ORIGINAL ARTICLE

Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe

S.T. Agnandji, A. Huttner, M.E. Zinser, P. Njuguna, C. Dahlke, J.F. Fernandes,
S. Yerly, J.-A. Dayer, V. Kraehling, R. Kasonta, A.A. Adegnika, M. Altfeld,
F. Auderset, E.B. Bache, N. Biedenkopf, S. Borregaard, J.S. Brosnahan, R. Burrow,
C. Combescure, J. Desmeules, M. Eickmann, S.K. Fehling, A. Finckh,
A.R. Goncalves, M.P. Grobusch, J. Hooper, A. Jambrecina, A.L. Kabwende,
G. Kaya, D. Kimani, B. Lell, B. Lemaître, A.W. Lohse, M. Massinga-Loembe,
A. Matthey, B. Mordmüller, A. Nolting, C. Ogwang, M. Ramharter,
J. Schmidt-Chanasit, S. Schmiedel, P. Silvera, F.R. Stahl, H.M. Staines, T. Strecker,
H.C. Stubbe, B. Tsofa, S. Zaki, P. Fast, V. Moorthy, L. Kaiser, S. Krishna, S. Becker,
M.-P. Kieny, P. Bejon, P.G. Kremsner, M.M. Addo, and C.-A. Siegrist*

ABSTRACT

BACKGROUND

The replication-competent recombinant vesicular stomatitis virus (rVSV)–based vaccine expressing a *Zaire ebolavirus* (ZEBOV) glycoprotein was selected for rapid safety and immunogenicity testing before its use in West Africa.

METHODS

We performed three open-label, dose-escalation phase 1 trials and one randomized, double-blind, controlled phase 1 trial to assess the safety, side-effect profile, and immunogenicity of rVSV-ZEBOV at various doses in 158 healthy adults in Europe and Africa. All participants were injected with doses of vaccine ranging from 300,000 to 50 million plaque-forming units (PFU) or placebo.

RESULTS

No serious vaccine-related adverse events were reported. Mild-to-moderate early-onset reactogenicity was frequent but transient (median, 1 day). Fever was observed in up to 30% of vaccinees. Vaccine viremia was detected within 3 days in 123 of the 130 participants (95%) receiving 3 million PFU or more; rVSV was not detected in saliva or urine. In the second week after injection, arthritis affecting one to four joints developed in 11 of 51 participants (22%) in Geneva, with pain lasting a median of 8 days (interquartile range, 4 to 87); 2 self-limited cases occurred in 60 participants (3%) in Hamburg, Germany, and Kilifi, Kenya. The virus was identified in one synovial-fluid aspirate and in skin vesicles of 2 other vaccinees, showing peripheral viral replication in the second week after immunization. ZEBOV-glycoprotein–specific antibody responses were detected in all the participants, with similar glycoprotein-binding antibody titers but significantly higher neutralizing antibody titers at higher doses. Glycoprotein-binding antibody titers were sustained through 180 days in all participants.

CONCLUSIONS

In these studies, rVSV-ZEBOV was reactogenic but immunogenic after a single dose and warrants further evaluation for safety and efficacy. (Funded by the Wellcome Trust and others; ClinicalTrials.gov numbers, NCT02283099, NCT02287480, and NCT02296983; Pan African Clinical Trials Registry number, PACTR201411000919191.)

In August 2014, after the outbreak of Ebola virus disease was declared a public health emergency of international concern by the World Health Organization (WHO), the Canadian government donated 800 vials of the replication-competent recombinant vesicular stomatitis virus (rVSV)–vectored *Zaire ebolavirus* (rVSV-ZEBOV) candidate vaccine to the WHO. The VSV Ebola Consortium (VEBCON) was created under the auspices of the WHO to initiate phase 1 studies to facilitate rapid progression to phase 2 and 3 trials in affected countries.[1]

Live replicating viral vaccines elicit humoral and cellular immune responses against viral pathogens.[2,3] A single injection of 10 million plaque-forming units (PFU) of rVSV-ZEBOV protected nonhuman primates exposed to lethal doses of ZEBOV.[4-7] Vesicular stomatitis virus belongs to the Rhabdoviridae family.[8] In livestock, wild-type VSV causes vesicles and ulcerations of the oral tissues, feet, and teats.[9] Human infections are rare and asymptomatic or typically cause mild influenza-like illness, although more severe infections have been described.[9-14] The wild-type virus is not endemic in Africa and Europe.[15,16] The preclinical safety record of the rVSV vector is encouraging: among approximately 80 immunized nonhuman primates, none had detectable toxic effects.[3] Viremia associated with rVSV-ZEBOV was detected on day 2 only, suggesting rapid viral clearance through the innate immune response. Safety in immunocompromised hosts was assessed in a few nonhuman primates infected with the human immunodeficiency virus[6] and in mice with severe combined immunodeficiency.[17] None of the animals had detectable illness after immunization. Viral shedding in saliva and urine was not observed.[3]

To assess the safety and immunogenicity of various doses of rVSV-ZEBOV in countries with or without previous outbreaks of Ebola virus disease, we initiated parallel, harmonized VEBCON trials in Lambaréné, Gabon; Kilifi, Kenya; Hamburg, Germany; and Geneva, Switzerland. We report the 6-month safety and immunogenicity data from these ongoing studies.

METHODS

STUDY DESIGNS AND PARTICIPANTS

The studies in Lambaréné, Kilifi, and Hamburg were open-label, uncontrolled, phase 1 trials designed to assess the safety, side-effect pro-

files, and immunogenicity of ascending doses of rVSV-ZEBOV vaccine (BPSC1001) at doses ranging from 300,000 to 20 million PFU in healthy adults of both sexes between the ages of 18 and 55 years. The Geneva study was a double-blind, randomized, placebo-controlled, phase 1 trial assessing the safety and immunogenicity of the rVSV–ZEBOV vaccine at doses of 10 million and 50 million PFU in healthy adults between the ages of 18 and 65 years. Full details regarding the study centers, entry criteria, and procedures are provided in the study protocol, available with the full text of this article at NEJM.org. The studies were reviewed and approved by the respective national competent authorities, local ethics committees, the German authority for genetic engineering, and the WHO research ethics review committee. All the participants provided written informed consent. An independent consortium-wide data and safety monitoring board provided oversight.

All four studies were investigator-initiated trials sponsored by each local institution. The Wellcome Trust provided funding through a grant to the WHO. A total of 800 vaccine doses were donated to the WHO by the Public Health Agency of Canada. Funding bodies and the vaccine manufacturers were not involved in the analysis of the data, nor did they contribute to the preparation or writing of the manuscript.

VACCINE AND PLACEBO

The rVSV-ZEBOV vaccine was developed by the Canadian National Microbiology Laboratory and was licensed to BioProtection Systems (a subsidiary of NewLink Genetics). The vaccine was subsequently sublicensed to Merck, which has assumed responsibility for ongoing research and development. The vaccine was manufactured at IDT Biologika in Dessau-Rosslau, Germany, and stored in a manner consistent with good manufacturing practices. The same lot (no. 003 05 13), which was dispensed in single-dose vials as 100 million PFU per milliliter, was sent from Canada to Geneva and subsequently to the other sites. (Additional details regarding reconstitution are provided in the Supplementary Appendix.) Placebo syringes containing 0.5 ml of saline were packaged identically.

VACCINATION

Injections were administered intramuscularly into the deltoid. Dose-escalation studies were

staggered (for details, see the Methods section in the Supplementary Appendix). In the Lambaréné cohort, participants received doses of 300,000 or 3 million PFU. In Hamburg, participants received doses of 3 million or 20 million PFU. In Kilifi, participants received doses of 3 million or 20 million PFU. In Geneva, the first 19 run-in participants received a single open-label injection of 10 million PFU and were observed for at least 1 week. Thereafter, participants who were planning to deploy to Ebola-affected regions were randomly assigned in a 1:1 ratio in a double-blind fashion to receive a vaccine dose of either 10 million or 50 million PFU, whereas those who were not planning to deploy to such regions were randomly assigned in a 1:1:1 ratio to receive either one of the vaccine doses or placebo. (An overview of the four trials is provided in Fig. S4 in the Supplementary Appendix.)

