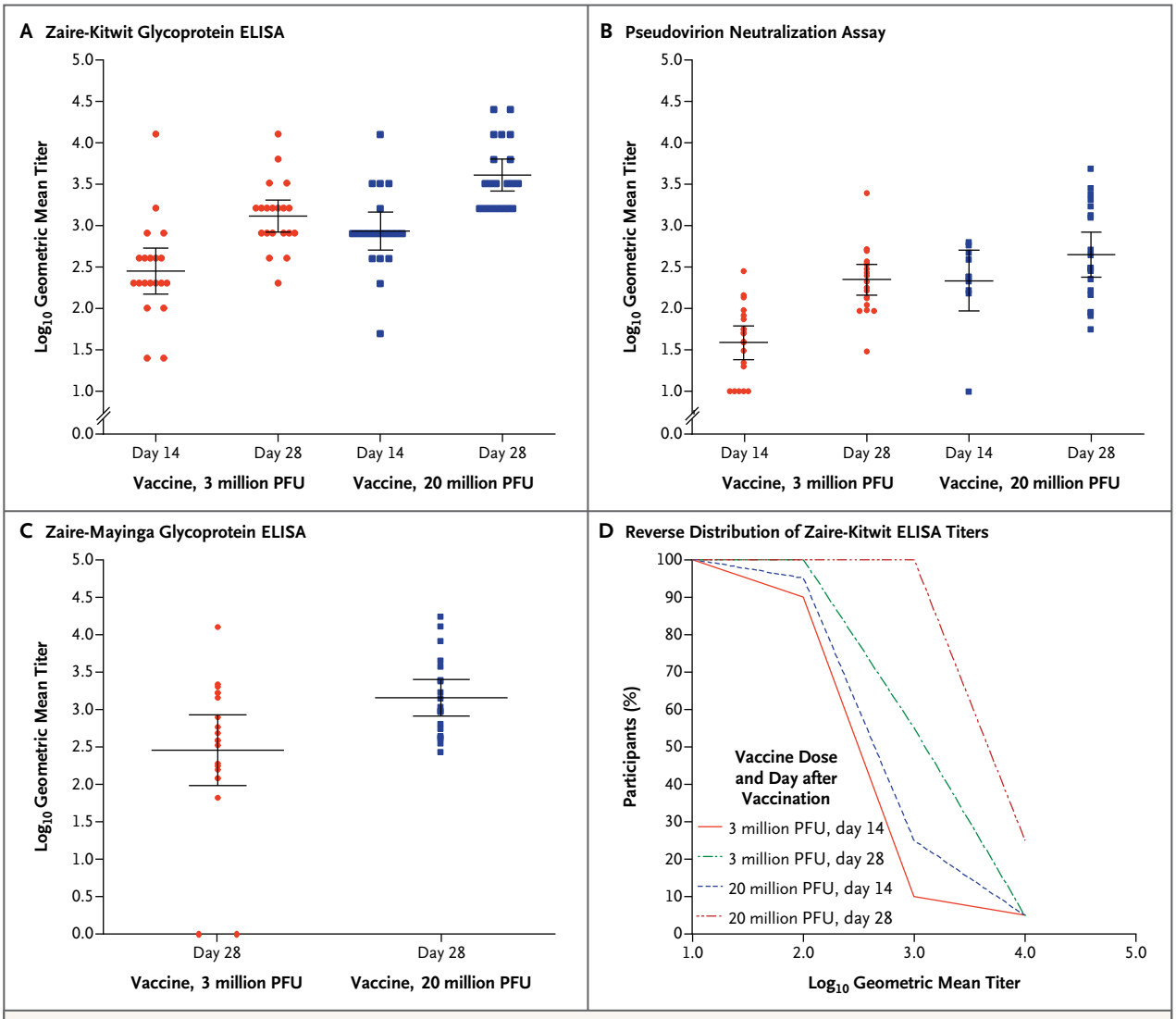


Figure 2. Antibody Responses to Ebola Glycoprotein.

