A Multicenter Study of the Immunogenicity of Recombinant Vesicular Stomatitis Vaccine for Ebola-Zaire (rVSVΔG-ZEBOV-GP) for Pre-Exposure Prophylaxis In Individuals at Potential Occupational Risk for Ebola Virus Exposure (PREPARE)

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Proposed Study Sites: An initial list of proposed study sites and lead investigators and/or points of contact at those sites is contained in study Appendix B. Minor additions, deletions, or substitutions from this list may occur over time and hence this list is subject to revision. Appendix B will be updated with the most current list annually at the time of the Continuing Review rather than submitting any interim updates in the form of formal protocol amendments.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDBV	Bundibugyo virus
cGLP	Current Good Laboratory Practice
cGMP	Current Good Manufacturing Process
CBC	Complete Blood Count
CFR	Code of Federal Regulations (US)
CI	Confidence Interval
CRF	Case Report Form
CRIS	Clinical Research Information System
CRIMSON	Clinical Research Information Management System of the NIAID
CSO	Clinical Safety Office
CTM	Clinical trial material
DCR	Division of Clinical Research
DSMB	Data and Safety Monitoring Board
DSUR	Development Safety Update Report
EBOV	Ebolavirus
ELISA	Enzyme-linked ImmunoSorbent assay
EMA	European Medicines Agency
EVD	Ebola Virus Disease
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practices
GP	Glycoprotein
HIV	Human Immunodeficiency Virus
HRPP	Human Research Protections Program
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular/ intramuscularly
IND	Investigational New Drug
IRB	Institutional Review Board
LD_{50}	Median lethal dose
LIR	Laboratory of Immune Regulation
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NIAID IRF	National Institute of Allergy and Infectious Diseases Integrated Research Facility
NIH	National Institutes of Health
NK	Natural killer
OCRPRO	Office of Clinical Research and Regulatory Operations

OHRP	Office for Human Research Protections
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cells
PFU	Plaque Forming Units
PI	Principal Investigator
PK	Pharmacokinetics
PPE	Personal Protective Equipment
REDCap	Research Electronic Data Capture
RESTV	Reston virus
rVSV	Recombinant vesicular stomatitis virus
rVSVΔG	Recombinant VSV with G protein deletion
SAE	Serious Adverse Event/Serious Adverse Experience
SERF	Safety Expedited Report Form
SMM	Sponsor Medical Monitor
SUDV	Sudan virus
SRCP	Safety Review and Communications Plan
SUSAR	Serious Unexpected Suspected Adverse Reactions
TAFV	Taï Forest virus
UP	Unanticipated Problem
UPnonAE	Unanticipated Problem that is not an Adverse Event
USAMRIID	United States Army Medical Research Institute of Infectious Diseases
ZEBOV	Zaire Ebola virus
VSV	Vesicular stomatitis virus
WBC	White Blood Cell Count
WRAIR	Walter Reed Army Institute of Research
WT	Wild-type
ZEBOV	Zaire ebolavirus

PROTOCOL SUMMARY

Full Title:	A Multicenter Study of the Immunogenicity of Recombinant Vesicular Stomatitis Vaccine for Ebola-Zaire (rVSVΔG-ZEBOV-GP) for Pre-Exposure Prophylaxis (PREP) In Individuals at Potential Occupational Risk for Ebola Virus Exposure
Short Title:	PREPARE Pre-Exposure Prophylaxis for Adults at High Risk of Occupational Exposure to Ebola Virus
Clinical Phase:	2
IND Sponsor:	Office of Clinical Research Policy and Regulatory Operations (OCRPRO), NIAID, NIH
NIH Principal Investigator:	Richard T. Davey, Jr., MD
Other Site Principal Investigators: TBD	
Sample Size:	400
Accrual Ceiling:	800
Study Population:	Adults at high risk of occupational (laboratory, clinical, or field work) exposure to Ebola virus.
Accrual Period:	October 2016-December 2020
Study Design:	Open-label, multi-center study
Study Duration:	Start Date: October 2016 End Date: December 2023
Study Agent:	V920, a recombinant vesicular stomatitis virus (rVSV) expressing the envelope glycoprotein of Ebola virus Zaire (rVSVΔG-ZEBOV-GP) to be administered at a dose of $\geq 7.2 \times 10^7$ pfu/mL.
Primary Objective:	In the setting of pre-exposure prophylaxis, to compare the durability of the immune response 3 years after primary vaccination with rVSVΔG-ZEBOV-GP vaccine (V920) with and without a homologous booster immunization at 18 months.
Primary Endpoint:	Immunogenicity as measured by ELISA titers

Study Synopsis:

Title	A Multicenter Study of the Immunogenicity of Recombinant Vesicular Stomatitis Vaccine for Ebola-Zaire (rVSVΔG-ZEBOV-GP) for Pre-Exposure Prophylaxis (PREP) In Individuals at Potential Occupational Risk for Ebola Virus Exposure
Sponsor	IND/Study Sponsor: Office of Clinical Research Policy and Regulatory Operations (OCRPRO), NIAID, NIH
Trial Phase	2
Investigational Vaccine EMA approval in November 2019, FDA approval in December 2019	V920, a recombinant vesicular stomatitis virus (rVSV) expressing the envelope glycoprotein of Ebola virus Zaire (ZEBOV GP) to be administered as $\geq 7.2 \times 10^7$ plaque forming units (PFU)
Clinical Indication	Immunization of at-risk individuals 18 years and older to provide potential protection against Ebola Virus Disease (EVD) caused by Ebola virus Zaire strain
Trial Type	Randomized non-blinded interventional trial
Type of control	Randomized: Booster or no booster at 18 months
Route of administration	Intramuscular, 1.0 mL
Trial Blinding	Open Label
Study Groups	V920 (rVSVΔG-ZEBOV-GP) $\geq 7.2 \times 10^7$ pfu/ml primary immunization followed by 1:1 randomization to a homologous booster immunization versus no booster at month 18
Number of trial subjects	Up to 800 subjects may be enrolled.
Rationale	Due to the public health emergency of the 2014-2015 West African Ebola outbreak, the V920 (rVSVΔG-ZEBOV-GP) vaccine has been administered to thousands of human subjects in clinical trials. The data emerging from these studies suggest that a single dose of the vaccine induces an immune response and may provide protection against EVD with an acceptable safety profile (Henao-Restrepo Lancet 2015). Short-term protection was assessed in a ring vaccination design in which contacts of cases were vaccinated, however the durability of the immune response associated with protection has not been assessed.
Objectives	Primary: To compare the immune response 3 years following primary vaccination with rVSVΔG-ZEBOV-GP vaccine (V920) and a homologous booster immunization at 18 months versus primary vaccination with rVSVΔG-ZEBOV-GP vaccine (V920) without a booster at month 18. At month 18 following primary vaccination, eligible and consenting participants will be randomized to a single booster immunization with the same dose of study vaccine as the primary dose ($\geq 7.2 \times 10^7$ pfu/mL) or to no boost. The inclusion and exclusion criteria below will be assessed both at the beginning of the study and prior to randomization at month 18.

	If at any time during the observation period antibody levels fall below a pre-defined seroprotective threshold (yet to be defined in parallel or newly planned studies) a booster may be offered to study participants with antibody levels below that protective threshold. If this occurs before month 18, there will be no randomization. Participants will continue to be followed through 36 months and descriptive analyses will be performed.
Primary Endpoint	Immunogenicity response over 36 months as measured by Enzyme-linked ImmunoSorbent assay (ELISA) titers
Inclusion Criteria	1. Age ≥18 years 2. Signed informed consent for the trial. 3. At risk of occupational exposure to Ebola virus through laboratory, clinical contact, or field work, in the judgment of the investigator. 4. Females of childbearing potential must be willing to use effective methods of contraception from at least 30 days prior to vaccination through 1 month following vaccination/booster. 5. All males must be willing to use effective methods of contraception for at least 1 month following vaccination/booster. 6. Willing to minimize blood and body fluid exposure to others for at least 14 days after vaccination/booster. 7. Agrees not to receive another investigational agent between vaccination and the Month 1 study visit (and booster and Month 19 study visit). 8. Willing to forgo blood donation for one year from vaccination/booster. 9. Willing to accept randomization (boost versus no boost) at month 18 visit.
Exclusion Criteria	1. Any condition that would limit the ability of the participant to meet protocol requirements or would place the participant at unreasonable risk. 2. Pregnant or breastfeeding (must have negative serum or urine pregnancy test on the day of vaccination, prior to vaccination) 3. Known allergy to the components of the rVSVΔG-ZEBOV-GP vaccine (V920) vaccine product (VSV, albumin, tris). 4. History of severe local or systemic reactions to any vaccination. 5. Received an investigational drug within 5 half lives or 30 days, whichever is longer, prior to vaccination (Day 0)/booster (Month 18). 6. Received licensed killed vaccines 14 days before, or intention to receive within 7 days following, vaccination (Day 0)/booster (Month 18). 7. Received live virus vaccines within 30 days before, or intention to receive within 30 days following, vaccination (Day 0)/booster (Month 18).

	8. Received immunoglobulins and/or any blood products within the 120 days preceding vaccination (Day 0)/booster (Month 18). 9. Received allergy treatment with antigen injections within 30 days before vaccination (Day 0)/booster (Month 18). 10. Clinical evidence (e.g. oral temp >38 degrees Celsius, systemic symptoms) of a systemic infection or other acute intercurrent illness at the proposed time of vaccination (Day 0)/booster (Month 18).
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 5 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for 3 years following enrollment and the primary vaccination.

Randomization Ratio	1:1 randomization to booster versus no booster at 18 months
Safety Assessment	Injection site reactions and targeted symptoms will be assessed using a diary over the 14 days following primary vaccination and the booster. Serious adverse events (SAE) will be assessed for the duration of the study as indicated in Table 2. AEs will be graded using a standard toxicity grading scale.
Immunogenicity Assessment	Study visits for immunogenicity assessments and serum collection will occur pre-vaccination and Months 1, 3, 6, 12, 18, 19, 24, 30, 36 as indicated in Table 2. PBMC may be collected at interested and qualified sites.
Statistical Methods	The major objective of this open-label protocol is to measure the durability of the immune response over 36 months to rVSVΔG-ZEBOV-GP (V920) vaccination followed by a booser immunization at 18 months versus vaccination with rVSVΔG-ZEBOV-GP (V920) without a booster immunization. Up to 1,000 participants are expected to participate in the study based on assessment by sites regarding the number of individuals at risk. If 80% of participants enrolled and given the primary vaccination are eligible and consent to the booster randomization at 18 months, power is excellent for comparing the percent with an immune response (e.g. seroconversion and/or seroprotection) at 36 months for those randomized to the booster versus no booster. For example, if 70% of participants have an immune response without the boost at 36 months, with 400 participants per group, power is 90% at the 2-sided 0.05 level of significance to detect an increase with the boost to 80%. The percent of participants responding at 36 months will be compared using Fisher's exact test for proportions. Similar methods will be used to compare the two groups for serious adverse events through 36 months of follow-up. Immunogenicity summaries will include means and 95% CIs of the Geometric Mean Titers (GMT) of all endpoints at all timepoints. The percentage of subjects achieving a seroconversion and/or seroprotection levels (to be defined in other studies) may be summarized. Adverse events following vaccination will be summarized with counts and percentages.