SAFETY MONITORING

Injection-site and systemic reactogenicity and medication use were recorded for 7 days after injection and at follow-up (days 14 and 28). Clinical and laboratory evaluations were performed during each study visit (for details, see the Methods section in the Supplementary Appendix). Laboratory analyses included a complete blood count and measurements of creatinine, C-reactive protein, and liver function. Adverse events were listed for each participant according to the Common Terminology Criteria for Adverse Events and the *Medical Dictionary for Regulatory Activities* and are reported individually and in aggregate.

INVESTIGATION OF ARTHRITIS AND SKIN LESIONS

After the observation of arthralgia in some Geneva participants, all but the first participant with swollen joints or axial involvement in Geneva underwent joint imaging by means of ultrasonography or magnetic resonance imaging (MRI), and all but two participants were referred to a rheumatologist. Arthritis was confirmed if the study team observed swelling or imaging revealed effusion. Participants in Geneva who had skin lesions underwent biopsy, swabbing, or puncture of lesions.

DETECTION OF rVSV

We developed quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays (TaqMan) targeting the VSV nucleoprotein gene (see the Methods section in the Supplementary Appendix). Results are expressed in copies per milliliter. In the dose-escalation trials, rVSV viral loads were monitored from day 0 to day 28 and included daily sampling of plasma, urine, and saliva through day 7 in Hamburg. In Lambaréné and Kilifi, total RNA from plasma, urine (400 μl), and saliva (200 μl) (Viral Transport Kit, BD) was stored in TRIzol LS Reagent (Life Technologies) and analyzed at St. George's University of London. In Hamburg, samples were assessed on site. In Geneva, RT-PCR was performed on days 1, 3, and 7 on all plasma specimens, on saliva and urine in the first 20 participants vaccinated with 10 million PFU and 10 participants vaccinated with 50 million PFU, and later on skin vesicles and synovial fluid. RT-PCR assay to detect rVSV was performed on oral lesions observed in Hamburg and Geneva. Virus isolation was performed in Geneva by means of plaque assay on Vero E6 cells from selected samples and confirmed on PCR and immunostaining (see the Methods section in the Supplementary Appendix).

IMMUNOGENICITY

We assessed serum samples at baseline and at 28 and 180 days after injection. We performed the enzyme-linked immunosorbent assay (ELISA) for ZEBOV-glycoprotein–specific antibodies using the homologous Zaire–Kikwit strain glycoprotein (following the standard operating procedure of the U.S. Army Medical Research Institute for Infectious Diseases [SOP AP-03-35-00]) or inactivated whole virions of the Zaire–Guéckédou strain. The relative amounts of ZEBOV-glycoprotein–specific antibodies were reported as endpoint titers or as geometric mean concentrations of arbitrary ELISA units per milliliter. Neutralizing antibodies were detected with the use of VSV pseudovirions expressing the luciferase reporter gene complemented by glycoprotein from the ZEBOV 95 Kikwit strain, as described previously,[18] or infectious ZEBOV isolate Mayinga. (For detailed descriptions, see the Methods section in the Supplementary Appendix.)

STATISTICAL ANALYSIS

We determined the frequencies of all adverse events according to study center and dose group. Categorical variables are described with counts and percentages, and continuous variables with means and standard deviations or medians and interquartile ranges for skewed variables. Antibody responses are reported as the geometric

mean titer or geometric mean concentration with 95% confidence intervals. We obtained reverse cumulative distributions by plotting for each possible value of the titer the proportion of participants with a titer greater than this value. We used Fisher's exact test, the Mann–Whitney test, and the Kruskal–Wallis test or Spearman's correlation coefficient to calculate intergroup associations. We compared geometric mean titers or concentrations, seropositivity rates, and seroresponse rates between days 0 and 28 using Wilcoxon's test for paired data and McNemar's test. Antibody persistence and correlation among assays were assessed by comparing geometric mean titers or concentrations at 28 days with those at 180 days with the use of Wilcoxon's test for paired data and Spearman's correlation coefficient, respectively.

The blinding was broken after the 3-month visit for all Geneva participants. For the Geneva trial, immunogenicity analyses were conducted according to both intention-to-treat and per-protocol principles. In the intention-to-treat analyses, all participants who received an injection were included; per-protocol analyses excluded participants who might have been exposed to Ebola virus or who had received an unplanned additional vaccine dose after the initial administration of vaccine. In the absence of significant differences (see the Supplementary Appendix), results of the intention-to-treat analysis are reported. All statistical testing was two-sided with an alpha level of 0.05. The statistical analysis plans are provided in the study protocol at NEJM.org.

RESULTS

STUDY POPULATIONS

A total of 158 participants received either vaccine (150 participants) or placebo (8 participants) in the three dose-escalation studies from November 17, 2014, through January 19, 2015, and in the Geneva randomized, controlled trial from November 10, 2014, through December 9, 2014, before a safety-driven study hold and subsequent resumption of vaccination with a lower dose (3 million PFU) (Fig. S4 in the Supplementary Appendix). The study populations are described in Table 1, and in Table S2 in the Supplementary Appendix. In Geneva, the run-in participants and those who underwent randomization were compared for baseline characteristics and adverse-event outcomes. In the absence of significant differences, pooled results are reported. Vaccine was administered in doses as follows: 300,000 PFU in 20 participants, 3 million PFU in 49 participants, 10 million PFUs in 35 participants, 20 million PFU in 30 participants, and 50 million PFU in 16 participants. All but 3 participants were followed for at least 6 months (Fig. S4 in the Supplementary Appendix).

Nine participants in Geneva were excluded from the 6-month per-protocol analyses: eight had been deployed to Ebola-affected countries and reported potential exposure to Ebola virus, and one had received an extra-study booster dose at 3 months while in Guinea. The results reported here are from interim databases for ongoing trials.

SAFETY

Serious Adverse Events

There were no serious adverse events associated with the vaccine. Seven hospitalizations occurred in Lambaréné for malaria (4 patients), appendicitis (1 patient), gastritis (1 patient), and bleeding after tooth extraction (1 patient).

Acute Reactogenicity

Solicited and unsolicited adverse events were frequent. Of the 158 participants, 145 (92%) had at least one adverse event, with the majority of events reported as mild or moderate. Grade 3 symptoms were reported in 4 of 40 participants (10%) in Kilifi, 2 of 20 (10%) in Hamburg, and 11 of 51 (22%) in Geneva; none were reported in Lambaréné. Local reactogenicity was common but generally mild. Most adverse events appeared early (median, 1 day; interquartile range, <24 hours to 1 day), subsided rapidly (median, 1 day; interquartile range, <24 hours to 1 day), and were alleviated with the use of acetaminophen or nonsteroidal antiinflammatory drugs as needed. The incidence and intensity of the events varied according to both the dose and the study site: objective fever was reported in 5 of 20 participants (25%) in Hamburg, 13 of 51 (25%) in Geneva, 12 of 40 (30%) in Kilifi, and 5 of 39 (13%) in Lambaréné. At a given dose, such as 3 million PFU, inflammatory reactions were more frequently reported in hospitalized participants in Hamburg than in Lambaréné. A detailed list of adverse events is provided in Table S3 in the Supplementary Appendix.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hamburg		Lambaréné		Kilifi		Geneva			All Participants (N=158)
	Vaccine, 3 Million PFU (N=10)	Vaccine, 20 Million PFU (N=10)	Vaccine, 300,000 PFU (N=20)	Vaccine, 3 Million PFU (N=19)	Vaccine, 3 Million PFU (N=20)	Vaccine, 20 Million PFU (N=20)	Vaccine, 10 Million PFU (N=35)	Vaccine, 50 Million PFU (N=16)	Placebo (N=8)	
Sex — no. (%)										
Male	6 (60)	7 (70)	14 (70)	17 (89)	14 (70)	16 (80)	21 (60)	11 (69)	4 (50)	110 (70)
Female	4 (40)	3 (30)	6 (30)	2 (11)	6 (30)	4 (20)	14 (40)	5 (31)	4 (50)	48 (30)
Age — yr										
Mean	32±8	40±9	30±8	27±6	34±7	34±8	42±11	43±14	39±12	36±11
Range	24–47	24–51	24–47	20–44	27–49	22–52	21–59	24–59	23–58	20–59
Race — no. (%)†										
Asian	1 (10)	0	0	0	0	0	2 (6)	1 (6)	0	4 (3)
Black	0	0	20 (100)	19 (100)	17 (85)	20 (100)	2 (6)	0	0	78 (49)
White	9 (90)	10 (100)	0	0	3 (15)	0	29 (83)	15 (94)	8 (100)	74 (47)
Body-mass index‡	25±3	24±3	23±3	22±3	24±4	25±4	25±4	25±3	25±4	24±4

