



Published in final edited form as:

N Engl J Med. 2025 November 06; 393(18): 1807–1818. doi:10.1056/NEJMoa2501073.

Phase 1 Safety and Immunogenicity of a rVSV Lassa Fever Vaccine Candidate

Elissa Malkin^{1,*}, Marija Zaric^{2,3,*}, Mark Kieh⁴, Lindsey Baden⁵, David Fitz-Patrick⁶, Arianna Marini^{2,3}, Heejin Yun^{2,3}, Peter Hayes^{2,3}, Rachel Bromell², Morolayo Ayorinde², Natalia Fernandez^{2,3}, Ruhani Varma^{2,3}, Faith Sigel^{2,3}, Matthew Ward^{2,3}, Hema Pindolia², Shayna Sewell^{2,3}, Fahimah Amini^{2,3}, Julie Blie⁴, Barthalomew Wilson⁴, Patrick Faley⁴, John McCullough⁴, Franklin Tokpah⁴, Cecelia Wisseh⁴, Elvis Towalid⁴, Swapnil Hadawale³, Eddy Sayeed³, Devin Hunt³, Nahid Keshavarzi³, Burc Barin⁷, Irina Maljkovic Berry⁸, Christopher L Parks³, Shobhna Gopal Truter³, Kathleen Walker³, Johan Vekemans³, Jennifer Lehrman³, Michelle Engelbrecht³, Mariette Malherbe³, Dagna Laufer³, Vincent Philiponis³, Elizabeth Higgs⁹, Gaudensia Mutua³, Patricia E Fast³, Swati B Gupta³ for the rVSVΔG-LASV-GPC Study Group

¹George Washington University, Vaccine Research Unit, Washington DC, USA

²IAVI Human Immunology Laboratory, Imperial College London, UK

³IAVI, New York, USA

⁴The Partnership for Research on Vaccines and other Infectious diseases in Liberia

⁵Brigham and Women's Hospital, Boston, USA

⁶East West Medical Research Institute, Honolulu, USA

⁷The Emmes Company, Rockville, USA

⁸Integrated Research Facility at Fort Detrick, Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Fort Detrick, Frederick, USA

⁹Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, USA

Abstract

Background: There is no vaccine available for Lassa fever, a viral hemorrhagic disease that is estimated to cause thousands of deaths yearly in Western Africa. A replication-competent recombinant vesicular stomatitis virus vectored vaccine encoding a Lassa Virus (LASV) glycoprotein complex (rVSVΔG-LASV-GPC) has been developed, but data are needed on its safety and immunogenicity.

This Author Accepted Manuscript is licensed for use under the CC-BY-NC-ND license.

*Contributed equally

Publisher's Disclaimer: This is an Author Accepted Manuscript, which is the version after external peer review and before publication in the Journal. The publisher's version of record, which includes all New England Journal of Medicine editing and enhancements, is available at <https://www.nejm.org/doi/full/10.1056/NEJMoa2501073>.

†A complete list of members of the rVSVΔG-LASV-GPC Study Group is provided in the Supplementary Appendix

Methods: In this Phase 1, first-in-human, double-blind study, 114 healthy adults (18-50 years of age) were randomized to receive rVSVΔG-LASV-GPC or placebo intramuscularly: participant groups were vaccinated with a single dose of 2×10^4 PFU, 2×10^5 PFU, 2×10^6 PFU, 2×10^7 PFU or placebo or with two doses of 2×10^7 PFU or placebo, using a 6-20-week window period. Safety and tolerability were assessed by rates of solicited and unsolicited AEs. Because LF can cause sensorineural hearing loss, hearing acuity was measured before and after vaccination. Secondary endpoints were binding antibodies against LASV glycoprotein, neutralizing antibodies, and vaccine vector-derived viral RNA and plaque-forming units in plasma, urine, and saliva.

Results: No serious vaccine-related adverse events were reported. The rVSVΔG-LASV-GPC vaccine caused minimal local reactions and dose-dependent, mild-to-severe early-onset systemic reactogenicity that was transient. No hearing loss was detected. All doses induced robust long-lasting cellular and humoral (binding and neutralizing) responses that cross-reacted against common LASV lineages. No infectious vaccine virus particles were found in plasma, urine or saliva.

Conclusions: rVSVΔG-LASV-GPC vaccine demonstrated an acceptable safety profile and was immunogenic over a wide dose range in healthy adults in the United States and Liberia.

(Funded by Coalition for Epidemic Preparedness Innovations (CEPI) and others. Trial reg: [NCT04794218](#)).

INTRODUCTION

Seasonal acute viral hemorrhagic Lassa fever, caused by at least seven LASV phylogenetic lineages, has pandemic potential.¹⁻⁴ There have been recent Nigerian outbreaks,^{5,6} and cases of European⁷ and US⁸ introduction; additionally, endemicity has been established in West Africa.⁹ No vaccines are approved for Lassa fever to alleviate health and economic burdens or to prepare for pandemics.

A consortium led by International Aids Vaccine Initiative (IAVI) is advancing a Lassa fever vaccine based on replication-competent recombinant vesicular stomatitis virus (rVSV) vector with VSV envelope glycoprotein gene exchanged for LASV glycoprotein complex (LASV-GPC; rVSVΔG-LASV-GPC).¹⁰ Based on the same approach, Merck developed a rVSVΔG Zaire Ebola virus (ERVEBO) chimera, approved by FDA, EMA, and African countries.¹¹⁻¹⁴ Since 2016, more than 300,000 ERVEBO doses have been administered during Ebola outbreaks¹⁵ and prophylactically for frontline workers.^{13,16}

rVSVΔG-LASV-GPC, developed at the Public Health Agency of Canada^{10,17} demonstrated 100% efficacy in non-human primates and other models.¹⁸⁻²⁰ A single rVSVΔG-LASV-GPC administration completely protected cynomolgus macaques from lethal LASV.²¹ This first-in-human study of rVSVΔG-LASV-GPC was designed to assess safety and immunogenicity in healthy US and Liberian adults.