PRÉCIS

Between 1994 and the present, there have been multiple Ebolavirus outbreaks affecting mostly central Africa. However, the 2014/2015 West African outbreak significantly exceeds all previous outbreaks in geographic range, number of individuals affected, and in disruption of typical activities of civil society.

This protocol is a multi-center study to evaluate the durability of the immune response following the open label administration of the rVSVΔG-ZEBOV-GP vaccine (V920) as pre-exposure prophylaxis for adults who have an occupational risk for potential exposure to Ebola virus. The vaccine uses a live replicating vesicular stomatitis virus (VSV) replacing the gene encoding the G envelope glycoprotein with the gene encoding the envelope glycoprotein from the Zaire strain of Ebola (rVSVΔG-ZEBOV-GP also known as V920).

All subjects will receive a single dose of rVSVΔG-ZEBOV-GP ($\geq 7.2 \times 10^7$ pfu) on Day 0. We will collect adverse events after vaccination and at Month 1 and Month 19, serious adverse events (SAE) for the duration of the study, and assess the immune response at Months 1, 3, 6, 12, 18, 19, 24, 30, and 36.

A single booster immunization with the same dose of study vaccine as the primary dose ($\geq 7.2 \times 10^7$ pfu/mL) will be given to those randomized at month 18 to the booster arm of the trial. However, if at any time during the observation period antibody levels fall below a predefined seroprotective threshold (yet to be defined in parallel or newly planned studies), a booster will be offered to those who have not previously received a booster injection.

BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background

1.1.1 Filoviruses

Ebolaviruses (EBOV) are members of the *Filoviridae* family and are known primarily as the underlying cause of severe viral hemorrhagic fevers with disturbingly high case-fatality rates. The *Ebolavirus* genus comprises 5 viral species: Bundibugyo virus (BDBV), Zaire Ebola virus (ZEBOV), Reston virus (RESTV), Sudan virus (SUDV), and Taï Forest virus (TAFV) (1). Since the identification of EBOV in the 1970's, at least 20 human outbreaks have been reported, affecting mostly Central Africa (2), with two large outbreaks in 1995 in Kikwit, DRC and in Gulu, Uganda in 2000-2001 (see Table 1). The 2014-2016 ZEBOV West African outbreak is the largest known outbreak to date, with more than 28,000 infections and a case-fatality rate of approximately 40% (as of September 2015), and it significantly exceeds all previous outbreaks in geographic range, number of individuals affected, and disruption of typical activities of civil society.

Table 1: Ebolavirus Outbreaks

Viral species	Year	Outbreak location	# of human cases (% fatality)
Zaire ebolavirus	1976	Yambuku, Zaire (DRC)	318 (88%)
	1977	Tandala, Zaire (DRC)	1 (100%)
	1994	Ogooue-Invindo province, Gabon	52 (60%)
	1995	Kikwit, Democratic Republic of Congo	315 (81%)
	1996	Mayibout, Gabon	37 (57%)
	1996	Booue, Gabon and Johannesburg, South Africa	62 (74%)
	2001-02	Ogooue-Invindo province, Republic of Congo (RC)	122 (79%)
	2002-03	Cuvette region, RC and Ogooue-Invindo province, Gabon	143 (89%)
	2003	Mboma and Mbandza, Republic of Congo	35 (83%)
	2007	Kasai Occidental province, Democratic Republic of Congo	264 (71%)
	2008/2009	Democratic Republic of the Congo	32 (47%)
	2014	Democratic Republic of the Congo	66 (74%)
	2014/2015	Guinea, Liberia, Sierra Leone (widespread)	28,331 (40%)
Sudan ebolavirus	1976	Nzara, Maridi, Tembura, Juba, Sudan	284 (53%)
	1979	Nzara, Yambio, Sudan	34 (65%)
	2000-01	Gulu, Masindi, Uganda	425 (53%)
	2004	Yambio, Sudan	17 (41%)
	2011	Uganda (Luwero District)	1 (100%)
Taï ebolavirus	1994	Taï forest, Ivory Coast	1 (0%)

Reston ebolavirus	1989	Reston, VA, USA	4 (0%)
	1992	Siena, Italy	0
	1996	Alice, TX, USA	0
	2008	Philippines	0
Bundibugyo ebolavirus	2007/2008	Uganda	149 (25%)

Source: Known cases and outbreaks of Ebola virus disease, in reverse chronological order. Centers for Disease Control and Prevention website. http://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html. Updated September 22, 2015. Accessed September 23, 2015.

Fatal ZEBOV infection is characterized by flu-like symptoms and high fever followed by multi-organ failure. While case-fatality rates vary between outbreaks and among the Ebola viruses, ZEBOV has been associated with up to 90% lethality (3). The standard treatment of Ebola hemorrhagic fever is strictly supportive, involving fluid and electrolyte replenishment and pain reduction. While specific treatment strategies including convalescent plasma, monoclonal antibodies, and/or direct-acting antiviral agents are being pursued, it is unlikely that treatment of active infections alone will be sufficient to control outbreaks. There is the need for a safe and effective prophylactic vaccine to provide protection to at-risk populations to prevent future outbreaks.

1.1.2 Vaccine Strategies for Prevention of Filovirus Hemorrhagic Fever

Several ZEBOV vaccines have been developed for human vaccination during the last 5-15 years utilizing: live-replication competent vectors such as paramyxoviruses and vesicular stomatitis virus (VSV); replication-deficient vectors, including adenoviruses, modified vaccinia Ankara virus, or Venezuela equine encephalitis virus; and “killed” vaccines such as DNA vaccines, virus-like-particles, and rabies virus virions (4). The ZEBOV vaccine candidates are in various stages of clinical development. One of the vaccines with the most clinical data available is the rVSVΔG-ZEBOV-GP vaccine (V920), which produced promising efficacy results in a Phase 3 trial in Guinea during the 2014/2015 West African ZEBOV outbreak (5).

1.2 Vesicular Stomatitis Virus

VSV is in the family Rhabdoviridae, genus Vesiculovirus. They are bullet-shaped, single-stranded, negative-sense RNA viruses containing 5 genes, one of which is the viral glycoprotein. In the U.S., the 2 most common strains are the New Jersey and Indiana strains.

VSV is an arthropod-borne virus that primarily affects rodents, cattle, swine, and horses, but can also infect humans and other species. It is thought that VSV is spread between hoofed animals and rodents via insect vectors (6).

1.2.1 VSV Infections in Humans

Naturally occurring human infections with VSV are rare. In general, natural infection with VSV produces an illness lasting 3 to 4 days and characterized by fever, headaches, myalgia, malaise, nausea, vomiting, and occasionally vesicular lesions of the mouth or at

the site of inoculation (7-9). Natural infection is rare and generally limited to individuals who are in rural environments or working with livestock manifesting vesicular stomatitis. Encephalitis has been reported in one case associated with a natural VSV-Indiana infection (9).

1.2.2 VSV as a vaccine vector

VSV is seen as an attractive prospect for vaccine vectors for several reasons, including a lack of antibodies in the general population, an extremely low incidence of complications in natural infections, and its broad tissue tropism. For these reasons, numerous VSV-based therapeutics are being developed for use against infectious and malignant disease. In addition to the VSV-based Ebola vaccine, the following VSV-based therapeutics are in use in human studies:

- VSV-expressing HIV gag protein as an HIV vaccine (ClinicalTrials.gov Identifier: NCT01438606 & NCT01578889)
- VSV-expressing interferon beta as treatment for hepatocellular carcinoma (ClinicalTrials.gov Identifier: NCT01628640)

1.3 rVSVΔG-ZEBOV-GP Vaccine

1.3.1 Introduction

The rVSVΔG-ZEBOV-GP vaccine (V920) consists of a single recombinant VSV (rVSV) isolate (11481 nt) modified to replace the gene encoding the G envelope glycoprotein (GP) with the gene encoding the envelope glycoprotein from ZEBOV. The available clinical and nonclinical data summarized below suggest that a single IM administration of the rVSVΔG-ZEBOV-GP vaccine is safe and produces protective immunity. The rVSVΔG-ZEBOV-GP vaccine was approved by the European Medicines Agency (EMA) in November 2019. It was also approved by the U.S. FDA in December 2019.

1.3.2 Nonclinical Efficacy Studies

The initial studies of the rVSVΔG-ZEBOV-GP vaccine demonstrated 100% protection against lethal ZEBOV challenge in cynomolgus macaques following a single IM immunization (10). This vaccine was able to protect cynomolgus macaques from homologous aerosol challenge with ZEBOV (11). However, 100% protection from aerosol challenge has not been replicated in more recent studies and vaccinated animals (both survivors and non-survivors) experienced pulmonary inflammation with significant lung pathology; the reasons for this difference are being studied further. Delivering the laboratory-grade vaccine by the oral, intranasal, or IM route 28 days prior to challenge protected all cynomolgus macaques from subsequent ZEBOV challenge (12).

In studies of post-exposure prophylaxis with the non-clinical grade rVSVΔG-ZEBOV-GP vaccine, crude vaccine administered to guinea pigs and mice 24 hours prior to lethal challenge, 1 hour post-challenge, and 24 hours post-challenge resulted in 67%, 83%, and 50% survival in small groups of guinea pigs, respectively, while all treated mice survived (13). All guinea pigs showed weight loss and clinical symptoms; however, in those that did not survive, time to death was delayed. More importantly, rVSVΔG-ZEBOV-GP vaccine also protected 50% of rhesus macaques when administered 30 minutes following

challenge. While all macaques developed fever and lymphopenia, 50% of the animals did not progress to more severe disease, including alterations in clinical chemistry and macular rash. As noted previously, rVSV viremia was detected on Day 3 post-immunization in most immunized animals; however, this did not correlate with survival. ZEBOV viremia in survivors was 2 to 4 logs lower than in non-survivors. Of note, animals treated with rVSV did not show a decrease in natural killer (NK) cells following challenge but instead showed a substantial increase.