* Plus–minus values are means ±SD. There were no significant differences among the groups except for race between all dose groups in Lambaréné and Kilifi and those in Hamburg and Geneva (P<0.001 for all comparisons). PFU denotes plaque-forming units.
† Race was self-reported. Two participants in the Geneva cohort receiving 10 million PFU were Hispanic.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Biologic Monitoring

Hematologic changes were observed in all participants who were monitored during the first days after vaccination (Table S4 in the Supplementary Appendix). In Lambaréné, transient leukocytopenia was observed in 12 of 20 participants (60%) receiving 300,000 PFU and in 8 of 19 participants (42%) receiving 3 million PFU; lymphocytopenia was observed in 2 of 19 participants (11%) in the group receiving 3 million PFU.

In Hamburg, an asymptomatic decrease in the number of circulating lymphocytes was observed 1 day after vaccination in all participants and resolved by day 2 (P<0.01 for all comparisons between screening and day 1). The decrease was unrelated to dose, reactogenicity, or substantial viremia, indicating biologic activity even at a dose of 3 million PFU. Among the 51 participants in Geneva, 36 (71%) had a decreased number of circulating lymphocytes on day 1, and 27 (53%) had a decreased number of neutrophils on day 3, with rapid resolution of both conditions (Table S4 in the Supplementary Appendix). Monocytosis on day 3 and a transient reduction in platelets were also observed. Liver-function and creatinine levels remained unchanged.

Viremia and Viral Shedding

Low levels of rVSV-ZEBOV RNA were identified in plasma on RT-PCR assay on days 1 to 3 in most participants who were tested (Fig. 1, and Table S5 in the Supplementary Appendix). Participants with positive results for rVSV on PCR assay ranged from 8 of 20 (40%) among Lambaréné vaccinees immunized with 300,000 PFU to 46 of 51 (90%) among Geneva vaccinees. In Lambaréné, 18 of 19 participants (95%) who received a dose of 3 million PFU had detectable viremia on day 1 or 2; 15 of 19 participants (79%) had complete resolution by day 7. The same pattern was observed in Kilifi, where 35 of 40 participants (88%) had values that were below the detection level by day 7. In Hamburg, all participants who received doses of 3 million and 20 million PFU who were monitored daily until day 7 had detectable viremia, with peaks on day 2 or 3 and complete resolution by day 5.

All but 11 plasma specimens from all studies were negative by day 7, and infectious virus was not recovered from any blood specimen tested. In the Geneva study, there was no correlation between peak viremia and vaccine dose, age, sex,

frequency or intensity of adverse events, or lymphocytopenia. Viral RNA was not detected in saliva or urine samples at any site; occasional oral lesions were all negative for rVSV on PCR assay.

Arthritis

In Geneva, 11 of 51 participants (22%) with no previous history of joint disease had an onset of arthralgia a median of 11 days (interquartile range, 9 to 13) after injection; 8 participants had received 10 million PFU and 3 had received 50 million PFU. These participants presented with asymmetric involvement of a median of 2 (range, 1 to 4) peripheral joints, with swelling on physical examination and, as seen on ultrasonography, tenosynovitis or bursitis in at least 1 joint (Table S6 in the Supplementary Appendix). Three participants had axial involvement; of these, 1 had evidence of arthritis on MRI. Thus, arthritis was confirmed in 9 of 11 participants. Pain was often migratory and generally mild. Among participants in whom pain was prolonged, the median duration was 8 days (interquartile range, 4 to 87), and pain generally became less intense and more intermittent after the first week. The functional effect of the arthritis was moderate, with a median score of 2.5 (interquartile range, 1.8 to 3.3) on the Routine Assessment of Patient Index Data 3 (RAPID3),[19] on a scale ranging from 1 to 10, with higher values indicating a greater severity. Results also indicated low inflammatory disease activity, with a median score of 1.8 (interquartile range, 1.7 to 2.0) on the disease activity score in 44 joints (DAS44),[20] on a scale ranging from 0 to 10, with higher values indicating more active disease. Post-vaccination elevations in autoantibodies were not observed. A knee arthrocentesis in 1 participant yielded 40 ml of fluid with 7190 leukocytes per milliliter (80% monocytes) and rVSV at 1200 copies per milliliter on PCR assay, whereas synovial viral and bacterial cultures and rVSV viremia remained negative. No association between the presence of arthritis and vaccine dose, age, sex, earlier arthralgia, or peak viremia was observed among the Geneva participants. Suspected, self-limited relapses, one with mild arthralgia and the other with mild arthritis, occurred in 2 participants after a prolonged pain-free interval (Table S6 in the Supplementary Appendix). At the 6-month visit, 10 of 11 participants with arthritis were symptom-free. Two self-limited cases of arthritis were observed, one each in Hamburg and Kilifi. (Details regarding these cases are provided in the Supplementary Appendix.)

Skin Lesions

Among the 11 participants in Geneva who had arthritis, a mild maculopapular rash mainly on the limbs developed in 3 participants between days 7 and 9 and lasted 7 to 15 days (Fig. 2A, subpanel a). The rash was associated with a few tender vesicles on fingers or toes (Fig. 2B, subpanel d). Histologic analysis of one papule revealed a dermal T-lymphocytic infiltrate (Fig. 2A, subpanels b and c). Vesicular lesions reflected subepidermal dermatitis with necrotic keratinocytes (Fig. 2B, subpanel d) containing abundant VSV antigens (Fig. 2B, subpanel f).[21] Among the 3 participants with rash, rVSV was identified on RT-PCR in all 3 up to day 17, and infectious rVSV was isolated from a specimen with the highest RNA level 9 days after immunization (Fig. 2C). Concomitantly obtained plasma samples remained negative, showing local replication. At other VEBCON trial sites, investigators screened participants for rVSV-associated dermatologic findings, but none were observed.

ZEBOV-GLYCOPROTEIN–SPECIFIC ANTIBODY RESPONSES

Serum antibodies induced by rVSV-ZEBOV were assessed with the use of four distinct assays. Baseline antibody levels were generally low, with outliers. Low-level baseline seropositivity was identified in 12 of 23 participants (52%) in Lambaréné and occasionally at other sites (Table 2 and Fig. 3A, and Tables S7 through S11 in the Supplementary Appendix).