METHODS

Trial design and oversight

This randomized, double-blind, placebo-controlled, dose-escalation, phase 1 study evaluated the safety, tolerability, and immunogenicity of rVSVΔG-LASV-GPC. Its manufacture is described in the supplementary appendix.

Healthy participants, aged 18-50 years, from 3 US and 1 Liberian sites were enrolled in eight groups and randomized (4:1) to intramuscular rVSVΔG-LASV-GPC or placebo (matched diluent).

In the Dose-Escalation phase, 10 US participants per group (Groups 1-3), were randomized within groups to receive a single dose 2×10^4 , 2×10^5 or 2×10^6 PFU, respectively or placebo. Twenty-two Group 4 participants received 2×10^7 PFU or placebo and were invited, per protocol amendment, to receive a second active dose or placebo between 6 and 20 weeks post-first immunization. Eleven participants opted to receive a second dose identical to the first, without unblinding (Group 4B). The assignment into Group 4A occurred for participants declining second dose or to balance the overall group sizes between Group 4A and 4B. There was no randomization/blinding between Group 4A and 4B schedules; randomization/blinding pertained only to active dose versus placebo. The authors vouch for the accuracy and completeness of data and data analyses, along with the conduct of the trial according to the protocol (available at [NEJM.org](https://www.nejm.org)).

In the Dose-Expansion phase, 60 Liberian participants were randomized to single dose 2×10^5 (Group 5), 2×10^6 (Group 6) or 2×10^7 PFU (Group 7) or placebo. An additional US participant was enrolled (Group 6) and administered a vaccine identical to Group 3. To facilitate data reporting of US vs. Liberian study populations, data from this single Group 6 US-based participant are reported with Group 3.

Participants were followed for 12 months post-vaccination. Randomization, blinding, US FDA and the Liberia Medicine and Health Regulatory Authority Investigational New Drug authorizations, Institutional Review, eligibility criteria and enrollment are detailed in the supplementary appendix.

Primary and Secondary Objectives

The primary objective was to evaluate rVSVΔG-LASV-GPC dose level safety and tolerability. Participants completed solicited local and systemic reactogenicity symptom diaries for 14 days post-vaccination; unsolicited events were recorded for 28 days and serious adverse events (SAEs) and adverse events of special interest (AESIs) (new hearing loss ≥ 30 decibels) for study duration. Since LF is associated with sensorineural hearing loss,²² participants were assessed before and 1-, 3- and 12-months post-vaccination by pure tone audiometry. Blood samples were collected for safety assessment (CBC, AST, ALT and creatinine). Details of assessments are provided in the supplementary appendix.

Secondary objectives included assessment of LASV-GPC-specific antibody responses and rVSVΔG-LASV-GPC plasma, urine and saliva distribution. These assessments were

performed in persons who received at least one vaccine or placebo and contributed both a pre-vaccination sample and at least one post-vaccination serum sample with valid results.

Blood was collected at baseline, days 8, 29, 85, 169, 253 and 337 for immunogenicity assessments. Additional Group 4B samples were collected before and two and four weeks post-second dose. Blood, saliva and urine samples were collected pre-vaccination and days 4, 8, 15 and 29 for rVSVΔG-LASV-GPC distribution analyses.

LASV GPC-specific IgG ELISA and pseudo-virus neutralization assay

Anti-LASV-GPC serum IgG antibodies were quantified by ELISA using a standard curve (first International Standard of Anti-LASV Antibodies [National Institute for Biological Standards and Control, 20/202]). Neutralizing serum antibodies were assessed using lentivirus luciferase reporters pseudotyped with LASV-GPC lineages II, III or IV.

LASV Nucleoprotein (NP) IgM and IgG ELISA

ReLASV[®] Pan-Lassa NP IgG/IgM ELISA Kit (Zalgen Labs) was used following manufacturer's instructions to screen Liberian participants for potential previous exposure to LASV.

Vaccine shedding

Plasma, urine and saliva rVSVΔG-LASV-GPC RNA was detected by reverse transcription quantitative PCR (RT-qPCR) specific for the VSV nucleocapsid N gene. RT-qPCR positive samples were tested for replication-competent rVSVΔG-LASV-GPC by Vero cell plaque assay.

Assessment of LASV-specific T-cells

Cryopreserved peripheral blood mononuclear cells (PBMC) were assessed for LASV-specific T-cells by IFN γ ELISpot assay using overlapping peptides matched to LASV-GPC.

Statistical analysis

This study was not powered for formal hypothesis testing and analyses were not adjusted for multiplicity. For each safety endpoint, the proportion of participants with an event was calculated by dose. The frequency and proportions of participants with LASV-GPC binding and neutralizing antibody responses were calculated by dose and time. Binding and neutralizing antibody levels were summarized by geometric mean (GM) and 95% confidence interval (CI). Antibody seroconversion was defined as: antibody response above assay cut-off in participants with negative baseline results, or at least 4-fold increase from baseline in baseline positive participants. Post-hoc correlation analyses used Spearman's rank test.

RESULTS:

Participants

The study was conducted from July 2021 to December 2023. Of 80 US volunteers screened, 53 (31 female, 22 male) were enrolled, median age 26 years (range: 18-49) (Table 1, Figure

S1A). Forty four (83.0%) completed the trial, and 9 (17.0%) terminated early; 7 (13.2%) were lost to follow-up despite efforts to contact them.

Of 175 Liberian volunteers screened, 61 (32 female, 29 male) were enrolled, median age 24 years (range: 18-43) (Table 1, Figure S1B). Most exclusions (45/175) were due to baseline hearing impairment ≥ 26 dB. One participant, found ineligible post-randomization, did not receive study vaccine; 60 completed the study. Tables S1 and S2 summarize participant demographics and characteristics. The representativeness of the enrolled individuals is summarized in Table S3.