Individual antibody titers as assessed at 14 and 28 days after vaccination are shown according vaccine dose group, as measured by an enzyme-linked immunosorbent assay (ELISA) against the Zaire-Kikwit strain glycoprotein (Panel A), a pseudovirion neutralization assay (Panel B), and an ELISA against the Zaire-Mayinga strain glycoprotein (Panel C). Geometric mean titers (horizontal lines) are shown for each group and time point; I bars indicate 95% confidence intervals. The values for the ELISA against the Zaire-Mayinga strain glycoprotein are calculated as the difference from day 0. Reverse cumulative distribution curves are shown for the ELISA against the Zaire-Kikwit strain glycoprotein (Panel D).

Table 3, and Tables S1 and S3 in the Supplementary Appendix. A total of 18 of 20 volunteers (90%) who received a dose of 3 million PFU and 19 of 20 volunteers (95%) who received a dose of 20 million PFU had seroconversion by day 14. All 40 vaccinated volunteers (100%) had seroconversion by day 28. IgG responses were observed after vaccination with either 3 million PFU or 20 million PFU; however, responses were greater in the group that received a dose of 20 million PFU, both on day 14 (857 vs. 283, P = 0.008) and on day 28 (4079 vs. 1300, P<0.001). Geometric mean titers against the Zaire-Kikwit strain showed an upward trend between day 14 and day 28 in both dose groups (increase from 283 to 1300 in the group receiving a dose of 3 million PFU [P<0.001] and from 857 to 4079 in the group receiving a dose of 20 million PFU [P<0.001]). The group receiving a dose of 20 million PFU had a higher geometric mean titer of antibodies against the Zaire-Mayinga strain than the group receiving a dose of 3 million PFU (1429 vs. 283, P = 0.008) on day 28 after vaccination.

PsVNA Titers

Neutralizing antibody titers against the Zaire-Kikwit strain glycoprotein are shown in Figure 2 and Table 3, and Table S2 in the Supplementary Appendix. For both dose groups, antibody geometric mean titers followed a pattern similar to the ELISA results. All the vaccinated volunteers had neutralizing antibodies by day 28 after vaccination, with an increase in geometric mean titers between day 14 and day 28 (from 39 to 223 in the group receiving a dose of 3 million PFU [P<0.001] and from 217 to 441 in the group receiving a dose of 20 million PFU [P = 0.08]). The geometric mean titers in the group receiving a dose of 20 million PFU were higher than those in the group receiving a dose of 3 million PFU, both on day 14 (217 vs. 39, P<0.001) and on day 28 (441 vs. 223, P = 0.07).

DISCUSSION

No safety concerns were identified after a single administration of the rVSV-ZEBOV Ebola vaccine candidate, though the number of participants studied (40) was small. The most common side effects were injection-site pain, myalgia, fatigue, headache, subjective fever, and chills. Immunogenicity as measured by means of IgG ELISA was concordant with antibody responses measured with the use of a functional (neutralization) assay, and the IgG ELISA results indicated a dose response, with the development of significantly higher IgG and neutralizing antibody levels after administration of a vaccine virus dose of 20 million PFU than after administration of a dose of 3 million PFU. These data support continued development of the rVSV-ZEBOV Ebola vaccine candidate in general and the selection of a dose of 20 million PFU for phase 2 and 3 trials. Although arthritis was reported in another ongoing clinical trial, it was not observed at the WRAIR or NIH sites.