Four weeks after immunization, ZEBOV-glycoprotein–specific antibodies were detected on ELISA in all vaccinees with similar anti-glycoprotein geometric mean titers and distribution, as seen on reverse cumulative distribution curves (Fig. 3E). The lowest dose (300,000 PFU) was immunogenic in Lambaréné, although among participants receiving this dose, a low response
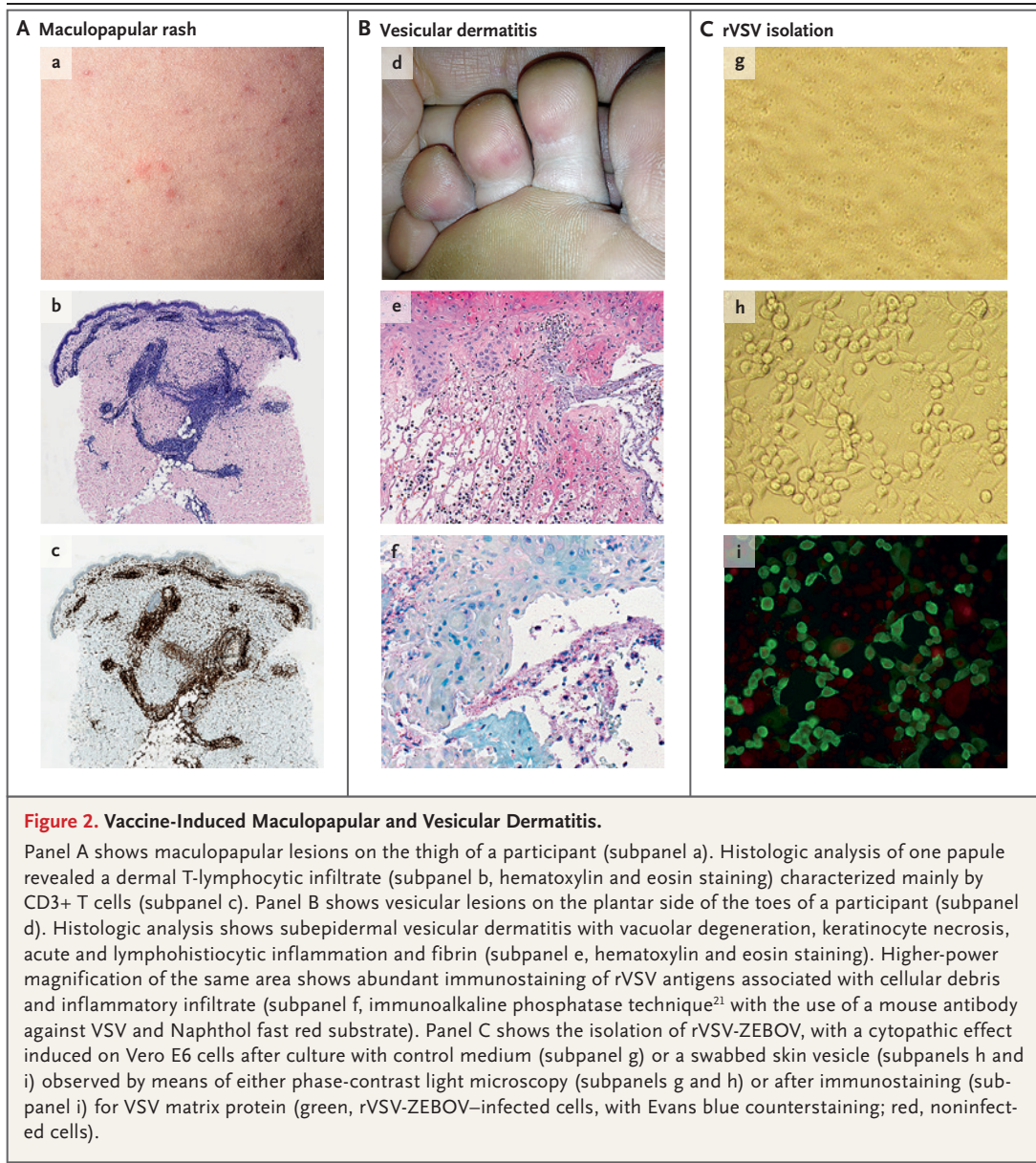
Figure 1. Plasma Recombinant Vesicular Stomatitis Virus (rVSV) Viremia in the Four Study Cohorts.

The presence of rVSV viremia was assessed with the use of quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays (TaqMan) of total RNA derived from plasma. The viral load is expressed as log_{10} rVSV RNA copies per milliliter. Each measurement included no-template and standard controls. The shaded area indicates values that are below the limit of quantification (≤100 copies per milliliter of RNA in Lambaréné, Kilifi, and Geneva and ≤200 copies per milliliter in Hamburg). Panels A and B show the plasma viral load through day 28 for the two Hamburg cohorts that received doses of 3 million or 20 million plaque-forming units (PFU), with daily sampling from day 1 to day 7. Panels C and D show individual viremia patterns in two cohorts that received doses of 300,000 or 3 million PFU, as monitored in Lambaréné. Plasma was analyzed between day 0 and day 2 and on day 7 in all participants. Panels E and F show the plasma viral load on days 0, 1, 3, and 7 among participants in Kilifi who received doses of 3 million or 20 million PFU. Panels G and H show rVSV RNA copy numbers on days 0, 1, 3, and 7 in participants in Geneva who received vaccine doses of 10 million or 50 million PFU.
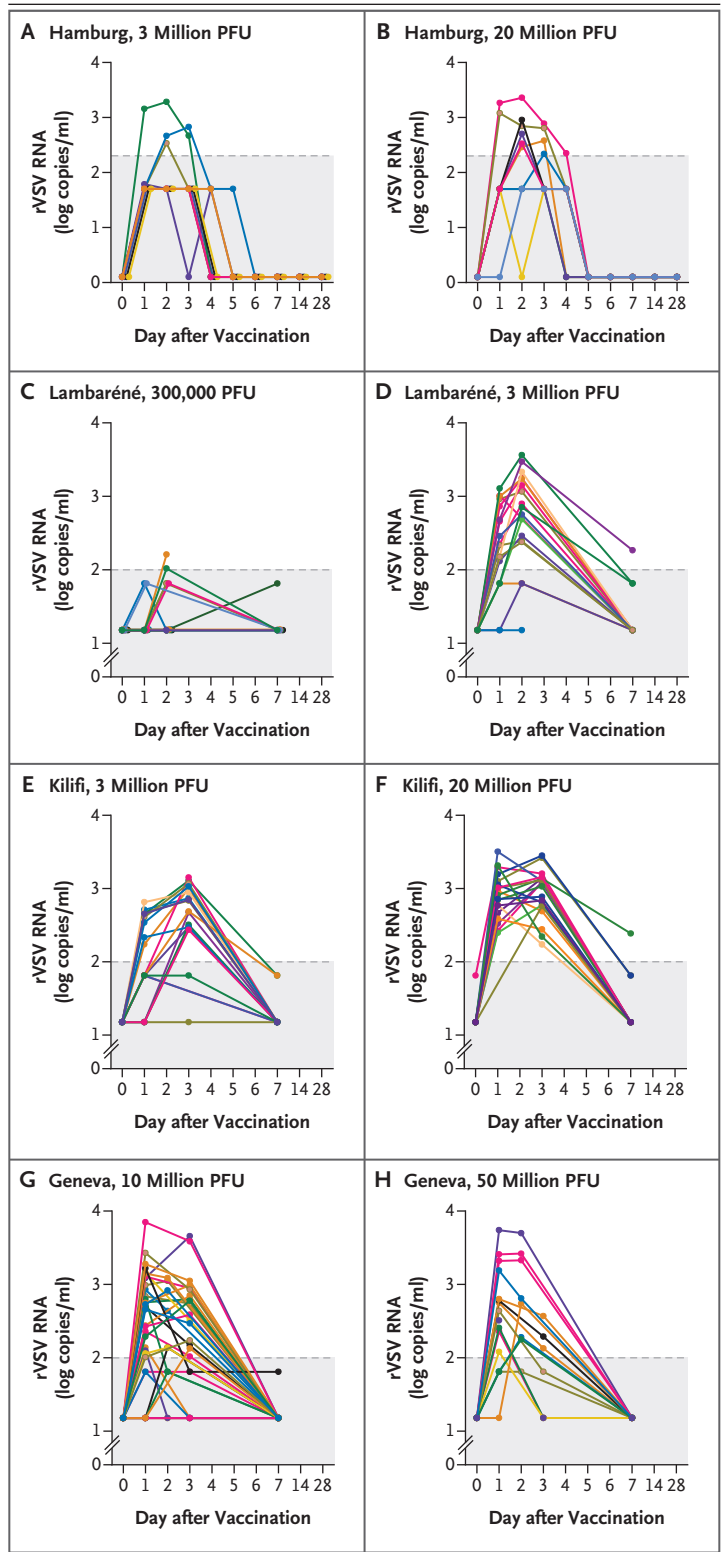
rate was more frequent than among those receiving higher doses (Fig. 3A through 3D). Rates of seropositivity (0 to 53%) and titers were lower on whole-virion ELISA (Fig. 3B, and Table S9 and Fig. S5 in the Supplementary Appendix), which identified baseline antibodies reacting with nucleocapsid or matrix proteins, but not glycoprotein, in samples from Lambaréné (Fig. S6 in the Supplementary Appendix).