Vaccine Safety and Reactogenicity

At least one local reactogenicity event, Grade 1 or 2, was reported by 67.4% (29/43) of US and 31.3% (15/48) of Liberian vaccinees, and 40.0% (4/10) of US and 0% (0/12) Liberian placebo recipients. (Figures 1, and S2, S3 and S4). Administration site tenderness (65.1% [28/43] US; 22.9% [11/48] Liberia) and pain (44.2% [19/43] US; 18.8% [9/48] Liberia) were the most vaccinee-reported local events.

At least one systemic reactogenicity event, Grades 1 to 3, was reported by 88.4% (38/43) of US and 52.1% (25/48) of Liberian vaccinees and 80.0% (8/10) of US and 41.7% (5/12) of Liberian placebo recipients. The most common events were malaise, headache, myalgia and chills (Figure 1, Table S4). Eleven (25.6%) US participants, all in Groups 4A and B, reported Grade 3 events. The most common was malaise, typically reported for 2-3 days with concurrent Grade 3 systemic events including myalgia, chills, headache, arthralgia and/or fever, resolving within 1-5 days. In Group 4B participants, reactogenicity appeared milder following the second dose than following the first (Figure S4). Two (4.2%) Liberian vaccinees reported Grade 3 systemic events, abdominal pain/diarrhea and fever, for 1-2 days. Laboratory abnormalities grade 2 or higher, not associated with clinical manifestations, occurred in 1 US and 3 Liberian vaccinees (Table S5).

Unsolicited AEs were reported by 51.2% (22/43) of US and 27.1% (13/48) of Liberian vaccinees (versus 20.0% (2/20) and 25% (3/12) of placebo recipients, respectively, through day 28 (Tables S6-S7). Most unsolicited events were Grades 1 or 2; Grade 3 unsolicited AEs were reported by 4.7% (2/43) US vaccinees and no Liberian vaccinees, versus 10% (1/10) and 16.7% (2/12) of respective placebo recipients. Among Grade 3 AEs, one was considered probably vaccine-related-elevated AST at Day 14 in a Group 4A participant lasting 5 days. Two other unsolicited AEs were assessed as definitely vaccine-related: Grade 1 lymphadenopathy in a Group 4A participant at day 4 lasting 3 days and Grade 1 sinus tachycardia in a Group 4B participant 1-day post-dose 1, resolving next day without treatment. There were no reports of arthritis or rashes.

There were no reported AESIs, vaccine-associated SAEs and no discontinuations due to AEs.

Immunogenicity

Serum LASV GPC-specific IgG antibody responses: Among US vaccinees, serum LASV GPC-specific IgG antibody responses were detected relative to baseline in 42/43

(97.7%), with 37/42 (88.1%) responding by day 29 (Figures 2A and S5). IgG levels typically peaked at day 85 in single-dose US vaccinees, with Geometric Means of 2258.4 (95% CI, 1177.7-4330.7), 1108.5 (95% CI, 539.5-2277.6), 3506.5 (95% CI, 1833.2-6707.3) and 2056.1 (95% CI, 808.7-5227.5) IU/mL in Groups 1, 2, 3 and 4A, respectively, compared to 1.9 (95% CI, 0.4-8.3) for placebo. In the two-dose group (4B), geometric mean was 1495.8 (95% CI, 782.5-2859.5) pre-second dose, with 1531.7 (95% CI, 915.3-2563.5) IU/mL observed 28 days post-second vaccination. At month 12, these antibody responses were detected in 31/36 (86.1%) vaccinees.

Among Liberian vaccinees, serum LASV GPC-specific IgG antibody responses were detected in 44/48 (91.7%) vaccinees (Figures 2B and S5). Most (27/48, 56.3%) generated responses by day 29, with 42/48 (87.5%) responding by day 85. Available month 12 test results demonstrated 30/48 (62.5%) vaccinee responses relative to baseline. Peak binding IgG levels, typically at day 85, were geometric means of 1400.8 (95% CI, 952.5-2060.0), 622.4 (95% CI, 145.1-2669.0) and 886.3 (95% CI, 528.4-1487.0) IU/mL in Groups 5, 6 and 7 respectively, compared to 28.6 (95% CI, 4.2-195.9) for placebo.

Vaccine-induced antibodies exhibited multiple LASV lineage cross-reactivity (Figure S6).

Serum neutralizing antibody responses: Serum neutralizing antibody responses developed in 42/43 (97.7%) US vaccinees (Figures 2C and S7), most within 3 months (32/43, 74.4%). At month 12, 34/36 (94.4%) vaccinees demonstrated responses relative to baseline. One vaccinee without binding and neutralizing antibody responses post-vaccination was lost to follow up after day 8. Peak geometric mean neutralizing antibody ID₅₀ values were 152.6 (95% CI, 96.4-241.5) in Group 1, 114.1 (95% CI, 51.6-252.3) Group 2, 119.8 (95% CI, 72.6-197.7) Group 3, 107.7 (95% CI, 49.8-233.3) Group 4A, 174.3 (95% CI, 135.4-224.5) Group 4B and 11.2 (95% CI, 9.5-13.2) in placebo.

Serum neutralizing activity was observed in 36/48 (75.0%) Liberian vaccinees (Figures 2D and S7), most responding within 3 months (35/48, 72.9%). Peak geometric mean neutralizing antibody ID₅₀ values were 129.0 (95% CI, 101.8-163.4) in Group 5, 159.0 (95% CI, 89.5-282.3) Group 6, 92.8 (95% CI, 68.0-126.5) Group 7 and 27.9 (95% CI, 15.2-51.2) in placebo. Like LASV GPC-specific IgG responses, neutralizing antibodies were not boosted post-second immunization (Group 4B) (Figures 2E, 2F, S5, and S7).

Vaccine-induced antibodies exhibited multiple LASV lineage pseudo-virus cross-neutralization (Figure S8).

Among Liberian participants, 4 of 60 (6.7%) had detectable LASV NP-specific IgG antibodies at screening, indicating previous LASV exposure. Two (1 placebo, 1 Group 5) had pre-existing anti-LASV neutralizing antibodies; the Group 5 vaccinee did not generate LASV-GPC-specific antibody responses post-vaccination (Figure S9).