Clinical trial material (CTM) has undergone challenge testing in murine and nonhuman primate (NHP) models of pre-and post-exposure prophylaxis. In the murine model, clinical trial material provided 100% protection in some pre- and post-exposure models. In rhesus macaques, 100% of animals were protected when vaccinated 28 days in advance of a 1,000 median lethal dose (LD_{50}) challenge dose. In the post-exposure model, 33% of cynomolgus macaques survived when vaccinated within one hour following a challenge with 1,000 LD_{50} of ZEBOV.

The kinetics of rVSVΔG-ZEBOV-GP vaccine replication *in vitro* suggest it replicates substantially faster than wild-type ZEBOV and interference with ZEBOV replication via competition for receptor or for intracellular resources is a potential mechanism for its effects as a post-exposure prophylactic (13). In contrast to control animals, which undergo a reduction in lymphocytes during infection, vaccinated animals either showed a stable or small increase in CD3+, CD4+, and CD8+ cells, typical of a secondary immune response and suggestive that a strong Th1 cell-mediated immune response is induced (12).

An additional NHP study is in progress to assess immunogenicity and protection from challenge at 42 days, three months, and one year following IM vaccination with $3x10^4$ pfu (2 animals in the one year group) or $3x10^6$ pfu (the rest of the animals) of rVSVΔG-ZEBOV-GP. Preliminary results indicate that 0/2 of the animals that received placebo, 4/4 animals challenged 42 days after vaccination, 2/6 animals challenged 3 months after vaccination, and 3/7 animals challenged one year after vaccination survived.

1.3.3 Toxicology

To date, the rVSV filovirus GP vectors have been used in over 80 nonhuman primates (NHPs) with no signs of toxicity as a result of vaccination. Current Good Laboratory Practice (cGLP) repeated dose toxicology studies are ongoing to evaluate the toxicity and local tolerance of V920 in mice and monkeys. In these studies BALB/C mice and cynomolgus monkeys were dosed with up to 2.0×10^7 plaque-forming units (pfu) and 1.0×10^8 pfu, respectively, V920 by 2 IM injections 14 days apart followed by a 30-Day recovery period. To date, there has been no evidence of systemic toxicity based on preliminary clinical pathology and necropsy data. Non-GLP Toxicology Data from a study performed at the Public Health Agency of Canada using CTM indicate limited hematologic or metabolic toxicities in healthy NHPs.

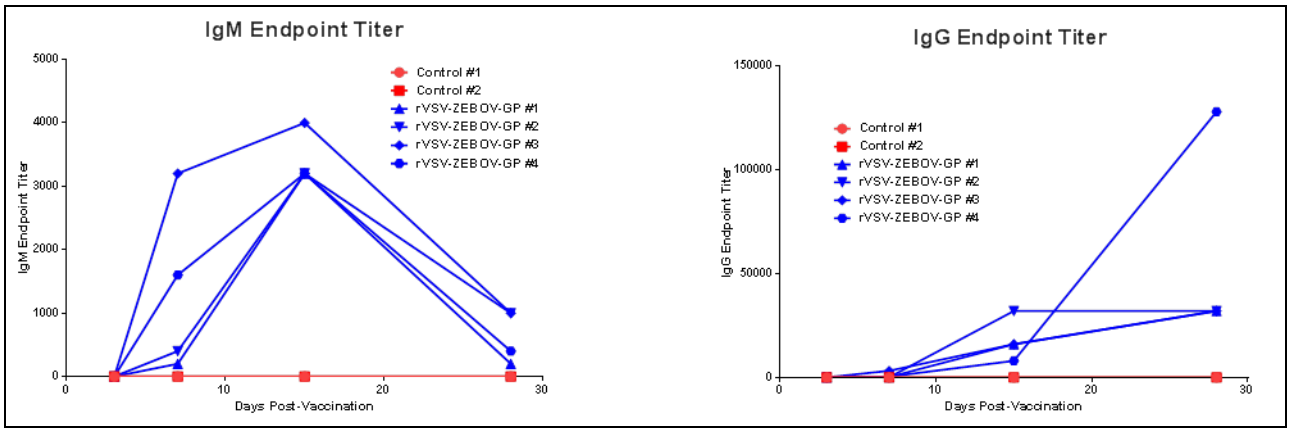
CTM was manufactured in compliance with current Good Manufacturing Practice (cGMPs). The final formulation was 1.0 mL of product per vial in 10 mM Tris pH 7.2 with 2.5 g/L human serum albumin. The CTM was sent to the Public Health Agency of

Canada for pre-exposure vaccination efficacy testing. Six (6) NHPs (cynomolgus macaques) were used (2 controls and 4 test subjects). Two (2) animals received diluent injections (10 mM Tris pH 7.2 with 2.5 g/L recombinant human serum albumin). Four (4) animals received 1 x 10^8 pfu of rVSVΔG-ZEBOV-GP vaccine. White blood cell (WBC) counts, platelet levels, and biochemistry values were monitored. There was no significant deviation from baseline values for any of these parameters. Animals were monitored for 28 days after vaccination and then challenged with the 1,000 LD_{50} of wild-type ZEBOV virus (Kikwit).

1.3.4 Immunogenicity

The antibody titers against the ZEBOV GP were measured and are presented in Figure 1 below. All 4 animals injected with rVSVΔG-ZEBOV-GP vaccine developed immunoglobulin M (IgM) antibodies by Day 7 post-vaccination while neither of 2 control animals had IgM titers. By Day 14 post-vaccination, all animals injected with rVSVΔG-ZEBOV-GP developed immunoglobulin G (IgG) antibody titers that remained high throughout the 28-day period. Neither control animal had detectable IgG titers. After challenge with 1,000 TCID50 of ZEBOV, both control animals were viremic by Day 3 and succumbed to infection at Day 6. None of the rVSVΔG-ZEBOV-GP–vaccinated animals had any clinical signs of illness. Two of the 4 animals had low-level ZEBOV viremia at Day 6 (average of 1.5 x 10^4 copies compared to an average of 1.1 x 10^8 copies in the control animals).

Figure 1: Antibody Titers Against ZEBOV GP



1.3.5 Neurovirulence

Wild-type VSV can cause neurovirulence in rodents, macaques, cattle, sheep, and horses. As VSV vaccines are replication-competent, there is potential for VSV neurovirulence. In a study of 21 cynomolgus macaques in which rVSV vaccines were administered intrathalamically, 7 animals received rVSVΔG-ZEBOV-GP, 7 received a rVSV vector expressing the Lake Victoria marburgvirus (MARV) GP, 3 received rVSV wild-type (wt) vector, and 4 received vehicle control (14).

Two of 3 animals given rVSV-wt showed severe neurological symptoms, whereas animals receiving vehicle control, rVSVΔG-ZEBOV-GP, or rVSV-MARV-GP did not develop these symptoms. Histological analysis revealed major lesions in neural tissues of all 3 rVSV-wt animals; however, no significant lesions were observed in any animals from the filovirus vaccine or vehicle control groups. These data suggest that rVSV filovirus GP vaccine vectors lack the neurovirulence properties associated with the wild-type VSV.

1.3.6 Clinical Experience

Due to the public health emergency of the 2014-2016 West African outbreak, rVSVΔG-ZEBOV-GP vaccine has been administered to over 16,000 human subjects in clinical trials. The data emerging from these studies suggest that a single dose of the vaccine induces an immune response and may provide protection against Ebola virus disease with an acceptable safety profile.

Safety data from 6 Phase 1 studies in which a total of 190 adult participants received a single rVSVΔG-ZEBOV-GP injection at doses ranging from $3x10^5$ pfu/ml to $5x10^6$ pfu/ml have been published; data from 178 participants were included in the final analyses (15, 16). The most common adverse events (AEs) were injection-site pain, myalgia, headache, fatigue, fever, and chills; transient changes in hematological parameters consistent with live attenuated virus vaccination were also observed. Less common AEs included injection-site erythema and swelling, gastrointestinal symptoms, arthralgia, arthritis, and oral ulcers. The majority of AEs were mild or moderate in severity; no serious adverse events (SAEs) were associated with rVSVΔG-ZEBOV-GP vaccination in these studies. Transient viremia occurred in the majority of vaccinees, with most cases resolving by 7 days post-vaccination. Rashes, including maculopapular, vesicular, petechial, and pruritic types were also seen in a small number of subjects in some studies.

Figure 2: Frequency of Solicited Adverse Events According to Cohort (Cohort 1=3x10^6 pfu/ml and Cohort 2=2x10^7 pfu/ml) and Grade (16).