On pseudovirion neutralization assay assessing the 50% serum neutralization capacity (PsVNA50), neutralizing antibodies were absent at baseline (including among participants in Lambaréné) but were elicited at day 28 in 107 of 126 vaccinees (85%) (Fig. 3C, and Table S10 in the Supplementary Appendix). With the use of infectious ZEBOV particles, low-level neutralizing antibodies (≥1:8) were detected at baseline in 6 of 20 participants (30%) in Hamburg, 7 of 40 (18%) in Kilifi, and 10 of 38 (26%) in Lambaréné (Fig. 3D, and Table S10 in the Supplementary Appendix). The two assays showed significant increases in neutralizing antibodies after any dose of rVSV-ZEBOV (Tables S10 and S11 in the Supplementary Appendix).

Figure 2. Vaccine-Induced Maculopapular and Vesicular Dermatitis.

Panel A shows maculopapular lesions on the thigh of a participant (subpanel a). Histologic analysis of one papule revealed a dermal T-lymphocytic infiltrate (subpanel b, hematoxylin and eosin staining) characterized mainly by CD3+ T cells (subpanel c). Panel B shows vesicular lesions on the plantar side of the toes of a participant (subpanel d). Histologic analysis shows subepidermal vesicular dermatitis with vacuolar degeneration, keratinocyte necrosis, acute and lymphohistiocytic inflammation and fibrin (subpanel e, hematoxylin and eosin staining). Higher-power magnification of the same area shows abundant immunostaining of rVSV antigens associated with cellular debris and inflammatory infiltrate (subpanel f, immunoalkaline phosphatase technique[21] with the use of a mouse antibody against VSV and Naphthol fast red substrate). Panel C shows the isolation of rVSV-ZEBOV, with a cytopathic effect induced on Vero E6 cells after culture with control medium (subpanel g) or a swabbed skin vesicle (subpanels h and i) observed by means of either phase-contrast light microscopy (subpanels g and h) or after immunostaining (subpanel i) for VSV matrix protein (green, rVSV-ZEBOV–infected cells, with Evans blue counterstaining; red, noninfected cells).

Despite strong correlations between day 28 antibody titers on glycoprotein ELISA and on PsVNA50 (Fig. S7 in the Supplementary Appendix), significant differences were observed. In the randomized, controlled Geneva study, a dose of 50 million PFU elicited titers of glycoprotein-binding antibodies that were similar to those elicited by 10 million PFU, with geometric mean titers of 1780 (95% confidence interval [CI], 1048 to 3022) and 1064 (95% CI, 757 to 1495), respectively, but significantly higher PsVNA50 antibody titers, with geometric mean titers of 273 (95% CI, 157 to 475) and 99 (95% CI, 62 to 159)

(P=0.02). The influence of increasing doses on the distribution of neutralizing antibodies was confirmed on reverse cumulative distribution (Fig. 3F) and correlation analyses (Tables S12 and S13 and Fig. S8 in the Supplementary Appendix). Thus, higher doses of rVSV-ZEBOV elicited similar glycoprotein-binding titers but higher neutralizing-antibody titers. Across the four study sites, a weak but significant correlation between vaccine dose and the level of glycoprotein-binding antibodies was observed (Fig. S8 in the Supplementary Appendix).

Six months after immunization, glycoprotein-

Table 2. End-Point Geometric Mean Titer (GMT) and Seropositivity Rate, According to Study Site, Dose of rVSV-ZEBOV, and Timing of Visit.*

Study Site and Dose	No. of Participants	GMT	GMT Ratio of Day 180 vs. Day 28	P Value for GMT			Seropositivity†	P Value for Seropositivity	
				Day 0 vs. 28	Day 0 vs. 180	Day 28 vs. 180	*no. (%)*	Day 0 vs. 28	Day 0 vs. 180
Geneva									
Placebo									
Day 0	8	25.0					0		
Day 28	8	25.0		NA			0	NA	
Day 180	8	25.0	1.00		NA	NA	0		NA
10 million PFU									
Day 0	34	33.9					8 (24)		
Day 28	34	1064.2		<0.001			34 (100)	<0.001	
Day 180	33	1634.0	1.59		<0.001	0.004	33 (100)		<0.001
50 million PFU									
Day 0	13	36.3					5 (38)		
Day 28	13	1780.1		0.002			13 (100)	0.008	
Day 180	15	1837.9	1.05		0.002	0.89	15 (100)		0.008
Lambaréné									
300,000 PFU									
Day 0	20	42.0		<0.001			11 (55)	0.004	
Day 28	20	1055.6					20 (100)		
Day 180	16	712.9	0.89		0.001	0.61	15 (94)		0.03
3 million PFU									
Day 0	19	38.7		<0.001			3 (19)	<0.001	
Day 28	19	2570.9					19 (100)		
Day 180	17	1359.2	0.59		<0.001	0.04	17 (100)		<0.001
Kilifi									
3 million PFU									
Day 0	20	33.0					3 (15)		
Day 28	20	1492.9		<0.001			20 (100)	<0.001	
Day 180	20	1392.6	0.93		<0.001	0.79	20 (100)		<0.001
20 million PFU									
Day 0	0	NA							
Day 28	0	NA		NA			NA	NA	
Day 180	20	1600.0	NA		NA	NA	20 (100)		NA
Hamburg									
3 million PFU									
Day 0	10	25.0		0.006			0	0.002	
Day 28	10	1392.9					10 (100)		
Day 180	9	903.9	0.71		0.009	0.40	9 (100)		0.004
20 million PFU									
Day 0	10	30.8		0.006			2 (20)	0.008	
Day 28	10	1969.8					10 (100)		
Day 180	10	1600.0	0.81		0.006	0.37	10 (100)		0.008