Table 3. Geometric Mean Antibody Titers.*

Study Group	Zaire-Kikwit Glycoprotein ELISA		PsVNA		Zaire-Mayinga Glycoprotein ELISA
	Day 14	Day 28	Day 14	Day 28	Day 28
	geometric mean titer (95% CI)				
Vaccine, 3 million PFU	283 (150–53)	1300 (831–2033)	39 (24–62)	223 (145–342)	283 (96–832)
Vaccine, 20 million PFU	857.42 (502–1465)	4079 (2601–6396)	217 (92–508)	441 (236–825)	1429 (808–2526)
Placebo	30 (20–44)	35 (24–53)	10 (10–10)	10 (10–10)	4 (2–10)

* Zaire-Kikwit enzyme-linked immunosorbent assay (ELISA) titers were significantly higher in the group receiving a vaccine dose of 20 million PFU than in the group receiving a dose of 3 million PFU, both on day 14 (P=0.008) and on day 28 (P<0.001). Pseudovirion neutralization assay (PsVNA) titers were significantly higher in the group receiving a dose of 20 million PFU than in the group receiving a dose of 3 million PFU only on day 14 (P<0.001). Zaire-Mayinga ELISA titers were significantly higher in the group receiving a dose of 20 million PFU than in the group receiving a dose of 3 million PFU (P=0.008). For the PsVNA, not all samples obtained on day 14 from participants receiving a dose of 20 million PFU have been tested at the time of this report, owing to limitations on laboratory capacity (data from the Walter Reed Army Institute of Research are presented here). CI denotes confidence interval.

As expected with a live virus-vectored vaccine, transient VSV viremia was associated with rVSV-ZEBOV immunization. The clinical symptoms associated with this viremia included fever and appeared to peak and then decrease in the 12 to 36 hours after vaccination. Although the temporal association with vaccination, with a characteristic brief pattern, may help to distinguish this clinical presentation from other infectious disease syndromes, vigilance is warranted. Moderate asymptomatic declines in leukocyte subsets (e.g., lymphopenia and neutropenia) were noted during the first 3 days after vaccination and resolved rapidly.

Given the accessibility to EZ1 reagents and ongoing efforts to develop a VSV assay at our study sites, we used a PCR assay that targeted the Ebola glycoprotein gene insert of the vaccine. This target has previously been used in ZEBOV-exposed patients who had received the rVSV-ZEBOV vaccine. This approach serves as a surrogate for the detection of the rVSV.[15,19] Analysis with a VSV-specific quantitative assay is needed. Results of previously published studies in nonhuman primates that were conducted with the use of preclinical-grade vaccine material showed a detectable early viremia, as is expected with a live vaccine vector, and a paucity of viable virus cultured from samples obtained outside the proximal window after vaccination.[21] The data from the clinical trials presented herein are consistent with this preclinical experience and, combined with the established attenuation of the vaccine vector, provide further support for the safety of rVSV vectors.[2,16,21]

The vaccine-induced immune responses for prevention of EVD are largely unknown. Successful protection in the nonhuman primate model has been shown with various vaccine candidates, in the context of a predominantly cellular correlate as well as a predominantly humoral correlate.[22,23] In the nonhuman primate challenge model, antibody response has been the strongest immune correlate of protection with the use of the rVSV-ZEBOV vaccine candidate, with high IgG antibody titers associated with protection.[10,24,25] Because the two ELISAs used in these trials were from two laboratories that used different methods, definitive comparisons cannot be made. Nonetheless, each assay provides valuable insights.

The rVSV-ZEBOV vaccine candidate appears to produce cross-strain glycoprotein-specific antibodies effectively, as evidenced by the achievement of Mayinga-strain glycoprotein titers similar to those described for the chimpanzee adenovirus 3 vaccine candidate.[3] The primary readout, the homologous Kikwit strain ELISA, also revealed a distinct IgG antibody response 14 to 28 days after vaccination, with a dose–response relationship. A preliminary comparison of data from nonhuman primates vaccinated with the same doses used in the WRAIR and NIH trials, then subsequently challenged with Ebola-Kikwit strain virus at the U.S. Army Medical Research Institute of Infectious Diseases, showed that survivors had significant prechallenge IgG antibody responses against Ebola glycoprotein, as seen in vaccinated human volunteers (Trefry J: personal communication).