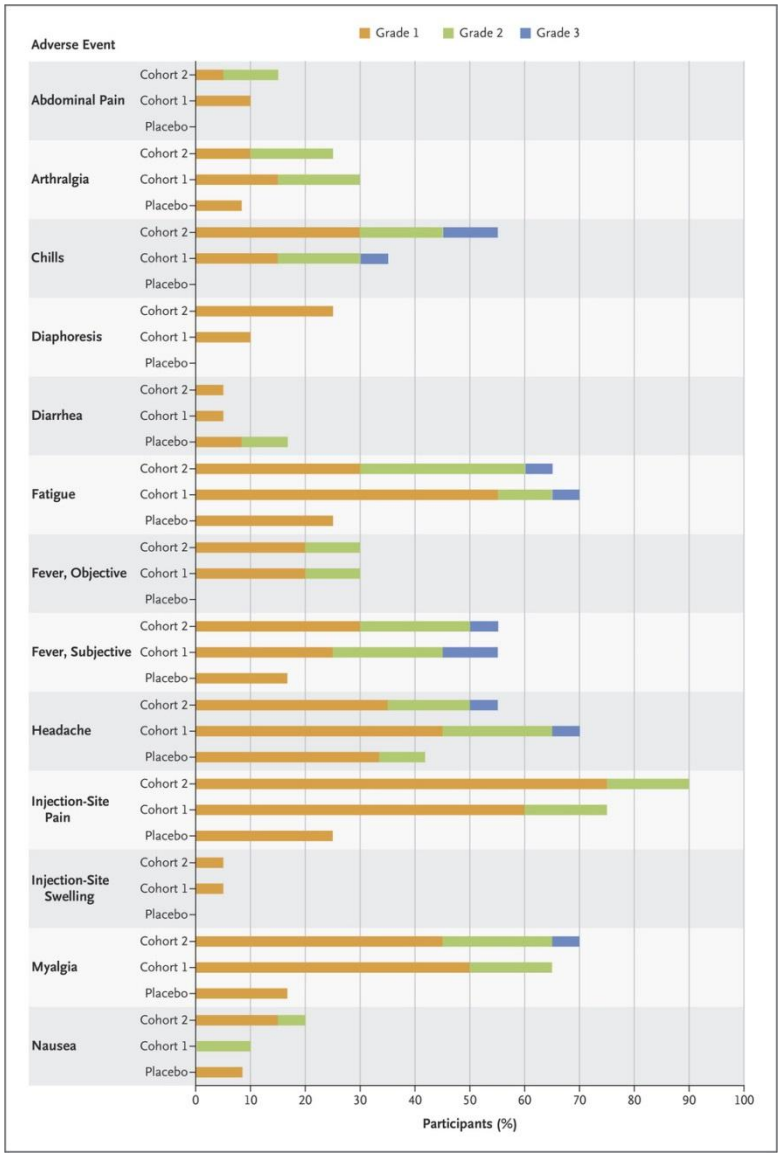
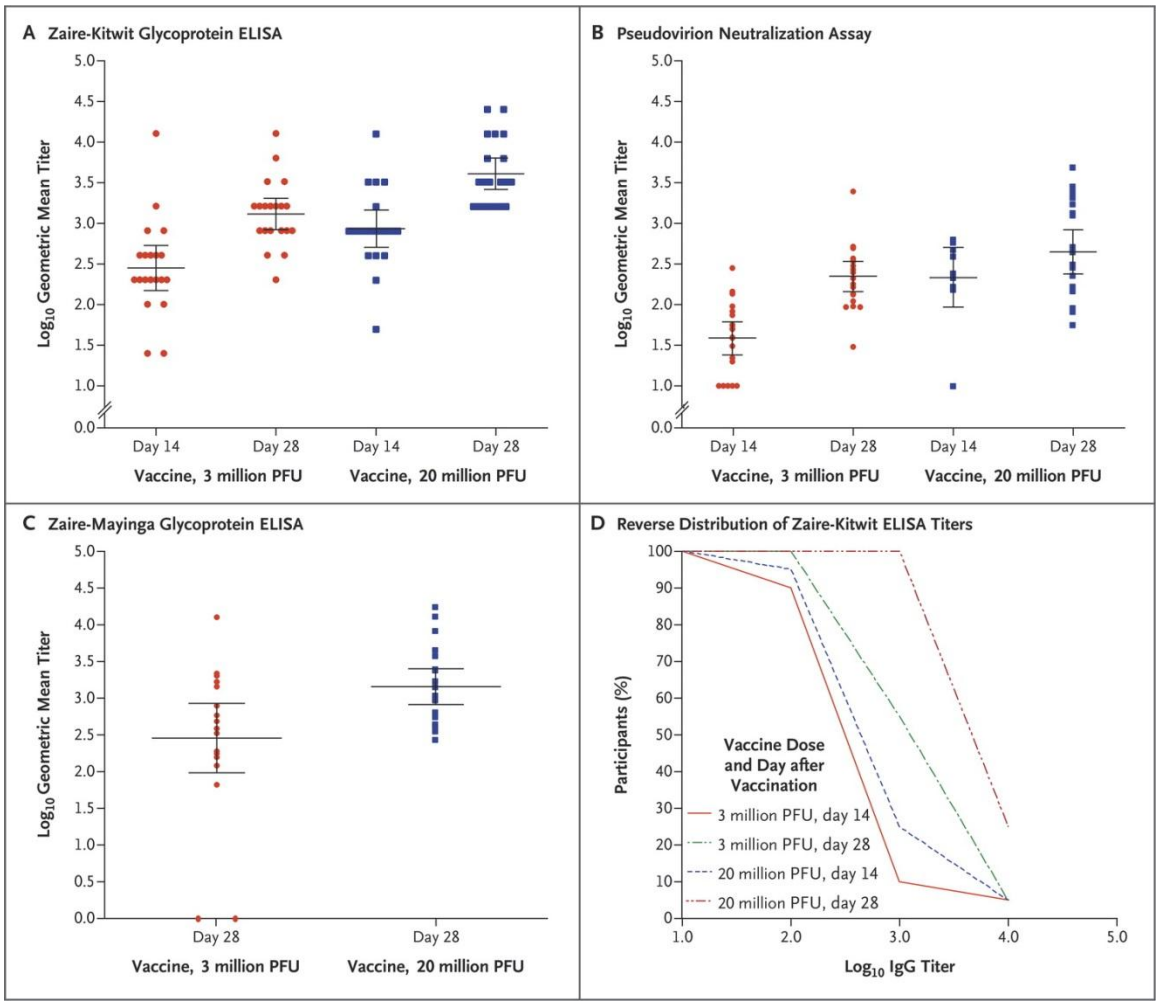


Figure 3: Antibody Responses to Ebola Glycoprotein (16).



Immunogenicity data from the Phase 1 studies showed that the rVSVΔG-ZEBOV-GP vaccine induced an immune response after a single vaccination in all subjects (15, 16). These results have been expanded upon in the large Guinea ring vaccination trial, in which a total of 3,512 adults received rVSVΔG-ZEBOV-GP at a dose of $2x10^7$ pfu (5). In this study, after a new Ebola case was confirmed, clusters of contacts and contacts of contacts were identified and randomly assigned to receive a single rVSVΔG-ZEBOV-GP vaccination either immediately (n=2,014 vaccinated) or after 21 days (n=1,498 vaccinated). When vaccinated individuals who developed infection within 10 days of immunization were excluded, the vaccine efficacy was found to be 100% in vaccinated subjects and 76.3% when all individuals (both eligible and not eligible for vaccination) were included. One SAE (a febrile episode) occurred that was judged to be related to vaccination and resolved without sequelae. Based on these promising results, the data and safety monitoring board (DSMB) with oversight of the study recommended that the randomization component be stopped and that all new clusters receive immediate vaccination. This change was approved by the ethics committees and regulatory

authorities, and immediate vaccination of all clusters was then implemented in the Guinea ring vaccination trial.

Very little is presently known about the need for, the response to, or the optimal timing of a booster immunization with rVSVΔG-ZEBOV-GP vaccine following the primary immunization. A homologous booster at Day 28 following the primary immunization, both given at the same dose, was studied in 30 normal volunteers at the dose-escalating trial conducted at NIH (16). In the group of 10/30 volunteers who received the $2x10^7$ pfu/mLml dose of rVSVΔG-ZEBOV GP, the geometric means titers (GMT) by ELISA were as follows: 1,101 (Day 14), 5,534 (Day 28 pre-boost), 9,022 (Day 42), 7,323 (Day 56), 4,195 (Day 84), and 3,646 (Day 180). Of note, there were no new or additional safety concerns caused by administration of the booster dose in this study cohort. However, the degree to which the titers measured at Day 42 (i.e. 14 days after the boost) and thereafter were substantially augmented by the Day 28 boost, or whether that increase in GMT potentially represents both a response to the boost coupled with evolving maturation of the original response to the primary immunization, cannot be determined from these data alone. Further, it is presently unknown how these GMT levels may or may not correspond to a seroprotective level potentially correlated with efficacy against infection following an exposure.

1.4 Rationale for Study

Currently there are no treatments, pre-exposure prophylactic, or post-exposure prophylactic strategies that are FDA-approved for Ebola virus infection. rVSVΔG-ZEBOV-GP vaccine (V920) has demonstrated pre-exposure utility when administered to NHP prior to infectious challenge as well as post-exposure prophylactic effect in these animals when administered within 24 hours following Ebola challenge. Safety, immunogenicity, and efficacy data collected in clinical trials of rVSVΔG-ZEBOV-GP to date are promising and demonstrate efficacy in a ring vaccination campaign setting in Guinea; however, the clinical utility for general use prophylaxis with capability of inducing a durable immune response needs further exploration through additional human studies.

2 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

To compare the immune response 36 months following primary vaccination with rVSVΔG-ZEBOV-GP vaccine (V920) and a homologous booster immunization at 18 months versus primary vaccination with rVSVΔG-ZEBOV-GP vaccine (V920) without a booster at month 18.

2.2 Study Design

This is a multi-center randomized trial to assess the immune response to the rVSVΔG-ZEBOV-GP vaccine (V920) as pre-exposure prophylaxis for individuals who have an occupational risk for potential exposure to Ebola virus.

Eighteen months following the primary vaccination with rVSVΔG-ZEBOV-GP vaccine, eligible and consenting participants will be randomized (1:1) to a single homologous booster immunization or no booster.

All participants who received the primary vaccination will be followed for 36 months irrespective of their eligibility/consent for undergoing randomization for the booster vaccination.

The study will not be blinded.

It is important to determine in the months following the second injection how the antibody levels respond to this second stimulus. Failure to induce a measurable or sustained response in a large percentage of booster recipients may raise concerns that a possible anti-VSV immune response induced by the primary immunization could blunt the replicative capacity of that same vector when used in the booster dose. If so, that finding may prompt reappraisal by the study team as to whether the rVSVΔG-ZEBOV-GP vaccine is still the most appropriate construct to be used in a booster strategy or whether an alternative non-VSV-based vaccine construct (e.g. MVA) should be considered in subsequent participants or in a future trial.

If at any time during the follow-up period antibody levels fall below a predetermined seroprotective threshold (yet to be defined in parallel or newly planned studies), AND that individual has not received a booster immunization, a single booster will be offered to boost the immune response above a protective threshold. If this occurs prior to 18 months, the randomization at 18 months will not be carried out. Descriptive analyses will be performed.

During the 14 days following the primary vaccination and, if given, the booster at 18 months, participants will be asked to maintain a daily diary of body temperature, injection site reactions and targeted symptoms. Study visits for immunogenicity assessments and serum collection will occur pre-vaccination and at Months 1, 3, 6, 12, 18, 19, 24, 30, and 36. If rVSVΔG-ZEBOV-GP is given at a time other than the 18 month timepoint, an additional assessment at one month following that boost will be scheduled.

2.3 Overview of Study Design

Review of immunogenicity titers will occur at 6 month intervals and, if a seroprotective antibody threshold is determined through analyses of other ongoing or planned studies, determination at an individual level as to whether a booster immunization should be given in an attempt to maintain the titer above that threshold will occur. However, if that seroprotective threshold is not determined during the planned follow-up period before 18 months, then 1:1 randomization of study participants to booster immunization versus no immunization at month 18 will proceed as planned.

2.4 Definitions for the Purpose of this Study

Enrolled

Subjects are considered enrolled if they meet the eligibility criteria, including informed consent, and are given the primary vaccination.

Screen Failures

Subjects are considered screen failures when they meet 1 of the following criteria after signing consent:

- Screening assessments reveal that the subject is ineligible.
- Subject withdraws consent before study agent administration.
- Subject fails re-screening for randomization at Month 18 visit. Data collection will continue for those who fail re-screening at Month 18 until study closure.