* An expanded version of this table with additional data and 95% confidence intervals is provided in Table S7 in the Supplementary Appendix. NA denotes not applicable.
† Seropositivity was defined as an end-point titer of 50 or more.
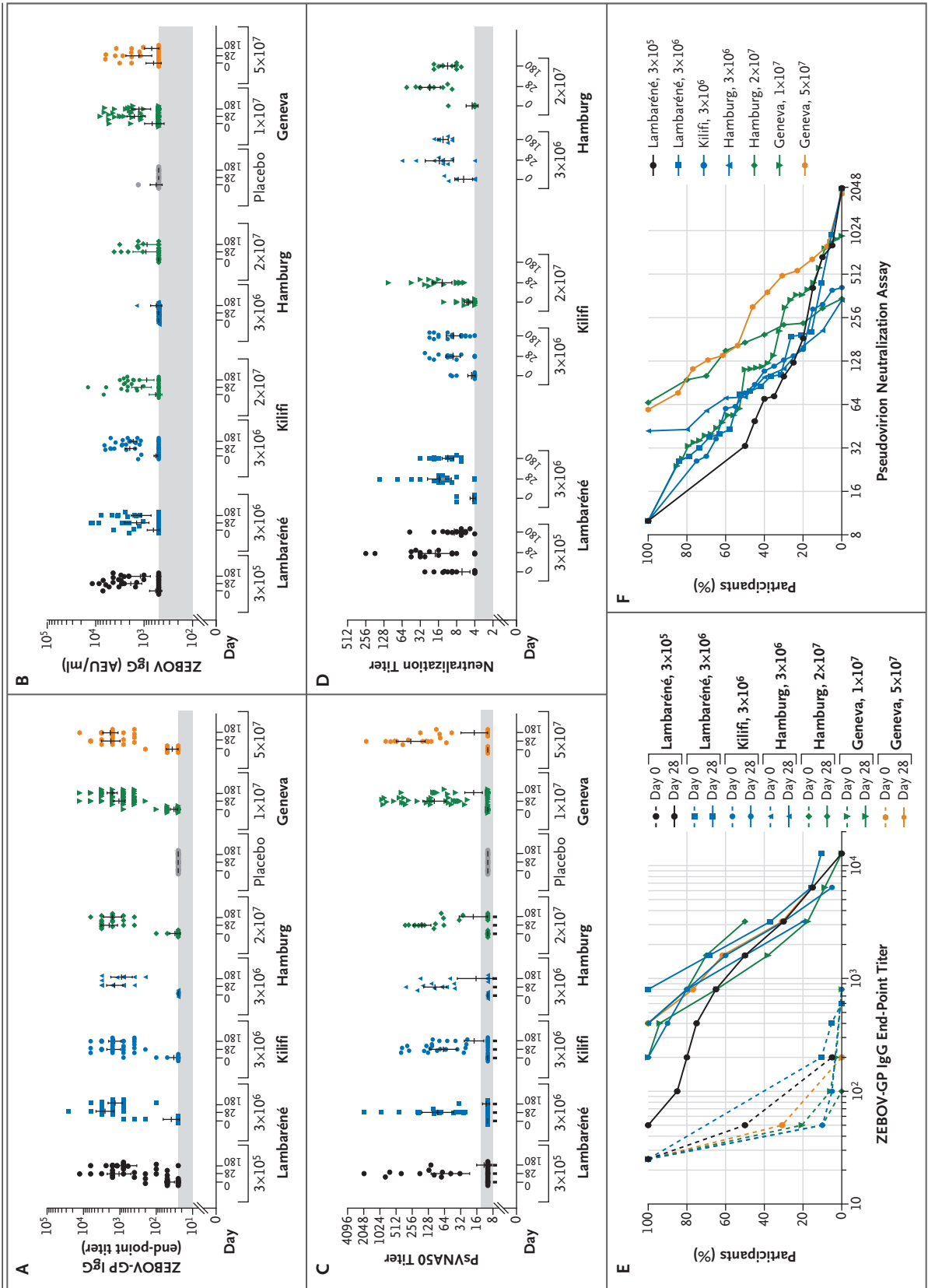
Figure 3 (facing page). Glycoprotein Antibody Titers, According to Vaccine Dose, Study Site, and Assay.

Individual antibody titers were assessed at baseline and at 28 and 180 days after vaccination in 158 participants, according to study site and dose group. The vaccine dose (in PFU) is indicated for each site in Panels A through D; the shaded areas indicate negative titers. The numbers of samples tested are provided in Figure S4 in the Supplementary Appendix. Antibodies were measured on enzyme-linked immunosorbent assay (ELISA) against the homologous glycoprotein (GP) of the Zaire–Kikwit strain (ZEBOV, Panel A) or inactivated whole virions of the Zaire–Guéckédou strain (Panel B). Results are expressed as end-point titers (Panel A) or the geometric mean concentration of arbitrary ELISA units (AEU) per milliliter (Panel B). Neutralizing antibodies were detected with the use of rVSV pseudovirion neutralization assay assessing the 50% serum neutralization capacity (PsVNA50) complemented by homologous glycoprotein (Panel C) or with infectious ZEBOV isolate Mayinga (Panel D). Geometric mean titers and 95% confidence intervals are shown for each study site, dose group, and time point. The results of glycoprotein ELISA (Panel E) and pseudoneutralization (Panel F) at 28 days were expressed as the reciprocal of the highest dilution showing a positive result. The curves represent the distribution of individual antibody titers in each cohort. The dashed curves in Panel E indicate baseline titers.

binding antibodies persisted in all participants, across doses and study sites, without a significant decline in geometric mean titers (Table 2 and Fig. 3A, and Table S7 in the Supplementary Appendix). Antibody titers more than doubled after day 28 in 41 of 126 participants (33%) and reached significantly higher geometric mean titers of 10 million PFU at 180 days in Geneva recipients (geometric mean ratio of 180-day titer to 28-day titer, 1.59; 95% CI, 1.21 to 2.09; P=0.004). The deployment of 8 participants to Ebola-affected countries during the Ebola outbreak was not reflected by an increase in antibody titers.

On the basis of whole-virion ELISA, we also observed sustained antibody titers, which declined significantly only in Geneva recipients of 50 million PFU (geometric mean ratio of 180-day titer to 28-day titer, 0.54; 95% CI, 0.32 to 0.91; P=0.03) (Fig. 3B, and Table S9 in the Supplementary Appendix). Neutralizing antibodies that were detected with infectious ZEBOV particles also persisted through 180 days in 45 of 73 participants (62%) (Fig. 3D, and Table S11 in the Supplementary Appendix). In contrast, antibod-

ies that were measured by means of the pseudovirion neutralization assay were up to 94% lower at 180 days than at 28 days and persisted in only 28 of 120 participants (23%) (Table S10 and Fig. 3C in the Supplementary Appendix). Nevertheless, a strong correlation between antibody titers on PsVNA50 and on glycoprotein ELISA persisted at 180 days, which suggests a rapid decline in initially modest PsVNA50 titers (Fig. S7 in the Supplementary Appendix).

DISCUSSION

The Zaire-variant candidate vaccine rVSV-ZEBOV expresses a viral surface glycoprotein that has immunogenic potential after a single dose for populations at risk for Ebola virus disease, as well as possibly for postexposure prophylaxis.[4,7,17,22] It is a replication-competent chimeric virus for which human-safety data were limited to a single postexposure case report[21] at the time of the initiation of these studies. We describe the safety and immunogenicity results for rVSV-ZEBOV in African and European populations, collected in four harmonized, ongoing trials, including three dose-escalating trials and one randomized, controlled trial.

Acute inflammatory symptoms were expected after immunization with rVSV-ZEBOV. The frequency and intensity of such symptoms were study-dependent. At a vaccine dose of 3 million PFU, objective fever was reported in 20 to 30% of vaccinees in Hamburg and Kilifi but in only 10% in Lambaréné. An influence of dose on adverse events was noted between a dose of 300,000 and 3 million PFU in Lambaréné but not between higher doses at other sites. It is likely that the early onset, short duration, and responsiveness to symptomatic treatment of these symptoms will facilitate acceptance of the vaccine, but vaccine-induced fever should be anticipated if rVSV-ZEBOV is administered to contacts of patients infected with Ebola virus disease.