All of 31 US study vaccinees with PBMC samples exhibited vaccine-specific IFN- γ ELISpot T-cell responses by day 29 (Figure 3A, Table S8). Twenty (64.5%) vaccinees responded to all 5 GPC pools on day 85, indicating multiple LASV-GPC epitope recognition

(Figure 3B, Table S8). Responses in Groups 4A and 4B appeared similar on days 169, 252 and 337 (Figure S10).

Overall, serum LASV GPC-specific IgG, neutralizing antibody and IFN γ responses demonstrated similar kinetics and magnitude across all dose groups. Positive associations among binding, neutralizing antibody and IFN γ responses were observed (Figure S11).

Vaccine viremia and shedding

Vector-derived RNA was measured in plasma, saliva or urine following the first dose in US participants (Figures S12 and 13; Table S9). By day 29, vector-derived plasma RNA was detected in 12.5% Group 1, 62.5% Group 2, 100% Group 3, 88.9% Group 4A and 100% Group 4B participants; it was not detected in any placebo group participants. Levels appeared highest on day 4 and fell below the lower quantification limit (500 copies/mL) by day 29. Peak antibody responses appeared to track weakly with plasma vaccine RNA levels (Figure S14). Data were insufficient to analyze associations between plasma RNA and clinical symptoms. Vector-derived saliva RNA was detected in 12.5% Group 1, 37.5% Group 2, 87.5% Group 3, 33.3% Group 4A and 66.7% Group 4B participants. Saliva vector RNA was detected in one placebo participant, a finding that was presumed to reflect sample contamination. Saliva vector-derived RNA levels were highest on day 15; 48% of participants had detectable saliva RNA levels on day 29. Vector RNA was undetectable in urine. No infectious vaccine virus was recovered by plaque assay from any RNA-positive samples.

DISCUSSION:

This first-in-human clinical study tested four rVSV Δ G-LASV-GPC doses and single or two-dose regimens. Consistent with preclinical studies conducted during human vaccine candidate development²¹ and with rVSV Δ G-LASV-GPC research vaccine^{18,19,20}, the vaccine had an acceptable safety profile with no vaccine-related SAEs and no cases of hearing loss. Like the similarly constructed ERVEBO vaccine²³ and other live-attenuated viral vaccines,²⁴⁻²⁶ VSV-based vaccines may cause fever, chills, malaise, myalgia, headache, nausea and/or arthralgia. These symptoms were less frequent and milder at 2×10^4 and 2×10^5 PFU doses. At 2×10^7 PFU, about half of US volunteers experienced Grade 3 symptoms on day 1-2, resolving within days. Transient liver enzyme elevation, as reported in one participant, was also reported in two ERVEBO studies.^{27,28} Reactogenicity appeared lower in Liberian participants, compared to US participants.

Prior studies have shown negligible risk of person-to-person or animal-to-animal infection with rVSV Δ G-ZEBOV-GP vaccine virus post-rVSV Δ G-ZEBOV-GP vaccination.²⁹ Consistent with findings with rVSV Δ G-ZEBOV-GP,^{23,30} our study of rVSV Δ G-LASV-GPC revealed that vector-derived plasma RNA was detected on day 4, but was undetectable on day 29. The time course for detection of saliva RNA differed, with little detected on day 4 and highest levels on days 15 and 29. In rVSV Δ G-ZEBOV-GP studies, saliva vaccine RNA appeared later than plasma.^{27,31,32} No infectious vaccine virus was detected by culture assay, in line with one rVSV Δ G-ZEBOV-GP study.³⁰ Although culture is less sensitive than PCR, it may give more accurate representation of infectiousness of biological fluids.

rVSVΔG-LASV-GPC immunogenicity was assessed over the course of one year. A single dose greater than 2×10^4 and up to 2×10^7 PFU elicited robust antibody responses, without an apparent dose response. IgG antibodies binding lineage IV LASV-GPC, predominant in Liberia and Sierra Leone,¹ were detected with all doses, usually by day 29, peaking on day 85, with minimal decline one year post-vaccination. Binding IgG to LASV lineages I, II, III, and VII GPCs were also detected. Unlike a measles-vectored Lassa vaccine study,³³ we detected homologous serum neutralizing antibodies persisting for a year, and neutralizing activity against LASV lineages II and III, predominant in Nigeria.¹ Currently there are no defined correlates of protection against LASV infection, and the immunological thresholds required for vaccine efficacy remain undefined.

Although mechanisms of LASV clearance are incompletely understood, T-cells are considered important.^{34,35} rVSVΔG-LASV-GPC vaccination induced broad, durable T-cell responses in US adults in our study. Second vaccination provided no appreciable benefit to humoral or cellular responses.

All US-based vaccinees with samples beyond day 15 generated LASV-GPC specific IgG binding and neutralizing antibodies, whereas a small proportion of Liberian vaccinees did not. Our study was not designed to compare vaccine responses between US and Liberian cohorts; however, response magnitudes appeared slightly lower in Liberian compared to US cohort. Environmental factors may contribute to differential antibody responses to vaccinations in different study populations.³⁶ For example, pre-existing immunity may influence vaccine responses. Pre-existing LASV NP IgG antibodies were detected in 4 Liberian participants. Additional participants had detectable baseline LASV GPC-specific antibodies. Baseline responses could be related to past LASV exposure, or cross-reactivity to GPCs from other arenaviruses.^{37,38} Antibody and T cell cross-reactivity to GPCs from LASV and Lymphocytic Choriomeningitis Virus have been previously demonstrated.^{39,40} Further studies in the LF endemic region are warranted to investigate this cross-reactivity and vaccine responses in previously exposed individuals.

Study limitations warrant comment. This was a Phase 1 study and hypothesis testing was not performed. It included a relatively small sample, among whom several US participants were lost to follow-up and a few participants in Liberia had pre-existing antibodies to LASV. Follow-up Phase 2/3 clinical studies are ongoing ([ClinicalTrials.org NCT05868733](https://clinicaltrials.org/ct2/show/study/NCT05868733)) or are planned to confirm these findings, expand the safety profile and assess efficacy in LASV-exposed populations.