Randomized

Subjects are considered randomized after a random assignment to boost or no boost at Month 18 is provided to the site investigator.

Discontinued

Subjects are considered discontinued when they meet 1 or more of the following criteria:

- Subject withdraws consent after study agent administration and prior to study completion (Month 36).
- Subject is withdrawn after enrollment by investigator.

Completed

Subjects are considered completed when they have been followed through all study visits and have completed the final study follow-up visit (currently designated as Month 36).

3 STUDY POPULATION

3.1 Rationale for Research Subject Selection

Adults deemed to be at current or future occupational risk (laboratory, clinical, or field) for exposure to Ebola virus, and for whom having pre-exposure prophylaxis available with an investigational agent might provide potential benefit, will be enrolled at the participating institutions. Inclusion and exclusion criteria were developed to allow further investigation of the durability of the immune response to the rVSVΔG-ZEBOV-GP vaccine in immunocompetent individuals at high risk for potential occupational exposure to Ebola, i.e. those who are perceived most likely to potentially benefit from vaccination. The inclusion and exclusion criteria must be met prior to enrollment and then again prior to randomization at Month 18.

3.2 Recruitment

Persons who have a potential occupational risk for exposure to Ebola virus through the course of their assigned duties, current or future, may be referred to this protocol from their home institutions or from other sources such as allied healthcare facilities or public

health agencies. Self-referral is also permitted, but subject to assessment of Ebola exposure risk by the principal investigator at each participating site.

3.2.1 Participation of Employees

Refer to site-specific procedures for enrollment of employees as outlined in site-specific appendices (e.g. for NIH see Appendix A).

3.3 Inclusion Criteria

1. Adults age ≥18 years.
2. Signed informed consent for the trial.
3. At risk of occupational exposure to Ebola virus through laboratory, clinical contact, or field work, in the judgment of the investigator.
4. Females of childbearing potential must be willing to use effective methods of contraception, from at least 30 days prior to vaccination through 1 month following vaccination/booster, which would include:
    - oral contraceptives, either combined or progestogen alone
    - injectable progestogen
    - implants of etenogestrel or levonorgestrel
    - oestrogenic vaginal ring
    - percutaneous contraceptive patches
    - intrauterine device or intrauterine system
    - committed to abstinence from potentially reproductive sexual contact [i.e. will NOT engage in heterosexual intercourse where both partners are capable of reproduction]
    - surgical sterilization
    - male condom combined with a spermicide
5. All males must be willing to use effective methods of contraception for at least 1 month following vaccination/booster, which would include:
    - surgical sterilization
    - male condom combined with a spermicide
6. Willing to minimize blood and body fluid exposure to others for at least 14 days after vaccination/booster. This includes:
    - Use of effective barrier prophylaxis, such as latex condoms, during any sexual interaction (regardless of childbearing status or sexual orientation)
    - Avoiding the sharing of needles, razors, eating utensils, drinking from the same cup, or toothbrushes
    - Avoiding open-mouth kissing
    - Use of universal precautions in the health-care setting
7. Agrees not to receive another investigational agent between vaccination and the Month 1 study visit (and booster and Month 19 study visit).

8. Willing to forgo blood donation for one year from vaccination/booster.
9. Willing to accept randomization (boost versus no boost) at month 18 visit.

3.4 Exclusion Criteria

1. Any condition that would limit the ability of the participant to meet protocol requirements or would place the participant at unreasonable risk. Examples include:

   Clinically significant medical condition, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health, per the investigator. A clinically significant condition or process includes but is not limited to:

   a. A process that would adversely affect the systemic immune response
   b. A process that would require medication that might adversely affect the systemic immune response
   c. Any contraindication to repeated injections or blood draws
   d. A condition that requires active medical intervention or monitoring to avert grave danger to the participant's health or well-being during the study period
   e. A condition or process for which signs or symptoms could be confused with reactions to vaccine

   Presence of any pre-existing illness or clinical history that, in the opinion of the investigator, would place the participant at an unreasonably increased risk through participation in this study. This includes but is not limited to:

   a. Active malignancy
   b. History of Guillain-Barré Syndrome
   c. History of neurological disorder that may increase risk (history of encephalitis, stroke, or seizure)
   d. Active autoimmune disorder requiring systemic immunosuppressive treatment

   Any concomitant medication for which reported side effects or adverse events, in the judgment of the investigator, may interfere with assessment of safety.

   Subjects who, in the judgment of the investigator, will be unlikely or unable to comply with the requirements of this protocol.

2. Pregnant or breast feeding (must have negative serum or urine pregnancy test on the day of vaccination, prior to vaccination)

3. Known allergy to the components of the rVSVΔG-ZEBOV-GP vaccine (V920) vaccine product (VSV, albumin, tris).
4. History of severe local or systemic reactions to any vaccination.
5. Received an investigational drug within 5 half-lives or 30 days, whichever is longer, prior to vaccination (Day 0)/booster (Month 18).
6. Received killed vaccines 14 days before, or intention to receive within 7 days following, vaccination (Day 0)/booster (Month 18).
7. Received live virus vaccines within 30 days before, or intention to receive live virus vaccines within 30 days following, vaccination (Day 0)/booster (Month 18).
8. Received immunoglobulins and/or any blood products within the 120 days preceding vaccination (Day 0)/booster (Month 18).
9. Received allergy treatment with antigen injections within 30 days before vaccination (Day 0)/booster (Month 18).
10. Clinical evidence (e.g. oral temp >38 degrees Celsius, systemic symptoms) of a systemic infection or other acute intercurrent illness at the proposed time of vaccination (Day 0)/booster (Month 18).

Lastly, while not exclusion criteria per se, there are some situations that incur at least a theoretical potential for increased risk of VSV viral shedding to susceptible populations. During the informed consent process site investigators should ensure that potential vaccine recipients are made aware of these considerations and, accordingly, should be strongly encouraged to undertake and remain adherent to personal measures (e.g. scrupulous attention to standard infection control precautions (http://www.cdc.gov/hicpac/2007IP/2007isolationPrecautions.html), minimizing mucus membrane exposures, adherence to social distancing when appropriate, etc.) intended to minimize exposure to potentially at-risk individuals during the shedding period of 14 days. These situations include:

- Healthcare workers who will have direct contact with patients within 14 days after vaccination.
- Animal care workers who will have direct contact with animals (livestock or domestic, besides subject's family pet) within 14 days after vaccination.
- Individuals with a household contact who theoretically might be at increased risk from exposure to VSV shedding (e.g. pregnant female, children 5 years of age or younger, an immune-compromised family member).
- Childcare workers who have direct contact with children 5 years of age or younger

If a subject enrolled in this study is known or suspected to transmit rVSVΔG-ZEBOV-GP vaccine (V920) to a vulnerable person, the Site Investigator will notify the PI and follow any procedures specified at that time to determine the outcome of that transmission.

3.5 Justification of Exclusions of Pregnant Women and Children

3.5.1 Exclusion of Pregnant and Breast-feeding Women

The vaccine includes a replication-competent VSV vector that induces viremia in the host. The risks from the study vaccine to human fetuses are unknown at this time. As such, pregnant females will be excluded from participation.

The risks from the study vaccine to nursing infants are unknown at this time. As such, actively breastfeeding females will be excluded from participation, and female subjects will be required to avoid breastfeeding during the first 30 days after vaccine administration to minimize any potential risk.

3.5.2 Exclusion of Children

This study is designed for pre-exposure prophylaxis in occupational settings where children are not employed nor placed at risk for potential exposure through job duties. Therefore, children will not be eligible for study participation.

4 STUDY AGENT

4.1 Disposition and Dispensation

rVSVΔG-ZEBOV-GP vaccine (V920) will be provided by Merck & Co., Inc. and dispensed at the study sites according to the study manual of procedures. The empty vials and the unused portion of a vial will be discarded in a biohazard containment bag and incinerated or autoclaved following the injection, according to standard practices for bio hazardous waste at the study site.

4.2 Formulation, Packaging, and Labeling Study Drugs

The rVSVΔG-ZEBOV-GP vaccine (V920) consists of a single recombinant VSV isolate modified to replace the gene encoding the G envelope glycoprotein with the gene encoding the envelope glycoprotein from Ebola virus-Zaire.

The vaccine product is supplied in sterile 1.0 mL vials. Each vial contains vaccine virus frozen in a mixture of water for injection, 2.5 g/L recombinant human serum albumin and 10 mM Tris. After thawing, the content of the vials is a clear liquid. The vaccine concentration in the vial is titered to $\geq 7.2 \times 10^7$ pfu/mL (stock).

4.3 Study Agent Storage and Stability

rVSVΔG-ZEBOV-GP vaccine product (V920) is to be stored at ≤-60ºC for long-term storage. Storage temperature will be continuously monitored and recorded. Vaccine product will be stored in a locked room with access restricted to only necessary study site personnel. Vaccine should be stored and transported at temperatures at or below -60°C.

4.4 Preparation, Administration, and Dosage

The study vaccine should be removed from the freezer and thawed at room temperature for approximately 10-15 minutes (not in a refrigerator or water bath). The thawed vial should then be gently inverted several times prior to withdrawal with the syringe. The study vaccine is considered to be thawed when there is no visible ice on the outside of the vial. The study vaccine should appear as a colorless liquid with no particulates visible. If the study vaccine appears cloudy or has particulates, the affected vial should be quarantined, a clinical complaint should be submitted to the manufacturer, and a replacement vial should be assigned and administered. The manufacturer will provide instructions on the final disposition of the affected vaccine upon completion of an investigation. If a Medline 3mL Luer Lock syringe (cat. #SYR103010) or equivalent is utilized, an additional cumulative time of 1 hour at 9-25°C and/or 8 hours at 2-8°C is permitted in the syringe. Re-freezing the study vaccine is not permitted.

Prior to injection, the area to be injected will be cleaned with an alcohol swab. Emergency medical supplies including epinephrine and advanced airway support will be available in case of serious allergic reaction.

To administer: withdraw 1.0 mL of study vaccine from the vial into a 3.0 mL syringe and administer intramuscularly (IM) in the deltoid muscle of the non-dominant arm at a 90º angle into the muscle tissue, using a needle long enough to ensure IM deposition of the study vaccine. A 1.5-inch #23-gauge needle is recommended. The vaccination arm must be recorded on the appropriate case report form (CRF) for future reference in the event of potential injection-site reaction(s).