Levels of rVSV RNA were transiently detected in early blood samples, suggesting that innate responses, especially those involving the type I interferon pathway, help to limit viral replication.[23-26] Viral seeding of joints and skin, mostly identified in the Geneva cohort, was unexpected. It showed that viral dissemination and replication can occur and persist for up to 2 to 3 weeks after immunization — in other words, that early

innate responses may not always be sufficient for complete viral control. Replication appeared to be restricted to permissive tissues: viral RNA remained below detection in plasma and peripheral-blood mononuclear cells, and replicating virus was retrieved only from skin vesicles. Skin vesicles in livestock infected with VSV or foot-and-mouth virus occur at similar locations, reflecting the relative resistance of keratinocytes to type I interferon.[27] The pattern of rVSV-ZEBOV replication in humans thus may be defined by the permissiveness of rVSV replication.[28,29]

In the Geneva cohort, arthritis was confirmed in 9 of 51 participants (18%) and suspected in another 2. Two cases were reported among 60 participants in Hamburg and Kilifi (3%), albeit at a lower intensity and of shorter duration than in Geneva. Possible mechanisms of virus-induced arthritis include autoimmunity, lytic effects of infected synovial cells, and the deposition of immune complexes. The induction of autoimmunity is not supported by the rapid onset (<2 weeks) and the lack of vaccine-induced pathogenic antibodies. We cannot rule out immune-complex deposition, but the detection of rVSV RNA in synovial fluid showed the seeding of rVSV-ZEBOV into joints. Since arthralgia or arthritis is not elicited by VSV and was not reported with other rVSV constructs that have been tested to date, the pathophysiology of the chimeric rVSV-ZEBOV vaccine may include features attributable to both its VSV and ZEBOV glycoprotein components. Although pain may be prolonged and relapse may occur, the prognosis of viral vaccine–induced arthritides is considered favorable on the basis of experience with rubella vaccination.[30] Accordingly, the VEBCON data and safety monitoring board concluded on January 1, 2015, that the trials could proceed as originally planned (including doses up to 100 million PFU) once informed-consent forms were updated. Of the 13 participants with arthritis, 10 were symptom-free at the 6-month visit, which suggests a favorable long-term prognosis for these vaccine-induced arthritides.

The rVSV-ZEBOV vaccine generated glycoprotein-binding antibodies in all participants at any dose, showing its immunogenicity in humans, in accordance with the field efficacy subsequently reported from Guinea.[31] Doses containing as few as 300,000 PFU may be sufficient to elicit glycoprotein-binding antibodies. Preexisting anti-

bodies to ZEBOV nucleocapsid or matrix proteins conferred no advantage for the induction of glycoprotein-specific responses (Fig. S6 in the Supplementary Appendix). Neutralizing antibodies were also generated in most participants, and a dose–response effect was shown. Despite similar glycoprotein-binding antibody titers, higher vaccine doses elicited higher titers of neutralizing antibodies. Since the relative roles of neutralizing and glycoprotein-binding antibodies in protection against Ebola virus disease are unknown, we cannot conclude whether higher vaccine doses are required for the most effective protection. A comparison of anti–glycoprotein-antibody titers detected in this study (in the Hamburg cohort receiving 20 million PFU) with those reported with a chimpanzee adenovirus vector[32] revealed similar values. This finding suggests that the two vaccines that are currently undergoing testing in West Africa may induce humoral responses of the same order of magnitude.

Antibody persistence is expected to play a critical role in the duration of protection induced by rVSV-ZEBOV, a factor that cannot currently be informed by efficacy studies. The persistence of glycoprotein-binding antibody titers through 180 days is promising and suggests that a single dose of rVSV-ZEBOV may be sufficient for early[31] and possibly longer-term protection. In the absence of established correlates of protection, the importance of the low titers and rapid decline of antibodies capable of inhibiting cell entry, as measured by means of the PsVNA50 assay, is uncertain.

These studies have contributed to the dose-selection process performed by the vaccine manufacturers and have raised the awareness of investigators, members of institutional review boards, and regulators about the specific adverse events to be expected with the use of the rVSV-ZEBOV vaccine. They have also resulted in the introduction of safety-driven changes in the protocols for the ongoing phase 2 and 3 studies.

In conclusion, in four rapidly implemented, parallel phase 1 studies that included in-depth safety investigations, the rVSV-ZEBOV vaccine was found to be reactogenic but immunogenic at doses ranging from 300,000 to 50 million PFU in African and European volunteers, with higher titers of antibodies at higher doses. The viral dissemination in skin and joints that was ob-

served in some participants appears to be self-limited, which has resulted in a favorable risk–benefit balance, given the possible protection[31] offered by this vaccine in the potential control of outbreaks of Ebola virus disease.

APPENDIX

The authors' full names and academic degrees are as follows: Selidji T. Agnandji, M.D., Angela Huttner, M.D., Madeleine E. Zinser, M.D., Patricia Njuguna, M.Med., Christine Dahlke, Ph.D., José F. Fernandes, M.D., Sabine Yerly, M.Sc., Julie-Anne Dayer, M.D., Verena Kraehling, Ph.D., Rahel Kasonta, Ph.D., Akim A. Adegnika, M.D., Ph.D., Marcus Altfeld, M.D., Ph.D., Floriane Auderset, Ph.D., Emmanuel B. Bache, M.Sc., Nadine Biedenkopf, Ph.D., Saskia Borregaard, Ph.D., Jessica S. Brosnahan, M.H.Sc., Rebekah Burrow, B.Sc., Christophe Combescure, Ph.D., Jules Desmeules, M.D., Markus Eickmann, Ph.D., Sarah K. Fehling, Ph.D., Axel Finckh, M.D., Ana Rita Goncalves, Ph.D., Martin P. Grobusch, M.D., Ph.D., Jay Hooper, Ph.D., Alen Jambrecina, M.D., Anita L. Kabwende, M.D., Gürkan Kaya, M.D., Ph.D., Domtila Kimani, B.Sc., Bertrand Lell, M.D., Barbara Lemaître, M.Sc., Ansgar W. Lohse, M.D., Marguerite Massinga-Loembe, Ph.D., Alain Matthey, M.D., Benjamin Mordmüller, M.D., Anne Nolting, M.D., Caroline Ogwang, M.B., Ch.B., Michael Ramharter, M.D., Jonas Schmidt-Chanasit, M.D., Stefan Schmiedel, M.D., Peter Silvera, Ph.D., Felix R. Stahl, M.D., Ph.D., Henry M. Staines, D.Phil., Thomas Strecker, Ph.D., Hans C. Stubbe, M.D., Benjamin Tsofa, Ph.D., Sherif Zaki, M.D., Ph.D., Patricia Fast, M.D., Ph.D., Vasee Moorthy, Ph.D., Laurent Kaiser, M.D., Sanjeev Krishna, Sc.D., Stephan Becker, Ph.D., Marie-Paule Kieny, Ph.D., Philip Bejon, Ph.D., Peter G. Kremsner, M.D., Marylyn M. Addo, M.D., Ph.D., and Claire-Anne Siegrist, M.D.

The authors' affiliations are as follows: the Centre de Recherches Médicales de Lambaréné, Lambaréné, Gabon (S.T.A., J.F.F., A.A.A., E.B.B., J.S.B., M.P.G., A.L.K., B. Lell, M.M.-L., B.M., M.R., S.K., P.G.K.); Institut für Tropenmedizin, Universitätsklinikum Tübingen, and German Center for Infection Research, Tübingen (S.T.A., J.F.F., A.A.A., E.B.B., J.S.B., M.P.G., A.L.K., B. Lell, M.M.-L., B.M., M.R., S.K., P.G.K.), University Medical Center Hamburg–Eppendorf, 1st Department of Medicine (M.E.Z., C.D., R.K., A.W.L., A.N., S.S., H.C.S., M.M.A.), and Institute for Clinical Chemistry and Laboratory Medicine (F.R.S.), German Center for Infection Research, partner site Standort Hamburg-Lübeck-Borstel (C.D., A.N., J.S.-C., H.C.S., M.M.A.), Heinrich-Pette-Institute, Leibniz Institute for Experimental Virology (M.A.), Clinical Trial Center North (S. Borregaard, A.J.), and Bernhard Nocht Institute for Tropical Medicine, World Health Organization (WHO) Collaborating Center for Arbovirus and Hemorrhagic Fever Reference and Research, National Reference Center for Tropical Infectious Diseases (J.S.-C.), Hamburg, Philipps University Marburg, Institute for Virology, and the German Center for Infection Research (DZIF), partner site Giessen-Marburg-Langen, Marburg (V.K., N.B., M.E., S.K.F., T.S., S. Becker), and the Division of Veterinary Medicine, Paul Ehrlich Institute, Langen (R.K.) — all in Germany; the Infection Control Program (A.H.), Divisions of Infectious Diseases (A.H., J.-A.D., L.K.), Clinical Epidemiology (C.C.), Rheumatology (A.F.), and Dermatology (G.K.), and Centers for Clinical Research (J.D., A.M.) and Vaccinology (C.-A.S.), Geneva University Hospitals and Faculty of Medicine, the Virology Laboratory, Geneva University Hospitals (S.Y., A.R.G., L.K.), WHO Collaborative Center for Vaccinology, Faculty of Medicine (F.A., B. Lemaître, C.-A.S.), and the WHO (P.F., V.M., M.-P.K.) — all in Geneva; the Kenya Medical Research Institute–Wellcome Trust Research Program, Center for Geographic Medicine Research, Kilifi (P.N., D.K., C.O., B.T., P.B.); the Department of Parasitology, Leiden University