Overall, rVSVΔG-LASV-GPC demonstrated favorable safety and immunogenicity, with a single dose inducing robust cellular and broad long-lasting antibody responses to major lineages. Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](https://www.nejm.org).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS:

We thank the CEPI project team for their continuous support and helpful discussions. We thank all volunteers for their participation in the trials; the entire clinical and trial-center teams for their assistance, dedication, and performance (from IAVI, George Washington University, Brigham and Women's Hospital and East West Medical Research Institute); members of all clinical research laboratories that supported clinical sample testing (Human Immunology Laboratory at Imperial College London, Neogenomics and Charles River Laboratories). The authors are grateful to Batavia Biosciences for facilitating the manufacture of the rVSVΔG-LASV-GPC vaccine candidate.

We thank Dr Bob Bailer for reviewing the manuscript, Dr Rachel Nowak and Anya Crane for editing support and the following persons for supporting roles in this work: Christopher Cooper (IAVI), Gavin Morrow (IAVI), Maoli Yuan (IAVI), Samantha Bowen (IAVI), Natasha Williams (IAVI), Amy Warren (IAVI), Amira Basel (IAVI), Amy Lynch (IAVI), Suzanna Francis (IAVI), Matt Price (IAVI), Ryan Swoyer (IAVI), Sanjeev Kumar (HIL), Elizabeth Ogunyadi (HIL), Carmel Raymundo (HIL), Jade Adeoti (HIL), Muhammad Anup (HIL), John Brennan (HIL), Samatha Cutler (HIL), Liam Fletcher (HIL), Kevin Mayers (HIL), Oxana Chernyavskaya (HIL), Superna Sohail (HIL), Lisa Hensley (NIH), Michael Chea (PREVAIL), Quiawiah Yarmie (PREVAIL), John Fayiah (PREVAIL), Madison Joe (PREVAIL), Lakshmi Chandramohan (Neogenomics), Luc Bertrand (Charles River Laboratories), Alyssa King (Emmes) and Holly Brindley (Emmes). We thank Luis Branco, Doug Simson and Zalgen Labs for providing recombinant LASV proteins.

The views and conclusions contained in this document are those of the authors and should not be interpreted as necessarily representing the official policies, either expressed or implied, of the U.S. Department of Health and Human Services or of the institutions and companies affiliated with the authors, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

SUPPORT STATEMENT:

This Phase 1 trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04794218) number [NCT04794218](https://clinicaltrials.gov/ct2/show/study/NCT04794218)) was funded by Coalition for Epidemic Preparedness Innovations (CEPI) (award reference number: 276869). The work was also supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health and the Liberian Ministry of Health. I.M.B. performed the work as an employee of Laulima Government Solutions, LLC. This work was supported in part through a Laulima Government Solutions, LLC, prime contract with the National Institute of Allergy and Infectious Diseases (Contract No. HHSN272201800013C).

REFERENCES:

1. Garry RF. Lassa fever - the road ahead. *Nat Rev Microbiol* 2023;21(2):87–96. (In eng). DOI: 10.1038/s41579-022-00789-8. [PubMed: 36097163]
2. Whitmer SLM, Strecker T, Cadar D, et al. New Lineage of Lassa Virus, Togo, 2016. *Emerg Infect Dis* 2018;24(3):599–602. (In eng). DOI: 10.3201/eid2403.171905. [PubMed: 29460758]
3. WHO. Prioritizing diseases for research and development in emergency contexts. (<https://www.who.int/activities/prioritizing-diseases-for-research-and-development-in-emergency-contexts#>).
4. Yadouleton A, Picard C, Rieger T, et al. Lassa fever in Benin: description of the 2014 and 2016 epidemics and genetic characterization of a new Lassa virus. *Emerg Microbes Infect* 2020;9(1):1761–1770. (In eng). DOI: 10.1080/22221751.2020.1796528. [PubMed: 32723007]
5. Adepoju P. Lassa fever in Nigeria. *Lancet Microbe* 2024;5(10):100960. (In eng). DOI: 10.1016/j.lanmic.2024.100960. [PubMed: 39178871]
6. Naeem A, Zahid S, Hafeez MH, Bibi A, Tabassum S, Akilimali A. Re-emergence of Lassa fever in Nigeria: A new challenge for public health authorities. *Health Sci Rep* 2023;6(10):e1628. (In eng). DOI: 10.1002/hsr2.1628. [PubMed: 37885466]
7. Overbosch F, de Boer M, Veldkamp KE, et al. Public health response to two imported, epidemiologically related cases of Lassa fever in the Netherlands (ex Sierra Leone), November 2019. *Euro Surveill* 2020;25(15) (In eng). DOI: 10.2807/1560-7917.Es.2020.25.15.2000265.
8. Amorosa V, MacNeil A, McConnell R, et al. Imported Lassa Fever, Pennsylvania, USA, 2010. *Emerging Infectious Disease journal* 2010;16(10):1598. DOI: 10.3201/eid1610.100774.
9. Aloke C, Obasi NA, Aja PM, et al. Combating Lassa Fever in West African Sub-Region: Progress, Challenges, and Future Perspectives. *Viruses* 2023;15(1) (In eng). DOI: 10.3390/v15010146.