4.5 Justification of Dose

The dose of rVSVΔG-ZEBOV-GP vaccine (V920) chosen for this study has been administered to thousands of human subjects in the ring vaccination study in Guinea (5) and similar ongoing trials in West Africa as well as in 8 Phase 1 dose-ranging studies (15, 16). According to published reports of these studies, this dose appears to have substantial immunogenicity, has an acceptable safety profile, and may potentially provide some protection against Ebola virus disease.

4.6 Vaccine Accountability

The site pharmacies will maintain accurate accountability records. Instructions and the required accountability documentation will be provided to the assigned study staff. Instructions will be provided for the return or disposal of study vaccine that remains unused at the end of the study. All records regarding the disposition of study drug must be available for inspection by the study monitors and regulatory authorities.

4.7 Concomitant Medications

A checklist of concomitant medications (e.g. immunosuppressives, anti-inflammatory, antiviral agents, etc.) and a write-in listing of any medications will be reported on a CRF at Baseline/Screening, Month 1, Month 18 and Month 19. Subjects will be specifically queried about the use of symptom relief medications during the first 14 days following

immunization. Any prescription medications, over-the-counter preparations (OTC), herbal remedies, and/or nutritional supplements reported to be taken during that time will be recorded in the research record.

4.8 Prohibited Medications

Subjects will refrain from receipt of any investigational drug within 5 half-lives or 30 days, whichever is longer, prior to Day 0 and for 30 days after study vaccination/booster. After this period, subjects may participate in other studies including investigational medications as long as they do not receive other investigational vaccines targeted at filoviruses. No vaccines should be administered from within 14 days before through 7 days after the planned study immunization/booster (30 days before and 30 days after the study vaccination in the case of live vaccines). While it is unknown whether the rVSVΔG-ZEBOV-GP vaccine would cause a similar phenomenon, vaccine recipients should be informed that other live viral vaccines (e.g. MMR) have been associated with an impaired response to other live vaccines when the latter have been administered ≤ 28 days following the former, so separating the two immunizations by at least a few months is preferable in order to minimize this risk.

5 STUDY PROCEDURES

A schedule for study visits is provided below. An order for the vaccine will be made according to site-specific procedures. Blood obtained for this study will be collected from subjects at study sites and may be shipped directly to the designated laboratory for testing or to the NIH repository for later testing and storage. A central laboratory will be chosen and used for performance of antibody testing; either United States Army Medical Research Institute of Infectious Diseases (USAMRIID), the National Institute of Allergy and Infectious Diseases Integrated Research Facility (NIAID IRF), or a designated contract laboratory may be used for this purpose. Initial testing may be performed using a non-validated assay. At least two serum specimens will be cryopreserved for possible future testing using a validated assay that may be performed in a subset of specimens based on scientific and regulatory needs. Validated assay results will supersede non-validated assay results. At their discretion individual sites may also collect additional blood for immunogenicity assays to be performed locally at their institutions as long as total blood volumes drawn conform to their institutional guidelines on safe phlebotomy limits.

All subjects will receive a single dose of study vaccine at Day 0. A single booster immunization with the same dose of study vaccine as the primary dose ($\geq 7.2 \times 10^7$ pfu) may be offered at any time during the course of the 3-year observation period if antibody levels fall below a seroprotective threshold yet to be defined in parallel or newly planned studies.

If a seroprotective threshold titer is determined for this vaccine as a result of ongoing or new studies, that information will be communicated to the IRB in the form of an updated or amended protocol. If individual antibody titers are then found to fall below that threshold (i.e. thereby suggesting a need for a booster immunization) affected participants will be asked to return to their primary site as soon as possible for consideration of a booster immunization.

Alternatively, if no seroprotective threshold is determined in advance, then all study participants will be consented to be randomized to either receive a booster dose or not at month 18.

If at any time during study participation a subject experiences an Ebola exposure event (e.g., contaminated needle stick), they will be referred to an appropriate medical facility for evaluation and follow-up. They may also continue to be followed as indicated on this study unless acute Ebola infection is subsequently diagnosed, in which case their protocol participation will end. It should be noted that any patient samples collected during the time that an individual is undergoing evaluation for ZEBOV infection following an occupational exposure must be treated as potentially infectious and therefore cannot be shipped to or stored in the central sample repository until and unless that individual is subsequently shown to be ZEBOV-free. Similarly, any patient samples collected from a protocol participant who is diagnosed with acute ZEBOV infection are considered infectious and cannot be shipped or stored centrally for this reason outside the regulatory requirements pertaining to Select Agents. Clinical outcome of EVD should be obtained as applicable.

5.1 Schedule of Assessments

Table 2. Schedule of Assessments

Visit	Screening	Baseline/ Vaccination		Diary at home	Follow-up Month [8] (± window in days)				Randomization			Diary at home	Follow-up Month [8] (± window in days)			
	Day -30 to 0	Day 0		Day 0-13	1 (±7)	3 (±7)	6 (±14)	12 (±14)	Month 18 (±14)			Day 0-13	19 (±7)	24 (±14)	30 (±14)	36 (±14)
		Pre	Post[5]						Booster Pre	Booster Post[5]	No Booster					
Informed consent	X															
Eligibility Criteria[1]	X								X							
Randomization									X[7]							
Demographics	X															
History & Physical	X								X							
Concomitant Medications		X			X				X				X			
Vaccination		X							X							
Injection Site Evaluation[2]			X	X						X		X				
Adverse Event [3]			X		X					X			X			
Serious Adverse Events			X		X	X	X	X		X			X	X	X	X
Targeted Symptoms				X	X					X		X	X			
Vital Signs		X		Temp only					X			Temp only				
Pregnancy test[4] (4ml)		X							X							
Serum Collection[6]		X			X	X	X	X	X		X		X	X	X	X

[1] This includes an oral review of the informed consent considerations with participants at Day 0 and Month 18 and documentation of an eligibility checklist.
[2] Evaluation during administration and 30 minutes after vaccination/booster
[3] Grade 3 to 4 AEs are collected post-vaccination/booster.
[4] Serum or urine; females of childbearing potential.
[5] Subject will be observed for at least 30 minutes after vaccination,site assessment at 30 mins, no post-vaccination vital signs required unless clinically indicated.
[6] Serum collection is 15-18mL whole blood to store 6 1-mL aliquots of serum.
[7]Participants may be randomized as early as Month 17. [8] At the discretion of the Investigator, Months 1-12 (and Month 18 if NOT randomized to BOOSTER arm) and Months 19-36 may be done remotely (phone call to update health status/medications may be performed and samples may be mailed in via Quest Lab).

5.2 Screening (Day -30 to 0)

Screening evaluations may be done up to 30 days before vaccination unless otherwise specified.

5.2.1 Informed Consent

The investigator or designee will review informed consent with the subject, which will be signed by the subject. Particular attention will be given to the significant lifestyle restrictions and other commitments required for participation, e.g., those related to avoiding potential exposure of other individuals or spread of the vector.

5.2.2 Demographics

The following information will be recorded:

- Age
- Gender at birth
- Ethnicity
- Race

5.2.3 Medical History

The following information will be recorded:

- Medical history including any chronic medical conditions within the previous 5 years. The medical history should specifically include any past history of (a) oral lesions (aphthous ulcers, herpetic lesions, etc.), (b)history of arthritis, and (c) neurologic conditions.

5.2.4 Physical Exam

A brief physical exam will be performed to ensure there are no medical conditions that would increase a subject's risk for participation in this study

5.2.5 Laboratory Testing

The following tests are not required but, at the discretion of the site investigator, may be performed as part of the assessment of the participants' eligibility at that site. In all cases, study staff must ensure that the volume of blood taken conforms to the institutional safety guidelines for phlebotomy limits. For example, at the National Institute of Health (NIH) Clinical Center guidance states that the amount of blood that may be drawn from adult patients and volunteers (i.e., those persons 18 years of age or older) for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight week period. If performed, there are no protocol-specified criteria for study exclusion based upon the results of the CBC or acute care panel; rather, these results may be incorporated into the principal investigator's overall assessment of the participant's baseline health status as to whether there may be subclinical conditions of which the participant is unaware:

- CBC with differential (optional)

- Acute care panel: Sodium, potassium, chloride, total bicarbonate, creatinine, glucose, urea nitrogen (optional).

5.2.6 Determination of Eligibility

Once the screening evaluation is complete, eligibility will be determined based on the inclusion and exclusion criteria. Eligible subjects who are interested in participating may proceed directly to the Day 0 procedures. Alternatively, they may be scheduled to return to the study site within 30 days for the Day 0 visit. Participants who are deemed eligible during the screening and then proceed to have positive pregnancy test or a fever > 38 degrees Celsius at the day of vaccination will be considered screening failures.

For subjects found to be ineligible, the reason for ineligibility will be discussed. If desired by the subject, and if applicable for the reason for ineligibility, the results will be shared with their health care provider and/or the subject will be assisted in finding definitive medical care for said condition.

5.3 Vaccination (Day 0)

The following procedures may be performed the same day as screening.

5.3.1 Vaccination Procedure

Subject to site-specific policies, participants will be asked to arrive to the study site generally at least 90 minutes prior to scheduled time of study drug administration. Subjects will be observed for at least 30 minutes after study vaccine administration.

5.3.1.1 Pre-Vaccination

Prior to vaccination vital signs will be measured to include weight, height, blood pressure, pulse, respiratory rate, and body temperature. Body temperature must be ≤38 degrees Celsius. All women of childbearing potential must have a negative serum or urine pregnancy test the day of, and preceding, vaccination. A checklist of concomitant treatment classes and a write-in listing of any medications, vitamins or herbal remedies the participant is currently taking will be collected.

The following baseline specimens will be collected and stored on Day0:

- Serum for immunogenicity
- Serum for storage
- (Optional) storage of cryopreserved PBMCs if collected

5.3.1.2 Vaccination

Vaccination in the non-dominant arm is recommended unless, in the judgement of the clinician, the other arm should be used. The arm vaccinated (right/left) is recorded.

5.3.1.3 Post -Vaccination

After vaccination, subjects will remain at the study site for at least 30 minutes. Approximately 30 minutes after vaccination (i.e. prior to discharge) an injection site evaluation is performed, and adverse events grades 3 and 4 recorded on the study CRF. Sites will collect all AEs (grades 1-4) on their source documents. **If clinically indicated**,

the subject will receive a physical exam including vital signs. Before leaving the post-vaccination waiting area the subject will be given a 14-day diary card access code and password with instructions for completion in REDCap. SAEs will be recorded on the study CRF.