1659

Medical Center, Leiden (A.A.A.), and the Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, Amsterdam (M.P.G.) — both in the Netherlands; the Institute for Infection and Immunity, St. George's, University of London, London (R.B., H.M.S., S.K.); the Department of Molecular Virology and Division of Translational Sciences, U.S. Army Medical Research Institute of Infectious Diseases, Frederick, MD (J.H., P.S.); the Department of Medicine I, Division of Infectious Diseases and Tropical Medicine, Medical University of Vienna, Vienna (M.R.); the Infectious Diseases Pathology Branch, Centers for Disease Control and Prevention, Atlanta (S.Z.); and the International AIDS Vaccine Initiative, New York (P.F.).

REFERENCES

1. Kanapathipillai R, Henao Restrepo AM, Fast P, et al. Ebola vaccine — an urgent international priority. N Engl J Med 2014;371:2249-51.
2. Pulendran B, Oh JZ, Nakaya HI, Ravindran R, Kazmin DA. Immunity to viruses: learning from successful human vaccines. Immunol Rev 2013;255:243-55.
3. Geisbert TW, Feldmann H. Recombinant vesicular stomatitis virus-based vaccines against Ebola and Marburg virus infections. J Infect Dis 2011;204:Suppl 3: S1075-81.
4. Jones SM, Feldmann H, Ströher U, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. Nat Med 2005; 11:786-90.
5. Qiu X, Fernando L, Alimonti JB, et al. Mucosal immunization of cynomolgus macaques with the VSVDeltaG/ZEBOVGP vaccine stimulates strong ebola GP-specific immune responses. PLoS One 2009; 4(5):e5547.
6. Geisbert TW, Daddario-Dicaprio KM, Lewis MG, et al. Vesicular stomatitis virus-based ebola vaccine is well-tolerated and protects immunocompromised nonhuman primates. PLoS Pathog 2008;4(11): e1000225.
7. Geisbert TW, Geisbert JB, Leung A, et al. Single-injection vaccine protects nonhuman primates against infection with Marburg virus and three species of Ebola virus. J Virol 2009;83:7296-304.
8. Roberts A, Buonocore L, Price R, Forman J, Rose JK. Attenuated vesicular stomatitis viruses as vaccine vectors. J Virol 1999;73:3723-32.
9. Krauss H, Schiefer HG, Weber A, et al. Viral zoonoses. In: Krauss H, ed. Zoonoses: infectious disease transmissible from animals to humans. 3rd ed. Washington, DC: ASM Press, 2003:119-21.
10. Quiroz E, Moreno N, Peralta PH, Tesh RB. A human case of encephalitis associated with vesicular stomatitis virus (Indiana serotype) infection. Am J Trop Med Hyg 1988;39:312-4.
11. Brandly CA, Hanson RP. Epizootiology of vesicular stomatitis. Am J Public Health Nations Health 1957;47:205-9.
12. Johnson KM, Vogel JE, Peralta PH. Clinical and serological response to laboratory-acquired human infection by Indiana type vesicular stomatitis virus (VSV). Am J Trop Med Hyg 1966;15:244-6.
13. Fields BN, Hawkins K. Human infection with the virus of vesicular stomatitis during an epizootic. N Engl J Med 1967; 277:989-94.
14. Reif JS, Webb PA, Monath TP, et al. Epizootic vesicular stomatitis in Colorado, 1982: infection in occupational risk groups. Am J Trop Med Hyg 1987;36:177-82.
15. Letchworth GJ, Rodriguez LL, Del cbarrera J. Vesicular stomatitis. Vet J 1999; 157:239-60.
16. Lichty BD, Power AT, Stojdl DF, Bell JC. Vesicular stomatitis virus: re-inventing the bullet. Trends Mol Med 2004;10:210-6.
17. Jones SM, Stroher U, Fernando L, et al. Assessment of a vesicular stomatitis virus-based vaccine by use of the mouse model of Ebola virus hemorrhagic fever. J Infect Dis 2007;196:Suppl 2:S404-12.
18. Kwilas S, Kishimori JM, Josleyn M, et al. A hantavirus pulmonary syndrome (HPS) DNA vaccine delivered using a spring-powered jet injector elicits a potent neutralizing antibody response in rabbits and nonhuman primates. Curr Gene Ther 2014;14:200-10.
19. Pincus T. RAPID3, an index of only 3 patient self-report core data set measures, but not ESR, recognizes incomplete responses to methotrexate in usual care of patients with rheumatoid arthritis. Bull Hosp Jt Dis 2013;71:117-20.
20. Fransen J, Welsing PM, de Keijzer RM, et al. Disease activity scores using C-reactive protein: CRP may replace ESR in the assessment of RA disease activity. Ann Rheum Dis 2004;62:Suppl 1:151.
21. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol 2010;177:166-75.
22. Günther S, Feldmann H, Geisbert TW, et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. J Infect Dis 2011;204:Suppl 3:S785-90.
23. Müller U, Steinhoff U, Reis LF, et al. Functional role of type I and type II interferons in antiviral defense. Science 1994; 264:1918-21.
24. Durbin JE, Hackenmiller R, Simon MC, Levy DE. Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. Cell 1996;84:443-50.
25. Stojdl DF, Abraham N, Knowles S, et al. The murine double-stranded RNA-dependent protein kinase PKR is required for resistance to vesicular stomatitis virus. J Virol 2000;74:9580-5.
26. Lai L, Davey R, Beck A, et al. Emergency postexposure vaccination with vesicular stomatitis virus-vectored Ebola vaccine after needlestick. JAMA 2015;313: 1249-55.
27. Zhu JJ, Arzt J, Puckette MC, Smoliga GR, Pacheco JM, Rodriguez LL. Mechanisms of foot-and-mouth disease virus tropism inferred from differential tissue gene expression. PLoS One 2013;8(5):e64119.
28. Hastie E, Cataldi M, Marriott I, Grdzelishvili VZ. Understanding and altering cell tropism of vesicular stomatitis virus. Virus Res 2013;176:16-32.
29. Cartwright T, Senussi O, Grady MD. The mechanism of the inactivation of human fibroblast interferon by mechanical stress. J Gen Virol 1977;36:317-21.
30. Weibel RE, Stokes J Jr, Buynak EB, Hilleman MR. Rubella vaccination in adult females. N Engl J Med 1969;280:682-5.
31. Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet 2015;386:857-66.
32. Ewer K, Rampling T, Venkatraman N, et al. A monovalent chimpanzee adenovirus Ebola vaccine boosted with MVA. N Engl J Med 2016;374:1635-46.

Copyright © 2016 Massachusetts Medical Society.