10. Garbutt M, Liebscher R, Wahl-Jensen V, et al. Properties of replication-competent vesicular stomatitis virus vectors expressing glycoproteins of filoviruses and arenaviruses. *J Virol* 2004;78(10):5458–65. (In eng). DOI: 10.1128/jvi.78.10.5458-5465.2004. [PubMed: 15113924]
11. Anderson EM, Collier BA. Translational success of fundamental virology: a VSV-vectored Ebola vaccine. *J Virol* 2024;98(3):e0162723. (In eng). DOI: 10.1128/jvi.01627-23. [PubMed: 38305150]
12. CDC. Ebola Vaccine Product Information. Centers for Disease Control and Prevention. May 1, 2024 (<https://www.cdc.gov/ebola/hcp/vaccines/index.html#>).
13. Kallay R, Doshi RH, Muhoza P, et al. Use of Ebola Vaccines - Worldwide, 2021-2023. *MMWR Morb Mortal Wkly Rep* 2024;73(16):360–364. (In eng). DOI: 10.15585/mmwr.mm7316a1. [PubMed: 38662631]
14. Wolf J, Jannat R, Dubey S, et al. Development of Pandemic Vaccines: ERVEBO Case Study. *Vaccines (Basel)* 2021;9(3) (In eng). DOI: 10.3390/vaccines9030190.
15. Woolsey C, Geisbert TW. Current state of Ebola virus vaccines: A snapshot. *PLoS Pathog* 2021;17(12):e1010078. (In eng). DOI: 10.1371/journal.ppat.1010078. [PubMed: 34882741]
16. WHO. Ebola vaccination starts in Sierra Leone to prevent new outbreak. 11 MAY 2021 (<https://www.afro.who.int/news/ebola-vaccination-starts-sierra-leone-prevent-new-outbreak>).
17. Geisbert TW, Jones S, Fritz EA, et al. Development of a new vaccine for the prevention of Lassa fever. *PLoS Med* 2005;2(6):e183. (In eng). DOI: 10.1371/journal.pmed.0020183. [PubMed: 15971954]
18. Cross RW, Woolsey C, Prasad AN, et al. A recombinant VSV-vectored vaccine rapidly protects nonhuman primates against heterologous lethal Lassa fever. *Cell Rep* 2022;40(3):111094. (In eng). DOI: 10.1016/j.celrep.2022.111094. [PubMed: 35858566]
19. Marzi A, Feldmann F, Geisbert TW, Feldmann H, Safronetz D. Vesicular stomatitis virus-based vaccines against Lassa and Ebola viruses. *Emerg Infect Dis* 2015;21(2):305–7. (In eng). DOI: 10.3201/eid2102.141649. [PubMed: 25625358]
20. Safronetz D, Mire C, Rosenke K, et al. A recombinant vesicular stomatitis virus-based Lassa fever vaccine protects guinea pigs and macaques against challenge with geographically and genetically distinct Lassa viruses. *PLoS Negl Trop Dis* 2015;9(4):e0003736. (In eng). DOI: 10.1371/journal.pntd.0003736. [PubMed: 25884628]
21. Cooper CL, Morrow G, Yuan M, et al. Preclinical development of a replication-competent vesicular stomatitis virus-based Lassa virus vaccine candidate advanced into human clinical trials. *EBioMedicine* 2025;114:105647. (In eng). DOI: 10.1016/j.ebiom.2025.105647. [PubMed: 40157130]
22. Mateer EJ, Huang C, Shehu NY, Paessler S. Lassa fever-induced sensorineural hearing loss: A neglected public health and social burden. *PLoS Negl Trop Dis* 2018;12(2):e0006187. (In eng). DOI: 10.1371/journal.pntd.0006187. [PubMed: 29470486]
23. Heppner DG Jr., Kemp TL, Martin BK, et al. Safety and immunogenicity of the rVSVΔG-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response study. *Lancet Infect Dis* 2017;17(8):854–866. (In eng). DOI: 10.1016/s1473-3099(17)30313-4. [PubMed: 28606591]
24. Gailhardou S, Skipetrova A, Dayan GH, et al. Safety Overview of a Recombinant Live-Attenuated Tetravalent Dengue Vaccine: Pooled Analysis of Data from 18 Clinical Trials. *PLoS Negl Trop Dis* 2016;10(7):e0004821. (In eng). DOI: 10.1371/journal.pntd.0004821. [PubMed: 27414655]
25. Guy B, Guirakhoo F, Barban V, Higgs S, Monath TP, Lang J. Preclinical and clinical development of YFV 17D-based chimeric vaccines against dengue, West Nile and Japanese encephalitis viruses. *Vaccine* 2010;28(3):632–49. (In eng). DOI: 10.1016/j.vaccine.2009.09.098. [PubMed: 19808029]
26. Martins RM, Maia Mde L, Farias RH, et al. 17DD yellow fever vaccine: a double blind, randomized clinical trial of immunogenicity and safety on a dose-response study. *Hum Vaccin Immunother* 2013;9(4):879–88. (In eng). DOI: 10.4161/hv.22982. [PubMed: 23364472]
27. Alabi A, Kokou K, Mahmoudou S, et al. Replication, safety and immunogenicity of the vectored Ebola vaccine rVSV-ΔG-ZEBOV-GP in a sub-Saharan African paediatric population: A randomised controlled, open-label trial in children aged 1-12 years living in Lambaréné, Gabon. *J Infect* 2024;89(4):106237. (In eng). DOI: 10.1016/j.jinf.2024.106237. [PubMed: 39121969]