Neutralizing antibody assays have been difficult to correlate with outcomes in animal studies involving EVD.[13,25,26] However, the assay used for this report showed a strong association with protection of nonhuman primates across multiple vaccine platforms.[27] The advantages of such a system are improved functional and qualitative assessment of humoral response and the ability to perform a functional assay for Ebola immune response in a biosafety level 2 environment rather than in a biosafety level 4 high-containment laboratory, which is required for plaque-reduction neutralization tests that use Ebola virus. Further assessment of this method is warranted.

The preliminary results reported here support the safety, side-effect profile, and immunogenicity of the rVSV-ZEBOV vaccine and encourage further investigation of this vaccine candidate. Live viral vaccines are generally associated with memory responses and long-lasting immunity; however, data regarding the duration of the protective response after vaccination with the rVSV vector are currently limited.[26,28]

The views expressed are those of the authors and should not be construed as official or representing the positions of the Departments of the Army, Navy, or Defense or the National Institutes of Health (NIH). The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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

APPENDIX

The authors' full names and academic degrees are as follows: Jason A. Regules, M.D., John H. Beigel, M.D., Kristopher M. Paolino, M.D., Jocelyn Voell, R.N., M.S., Amy R. Castellano, L.P.N., Paula Muñoz, B.S., James E. Moon, M.D., Richard C. Ruck, M.D., Jason W. Bennett, M.D., Patrick S. Twomey, M.D., Ramiro L. Gutiérrez, M.D., Shon A. Remich, M.D., Holly R. Hack, M.S., Meagan L. Wisniewski, Ph.D., Matthew D. Josleyn, M.S., Steven A. Kwilas, Ph.D., Nicole Van Deusen, B.S., Olivier Tshiani Mbaya, M.D., Yan Zhou, Ph.D., Daphne A. Stanley, M.S., Robin L. Bliss, Ph.D., Deborah Cebrik, M.S., M.P.H., Kirsten S. Smith, Ph.D., Meng Shi, M.A., Julie E. Ledgerwood, D.O., Barney S. Graham, M.D., Nancy J. Sullivan, Ph.D., Linda L. Jagodzinski, Ph.D., Sheila A. Peel, M.S.P.H., Ph.D., Judie B. Alimonti, Ph.D., Jay W. Hooper, Ph.D., Peter M. Silvera, Ph.D., Brian K. Martin, Ph.D., Thomas P. Monath, M.D., W. Jay Ramsey, M.D., Ph.D., Charles J. Link, M.D., H. Clifford Lane, M.D., Nelson L. Michael, M.D., Ph.D., Richard T. Davey, Jr., M.D., and Stephen J. Thomas, M.D.

The authors' affiliations are as follows: the Walter Reed Army Institute of Research (J.A.R., K.M.P., A.R.C., J.E.M., R.C.R., J.W.B., P.S.T., S.A.R., H.R.H., M.S., L.L.J., S.A.P., N.L.M., S.J.T.) and the Naval Medical Research Center (R.L.G.), Silver Spring, Leidos Biomedical Research, Frederick National Laboratory for Cancer Research (J.H.B.), and the U.S. Army Medical Research Institute of Infectious Diseases (M.L.W., M.D.J., S.A.K., N.V.D., K.S.S., J.W.H., P.M.S.), Frederick, and the National Institute of Allergy and Infectious Diseases (NIAID) (J.V., P.M., H.C.L., R.T.D.) and the NIAID Vaccine Research Center (O.T.M., Y.Z., D.A.S., J.E.L., B.S.G., N.J.S), Bethesda — all in Maryland; Veristat, Holliston, MA (R.L.B., D.C.); BioProtection Systems–NewLink Genetics, Ames, IA (B.K.M., T.P.M., W.J.R., C.J.L.); and the Public Health Agency of Canada, Ottawa (J.B.A.).

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