5.3.2 Diary (Day 0-13)

The 14-day diary is completed independently in REDCap at home by the participant every evening from the day of vaccination (Day 0) through Day 13. The participant is guided with written instructions to provide the current date, body temperature, injection site reactions (pain on a Likert scale, measured size of any redness or swelling), and rate targeted symptoms on a Likert scale. Additionally, the participant is requested to keep a record of current medication(s) for symptoms relief on a provided list template.

The online diary cards are classified as a memory aide in this protocol. Participants enter symptoms directly into REDCap based on their experience. Post-vaccination symptoms will be discussed with the participant at Month 1 and, potentially, Month 19 to ensure grading is consistent with the toxicity table. Information from the diary card will be entered into the Medical Record and Case Report Form after this discussion as assessed by a clinician.

OVERALL FOLLOW-UP:
At the discretion of the Principal Investigator, select participants residing outside of the local area of the enrollment site, may have follow-up serum samples collected at their local clinics or labs and sent to the enrollment site for processing and freezing (shipped as whole blood samples). This will be considered on a case-by-case basis. These 'blood draw only' visits may include Months 1, 3, 6, 12, 18 (if not randomized to booster vaccination), 19, 24, 30, and 36. Samples collected at clinics or local labs may be labeled with a coded identifier, gender, and date of birth, as required by the local facility. Phone follow-up will be performed by the study team at these timepoints. If a participant is experiencing a serious adverse event, he or she will be seen by a local Primary Care Provider or may return to the enrollment site for evaluation as appropriate.

5.3.3 Follow-up (Month 1)

Targeted symptoms that may be related to vaccine reaction or administration will be documented. Medical staff will record any injection site reactions reported by the subject. An in-person assessment of the injection site is not required unless the subject has reported injection site reaction. Subjects will be asked to report the most severe injection site reaction since vaccination, and provide an evaluation of targeted symptoms. A checklist of concomitant treatment classes and a write-in listing of any medications, vitamins or herbal remedies the participant is currently taking will be collected and recorded on the study CRF. Sites will collect all AEs (grades 1-4) occurring between Month 0 and Month 1 on their source documents. SAEs and any AEs grades 3 and 4 will be recorded on the study CRF.

The following specimens will be collected and stored:

- Serum for immunogenicity
- Serum for storage

- (Optional) storage of cryopreserved PBMCs if collected

5.3.4 Follow-up (Months 3, 6, 12)

The following specimens will be collected and stored:

- Serum for immunogenicity
- Serum for storage
- (Optional) storage of cryopreserved PBMCs if collected

SAEs will be recorded on the study CRF.

5.3.5 Booster Screening and Randomization (Month 18)

All enrolled participants will be screened for eligibility for randomization to the booster (rVSVΔG-ZEBOV-GP vaccine (V920) dose (≥7.2 x 10^7 pfu) or no booster arm of the study. Screening for the booster will have the same inclusion and exclusion criteria as the initial screening for this study however, pregnancy tests will be performed and temperature will be assessed on the day of booster vaccination if participant is randomized to receive a booster. Participants may be randomized remotely.

Participants who are deemed ineligible for randomization will not be randomized, and will follow the data collection plan of those who are randomized to no booster.
All participants may be randomized as early as Month 17 to allow sufficient time for planning visit to Clinical Center and potential booster dose. Required vital signs and pregnancy test will be done on the day of the booster vaccination prior to vaccination.

5.3.5.1 Re-screening and Randomization

The following information will be recorded for all participants at the Month 18 visit:

- Eligibility criteria will be re-assessed (follow-up will continue even if the participant cannot be randomized)

- Updated medical history including any past history of (a) oral lesions (aphthous ulcers, herpetic lesions, etc.), (b) history of arthritis, and (c) neurologic history.

- A brief physical exam will be performed to ensure there are no medical conditions that would increase a subject's risk for participation in this study

- Vital signs to include weight, height, blood pressure, pulse, respiratory rate, and body temperature (must be ≤ 38 degrees Celsius on the day of booster vaccination).

- Serum or urine pregnancy test (females of childbearing potential only) (must be negative on the day of vaccination)

- A checklist of concomitant treatment classes and a write-in listing of any medications, vitamins or herbal remedies the participant is currently taking will be collected and recorded on the study CRF.

- The following specimens will be collected and stored:
  - Serum for immunogenicity
  - Serum for storage
  - (optional) storage of cryopreserved PBMCs if collected

- SAEs will be recorded on the study CRF.

- Eligible subjects will be randomized to either the booster or the no booster arm of the study. Data collection will be differential in relation to relevance.

5.3.5.2 Booster Arm Subjects Only

The arm (right/left) vaccinated is recorded. After booster vaccination injection, subjects will remain at the study site for at least 30 minutes. Approximately 30 minutes (i.e. prior to discharge) an injection site evaluation is performed. Sites will collect all AEs (grades 1-4) on their source documents. If clinically indicated, the subject will receive a physical exam. Before leaving the post-vaccination waiting area, study staff will review the use of the online Diary Card in REDCap.

5.3.6 Diary for Booster Arm Subjects Only (Post Booster Day 0-13)

The 14-day diary is completed independently at home by the subject every evening from the day of booster vaccination injection (Day 0) through Day 13. The subject is guided with written instructions to provide the current date, body temperature, injection site reactions (pain on a Likert scale, measured size of any redness or swelling), and rate targeted symptoms on a Likert scale. Additionally, the subject is requested to keep a record of current medication(s) for symptoms relief on a provided list template.

5.3.7 Follow-up (Month 19)

The following information will be recorded for *all subjects* at the Month 19 visit.

A checklist of concomitant treatment classes and a write-in listing of any medications, vitamins or herbal remedies the subject is currently taking will be collected and recorded on the study CRF.

Review of of targeted symptoms reported by the subject.

The following specimens will be collected and stored:

- Serum for immunogenicity
- Serum for storage
- (Optional) storage of cryopreserved PBMCs if collected

Adverse Events grades 3 and 4 will be recorded on the study CRF.

SAEs will be recorded on the study CRF.

5.3.7.1 Booster Arm Subjects Only

Medical staff will record any injection site reactions reported by the subject, subjects will be asked to report the most severe injection site reaction since vaccination. An in-person assessment of the injection site is not required unless the subject has reported injection site reaction. Sites will collect all AEs (grades 1-4) occurring between Month 18 and Month 19 on their source documents.

5.3.8 Follow-up (Month 24, 30, 36)

The following information will be recorded for all participants at the Month 24, 30 and 26 visits.

The following specimens will be collected and stored:

- Serum for immunogenicity
- Serum for storage
- (Optional) storage of cryopreserved PBMCs if collected

SAEs will be recorded on the study CRFs

6 RISKS AND BENEFITS

6.1 Risks of rVSVΔG-ZEBOV-GP (V920)

In Phase 1 to 3 clinical trials of rVSVΔG-ZEBOV-GP (V920), some subjects reported flu-like symptoms in Days 1 to 3 postvaccination, similar to that seen with other injectable vaccines. Injection-site reactions were also reported in the days immediately following vaccination. In addition, some subjects reported arthralgia (joint pain) and/or arthritis (joint swelling), and petechial/purpuric skin lesions (bruise-like, non-blanching rash) events that occurred approximately 1 to 2 weeks following vaccination. Based on current data, most of these events were of mild-to-moderate intensity and resolved spontaneously within several days or weeks.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

6.1.1 Local Reactions

Local reactions to the study vaccination may include pain, swelling, and/or redness at the injection site. Although highly unlikely, IM injections, independent of investigational product, can result in acute muscle damage, bruising, and/or injection site infection.

The study vaccine will be administered by experienced and trained staff using aseptic technique to minimize or avoid these risks.

6.1.2 Systemic Reactions

Systemic reactions to the study vaccine may include myalgia, headache, fatigue, fever, chills, gastrointestinal symptoms, arthralgia, arthritis, oral ulcers, and rash. On occasion, individuals may feel light-headed or faint after the act of injection (vasovagal reaction). Interim assessments for these and other systemic symptoms commonly seen in investigational vaccine studies (e.g., allergic reaction) will be performed throughout the study, and addressed as required to maximize subject safety.

In a minority of sites participating in Phase I/II studies, arthritis has been described (15). Specifically, in the second week after injection, arthritis affecting 1 to 4 joints developed in 11 of 51 participants (22%) in a trial conducted in Geneva, with pain lasting a median of 8 days; 2 self-limited cases occurred in 40 participants (5%) in trials conducted in Hamburg, Germany, and Kilifi, Kenya. The discordance between trial sites in recording cases of true arthritis (i.e. as opposed to arthralgia) in recipients has yet to be fully explained. In the current study site investigators will be encouraged to take an interim history with a specific focus on eliciting any signs or symptoms consistent with joint disease in vaccine recipients.

6.1.3 Allergic Reaction

There is the potential risk of a serious, or even life-threatening, allergic reaction to 1 or more components of the product to be used in this study. To mitigate this risk, in the judgment of the principal investigator potential subjects with a history of severe allergic reactions to vaccinations or significant allergic reactions to a known component (VSV, albumin, tris) of the study product, will be excluded from participation.

Study sites must be familiar with the management of immediate adverse drug reactions and be ready to initiate emergency treatment, including administration of appropriate medications.

6.1.4 Unknown Risks

There is the possibility of risks that are unknown or that cannot be foreseen, based on available information. This would include late effects that have been seen with some vaccines. If any ongoing animal study or clinical trial results reveal additional significant risk to study subjects, the subjects will be informed and additional administration of study product will be held until presentation of the new safety data to the FDA and IRB.

6.1.5 Risks of Phlebotomy

The primary risks of phlebotomy include local discomfort, occasional bleeding or bruising of the skin at the site of needle puncture, hematoma and, rarely, infection or fainting. At the time of enrollment and during study visits, each subject will be asked about participation in other research studies. For subjects at the NIH Clinical Center, the

amount of blood drawn for research purposes will be no more than 10.5 mL/kg or 550 mL, whichever is smaller, over an 8-week period.

6.1.6 Risks to the Study Personnel and the Environment

There is a theoretical risk of vaccine transmission to study personnel through exposure to blood or body fluids. Adherence to universal precautions will reduce the risk of exposure.

Wild-type VSV is considered a threat for U.S. agriculture. Measures have been taken in this study to prevent transmission to animals (by cautioning those who might be most likely to transmit the virus to animals to undertake preventative measures). Also, the test article vaccine has been attenuated by deletion of the native glycoprotein from the VSV vector, making transmission less likely than wild-type VSV.

VSV is a live virus and therefore may be a risk to immunocompromised subjects or children. Subjects will be instructed to minimize bodily fluid transmission for at least 14 days post-vaccination.