28. Halperin SA, Arribas JR, Rupp R, et al. Six-Month Safety Data of Recombinant Vesicular Stomatitis Virus-Zaire Ebola Virus Envelope Glycoprotein Vaccine in a Phase 3 Double-Blind, Placebo-Controlled Randomized Study in Healthy Adults. *J Infect Dis* 2017;215(12):1789–1798. (In eng). DOI: 10.1093/infdis/jix189. [PubMed: 28549145]
29. Tell JG, Collier BG, Dubey SA, et al. Environmental Risk Assessment for rVSVΔG-ZEBOV-GP, a Genetically Modified Live Vaccine for Ebola Virus Disease. *Vaccines (Basel)* 2020;8(4) (In eng). DOI: 10.3390/vaccines8040779.
30. Agnandji ST, Huttner A, Zinser ME, et al. Phase 1 Trials of rVSV Ebola Vaccine in Africa and Europe. *N Engl J Med* 2016;374(17):1647–60. (In eng). DOI: 10.1056/NEJMoa1502924. [PubMed: 25830326]
31. Agnandji ST, Fernandes JF, Bache EB, et al. Safety and immunogenicity of rVSVΔG-ZEBOV-GP Ebola vaccine in adults and children in Lambaréné, Gabon: A phase I randomised trial. *PLoS Med* 2017;14(10):e1002402. (In eng). DOI: 10.1371/journal.pmed.1002402. [PubMed: 28985239]
32. Lee AW, Liu K, Lhomme E, et al. Immunogenicity and Vaccine Shedding After 1 or 2 Doses of rVSVΔG-ZEBOV-GP Ebola Vaccine (ERVEBO®): Results From a Phase 2, Randomized, Placebo-controlled Trial in Children and Adults. *Clin Infect Dis* 2024;78(4):870–879. (In eng). DOI: 10.1093/cid/ciad693. [PubMed: 37967326]
33. Tschismarov R, Van Damme P, Germain C, et al. Immunogenicity, safety, and tolerability of a recombinant measles-vectored Lassa fever vaccine: a randomised, placebo-controlled, first-in-human trial. *Lancet* 2023;401(10384):1267–1276. (In eng). DOI: 10.1016/s0140-6736(23)00048-x. [PubMed: 36934733]
34. Baillet N, Reynard S, Perthame E, et al. Systemic viral spreading and defective host responses are associated with fatal Lassa fever in macaques. *Commun Biol* 2021;4(1):27. (In eng). DOI: 10.1038/s42003-020-01543-7. [PubMed: 33398113]
35. Russier M, Pannetier D, Baize S. Immune responses and Lassa virus infection. *Viruses* 2012;4(11):2766–85. (In eng). DOI: 10.3390/v4112766. [PubMed: 23202504]
36. van Dorst M, Pyuza JJ, Nkununugi G, et al. Immunological factors linked to geographical variation in vaccine responses. *Nat Rev Immunol* 2024;24(4):250–263. (In eng). DOI: 10.1038/s41577-023-00941-2. [PubMed: 37770632]
37. Knust B, Macneil A, Wong SJ, et al. Exposure to lymphocytic choriomeningitis virus, New York, USA. *Emerg Infect Dis* 2011;17(7):1324–5. (In eng). DOI: 10.3201/eid1707.101349. [PubMed: 21762607]
38. N ND, Berthet N, Rougeron V, et al. Evidence of lymphocytic choriomeningitis virus (LCMV) in domestic mice in Gabon: risk of emergence of LCMV encephalitis in Central Africa. *J Virol* 2015;89(2):1456–60. (In eng). DOI: 10.1128/jvi.01009-14. [PubMed: 25378495]
39. Amanat F, Duehr J, Oestereich L, Hastie KM, Ollmann Saphire E, Krammer F. Antibodies to the Glycoprotein GP2 Subunit Cross-React between Old and New World Arenaviruses. *mSphere* 2018;3(3) (In eng). DOI: 10.1128/mSphere.00189-18.
40. Moon-Walker A, Zhang Z, Zyla DS, et al. Structural basis for antibody-mediated neutralization of lymphocytic choriomeningitis virus. *Cell Chem Biol* 2023;30(4):403–411.e4. (In eng). DOI: 10.1016/j.chembiol.2023.03.005. [PubMed: 36990092]

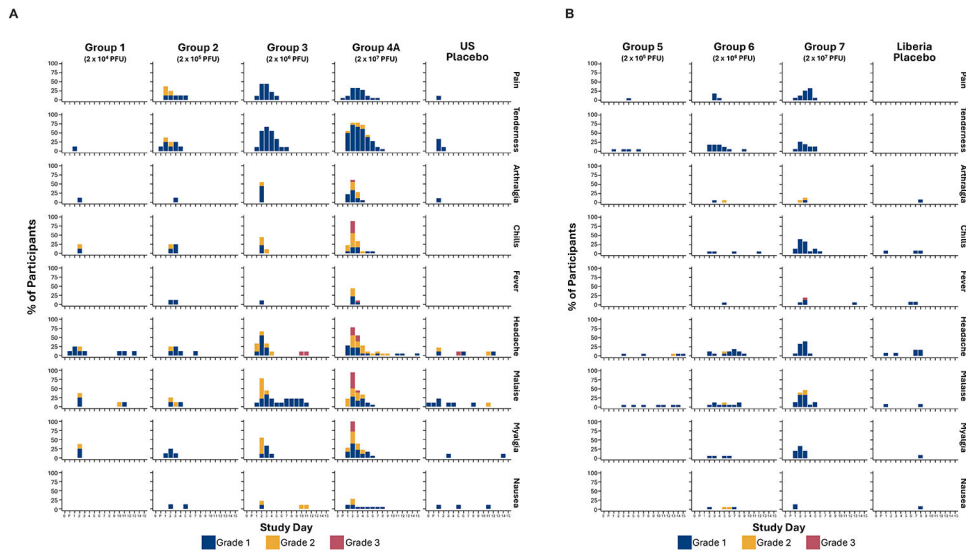


Figure 1: Proportion of participants experiencing the most common local and systemic solicited AEs by vaccine dose group and severity.

Proportion of participants with reactogenicity events detected after the single dose study vaccine or placebo in the United States (A) or in Liberia (B). The maximum severity for each event is shown.

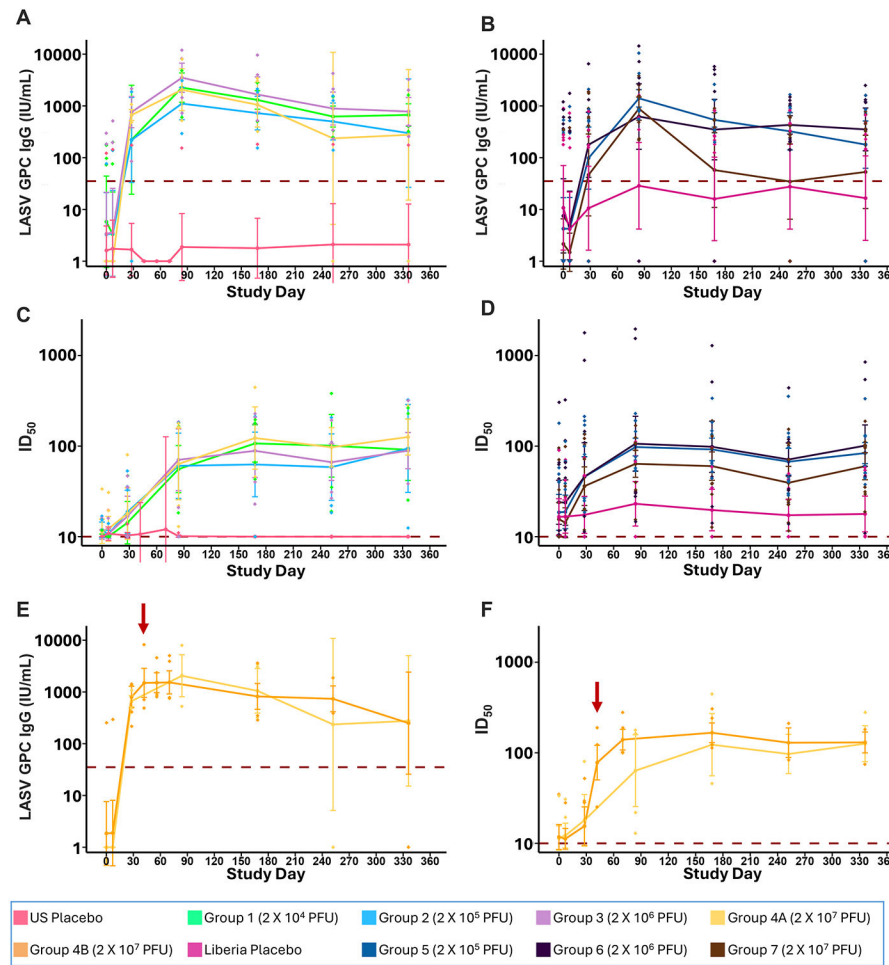


Figure 2: Antibody response (GM with 95% CI), according to vaccine dose and trial visit. Anti-LASV GPC IgG binding responses are shown for Groups 1-4A and Placebo (US) (A) and Groups 5-7 and Placebo (Liberia) (B). Pseudo-virus neutralizing antibody responses are shown for Groups 1-4A and Placebo (US) (C) and Groups 5-7 and Placebo (Liberia) (D). Anti-LASV GPC IgG binding responses are shown for Groups 4A and 4B (E) and pseudo-virus neutralizing antibody responses are shown for Groups 4A and 4B in (F). Data points lying outside the 95% CI are shown as solid diamond shape dots. Red arrows indicate the time of the second vaccine dose administration to Group 4B participants. The red dashed lines indicate Lower Limit of Quantification values for each assay.

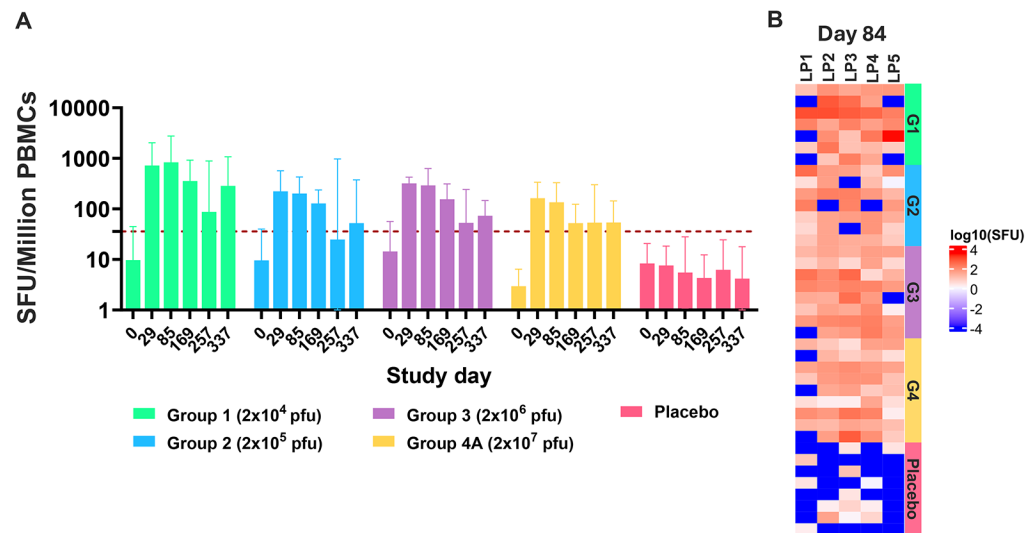


Figure 3: LASV-GPC-specific T-cell response.

Data are GM (with 95% CI) GPC-specific T-cell responses detected by IFN- γ ELISPOT assay for each dose group and placebo recipients at baseline, and study days 29, 85, 169, 257 and 337 (**A**). Red dashed line indicates Limit of Detection of the assay. Heat map of fold change in spot forming units (SFU) to each LASV GPC peptide pool (LP) for every participant from day 0 to study day 85 is shown in (**B**).

Table 1: Study Schema

	Study Group	rVSVΔG-LASV-GPC Vaccine Dosage (PFU) intramuscularly		N (Study Vaccine/Placebo)
		Day 1	Week 6 ¹	
Dose-escalation	1	2×10 ⁴		8/2
	2	2×10 ⁵		8/2
	3	2×10 ⁶		8/2
	4A ²	2×10 ⁷		9/2
	4B ²	2×10 ⁷	2×10 ⁷	9/2
Safety Monitoring Committee Review				
Dose group expansion	5	2×10 ⁵		17/4
	6	2×10 ⁶		17/4
	7	2×10 ⁷		16/4
Total = 114 (92/22)				

¹ An optional second dose of study vaccine was offered to participants already enrolled in Group 4 providing it could be administered between 6 and 20 weeks after receiving the first dose of study vaccine. Participants declining a second vaccination were assigned to Group 4A. Participants accepting a second dose were assigned to Group 4B.

² For participants in Group 4B, the second injection was administered at least 6 weeks but no more than 20 weeks after the first injection. An over-enrollment up to 10 participants was permitted in the study to facilitate rapid enrollment.