6.2 Potential Benefits

Subjects in clinical trials generally cannot expect to receive direct benefit from vaccination during participation, as clinical trials are designed to provide information about the safety and immunogenicity of an investigational vaccine. Specifically, data from the Guinea ring vaccination study suggest that the rVSVΔG-ZEBOV-GP (V920) vaccine may be effective at preventing development of Ebola virus disease in individuals exposed to the Ebola virus; however, this finding has yet to be confirmed in larger, randomized, placebo-controlled clinical trials. Therefore, subjects may potentially benefit from participation in this study by protection from the vaccine if they experience a high-risk exposure to Ebola virus in the future, but it is also possible that they may not. Subjects will be instructed that the rVSVΔG-ZEBOV-GP vaccine has not been approved for a PREP indication and thus there can be no guarantee that their immune response to this product will protect them from acquiring infection following a serious exposure to Ebola virus, whether it occurs in a laboratory, a clinical, or field setting.

Since participants in this protocol should by no means infer that receipt of rVSVΔG-ZEBOV-GP vaccine places them at lower risk of infection following a potential occupational exposure to Ebola virus, they will be instructed to continue to practice all appropriate mechanical (e.g. use of personal protective equipment [PPE]) and infection control-based means to mitigate the risk of exposure in their course of their occupational duties.

6.3 Alternatives

The alternative to participating in this protocol is simply not to participate. For individuals interested in other potential strategies to mitigate the risk of infection, there are other investigational vaccines under development that do not employ live viral vectors and that have supportive preclinical, animal, and limited human data suggesting that they may also be immunogenic.

7 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS, AND DATA

7.1 Intended Use of the Samples/Specimens/Data

Samples and data collected under this protocol will be used to investigate the durability of the immune response to the rVSVΔG-ZEBOV-GP (V920) vaccine. There are no plans to perform genetic testing at this time, and samples are not specifically being collected for this purpose. However, if subsequent studies should reveal that either the magnitude or the durability of the immune response may be affected by the recipient's genetic background, this question may be readdressed by the study team in a subsequent amendment to the protocol. If that occurs, IRB approval and informed consent by study participants will be performed prior to collection of any study specimens for genetic testing, and current participants may decline to have this testing performed. Similarly, a separate signed informed consent document will be obtained for any other research not described in this protocol according to local institutional guidelines.

7.2 Storage of Samples/Specimens/Data

Initially samples may be stored locally at the participating study sites, and then transferred at periodic intervals to storage sites (which may include facilities designated by the NIH, U.S. DoD, or other participating laboratories) for processing and testing by a central laboratory according to a uniform testing methodology. Testing by a designated central laboratory does not preclude the ability of individual sites to also perform on-site testing of samples in parallel assuming sufficient sample material has been collected to permit both. However, for study purposes (i.e. consistency of methodologies employed) it will be the results of sample analyses performed by the central laboratory that will be used to compare outcomes across the study. Access to stored samples will be limited using either a locked room or a locked freezer. Samples and data will be stored using codes assigned by the study team. Data will be kept in password-protected computers. Only the study sponsor and investigators will have access to the samples and data.

7.3 Tracking Samples

Samples will be tracked by a commercial software program.

7.4 Disposition at the Completion of the Protocol

In the future, other investigators (both at NIH and outside) may wish to study these samples and/or data. In that case, Institutional Review Board (IRB) approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval.

FDA regulations pertaining to retention of study documents will be followed. At the completion of the protocol (termination), samples and data will either be stored per institutional guidelines.

7.5 Reporting Loss or Destruction of Samples/Specimens/Data

Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that meets the definition of protocol deviation and/or compromises the

scientific integrity of the data collected for the study will be reported to the NIH IRB and local IRBs as applicable.

Subjects may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the subject and to the IRB. This decision will not affect the subject's participation in other protocols.

8 REMUNERATION PLAN

Subjects will not be compensated by the Sponsor for study participation. Local institutional guidelines and resources will apply to any site-specific considerations for reimbursement of travel, housing, or other study-related costs associated with protocol participation.

9 ASSESSMENT OF SAFETY

9.1 Definitions

Adverse Event (AE)
Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the research.

Adverse Reaction (AR)
An AE that is caused by an investigational agent (drug or biologic).

Suspected Adverse Reaction (SAR)
An AE for which there is a reasonable possibility that the investigational agent caused the AE. 'Reasonable possibility' means that there is evidence to suggest a causal relationship between the investigational agent and the AE. An SAR implies a lesser degree of certainty about causality than AR, which implies a high degree of certainty.

Serious Adverse Event (SAE)
An SAE is an AE that results in one or more of the following outcomes:

- death
- a life-threatening event (places the subject at an immediate risk of death from the event as it occurred)
- an inpatient hospitalization or prolongation of an existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly/birth defect
- a medically important event*

* Medical and scientific judgment should be exercised in characterizing events that may not be immediately life threatening or result in death or hospitalization but may

jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Unexpected Adverse Event
An AE is unexpected if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. It is the responsibility of the IND Sponsor to make this determination.

Serious and Unexpected Suspected Adverse Reaction (SUSAR)
A SUSAR is a SAR that is both serious and unexpected.

Unanticipated Problem (UP)
A UP is any event, incident, experience, or outcome that is

1. unexpected in terms of nature, severity, or frequency in relation to
    a. the research risks that are described in the IRB-approved research protocol and informed consent document, Investigator's Brochure, or other study documents; and
    b. the characteristics of the subject population being studied; and
2. possibly, probably, or definitely related to participation in the research; and
3. places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unanticipated Problem that is not an Adverse Event (UPnonAE)
A UP that does not fit the definition of an AE, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. Such events would be considered non-serious UPs. For example, we will report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

Protocol Deviation: Any change, divergence, or departure from the IRB-approved study procedures in a research protocol. Protocol deviations are designated as serious or non-serious and further characterized as:

1. Those that occur because a member of the research team deviates from the protocol.
2. Those that are identified before they occur, but cannot be prevented.
3. Those that are discovered after they occur.

Serious Protocol Deviation: A deviation that meets the definition of an SAE or compromises the safety, welfare, or rights of subjects or others.

9.2 Documenting, Recording, and Reporting Adverse Events

Sites will collect all AEs occurring from the time the informed consent is signed through the Month 1 study visit post-vaccination, and from the Month 18 booster immunization until the Month 19 visit post-boost on source documents. All grade 3 or 4 AEs will also be recorded in CRFs. Post-immunization signs or symptoms of lesser severity (i.e likely

falling into grade 1-2) occurring in the 14 day period following each injection will be solicited on the subjects' electronic diary.

At each contact with the subject, information regarding SAEs will be elicited by appropriate questioning and examinations and will be:

- documented in the subject's medical record/source document,
- recorded on the eCRF, and
- reported to the IND Sponsor as outlined below.

If a diagnosis is clinically evident (or subsequently determined), the diagnosis rather than the individual signs and symptoms or lab abnormalities will be recorded as the SAE.

9.3 Investigator Assessment of Adverse Events

The Investigator will evaluate all AEs with respect to seriousness (criteria listed above), severity (intensity or grade), and causality (relationship to study agent and relationship to research) according to the following guidelines.

9.3.1 Severity

The Investigator will grade the severity of each AE according to the FDA's Guidance "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074775.htm

9.3.2 Causality

Causality (likelihood that the event is related to the study agent) will be assessed considering the factors listed under the following categories:

Definitely Related

- reasonable temporal relationship
- follows a known response pattern
- clear evidence to suggest a causal relationship
- there is no alternative etiology

Probably Related

- reasonable temporal relationship
- follows a suspected response pattern (based on similar agents)
- no evidence of a more likely alternative etiology

Possibly Related

- reasonable temporal relationship
- little evidence for a more likely alternative etiology

Unlikely Related

- does not have a reasonable temporal relationship

OR

- good evidence for a more likely alternative etiology

Not Related

- does not have a temporal relationship

OR

- definitely due to an alternative etiology

Note: Other factors should also be considered for each causality category when appropriate. Causality assessment is based on available information at the time of the assessment of the AE. The investigator may revise the causality assessment as additional information becomes available.

9.4 Investigator Reporting Responsibilities to the Sponsor

9.4.1 Adverse Events

Grade 3 and 4 AE data will be submitted to the IND sponsor when requested for periodic safety assessments, review of IND annual reports, review of IND safety reports, and preparation of final study reports.

9.4.2 Serious Adverse Events

All SAEs (regardless of relationship and whether or not they are also UPs) must be recorded on the Safety Expedited Report Form (SERF) case report form in REDCap. Deaths and immediately life threatening SAEs must be recorded on the SERF case report form within 1 business day after the site becomes aware of the event. All other SAEs must be recorded on the SERF case report form within 3 business days of site awareness.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome is known. If it is not possible to obtain a final outcome for an SAE (e.g., the subject is lost to follow-up), the reason a final outcome could not be obtained will be recorded by the investigator on the SERF.

SAEs that occur after the study follow-up period that are reported to and are assessed by the investigator to be possibly, probably, or definitely related to study drug must be reported to the CSO.

9.4.3 Unanticipated Problems

UPs occurring in individual participants will be recorded on the UP case report form in REDCap no later than 7 calendar days of site awareness of the event. UPs must also be reported to IRBs per local requirements.

9.4.4 Pregnancy

Pregnancies occurring within one month of vaccination will be recorded on the Pregnancy Notification case report form within 1 business day from site awareness.

When known, pregnancy outcome data (e.g., delivery outcome, spontaneous or elective termination of the pregnancy) will be recorded on the Pregnancy Outcome case report form in REDCap within 3 business days of the site's awareness.

Although pregnancy itself is not an AE, events that meet SAE criteria during pregnancy, delivery, or in the neonate (e.g., congenital anomaly/birth defect) are reportable on the SERF.

In the event of pregnancy, the subject will continue to be followed as indicated by the study protocol, and the pregnancy will be reported to the IRB. The research subject will be advised to notify the obstetrician of study participation and study agent exposure.

9.5 Investigator Reporting Procedures to the IRB

9.5.1 Multi-Site Reporting Procedures

Investigators are responsible for reporting per their IRB's requirements. The IRB-specific reporting requirements are detailed in Appendix A.

9.6 Sponsor's Reporting Responsibilities

SUSARs, as defined in 21 CFR 312.32 and determined by the IND Sponsor, will be reported to FDA and all participating investigators as IND Safety Reports.

The IND Sponsor will also submit an IND Annual Report or Development Safety Update Report (DSUR) of the progress of the investigation to the FDA as defined in 21 CFR 312.33.

Grade 3 and 4 AEs that are also UPs will be summarized by the IND Sponsor and distributed to investigators if they are relevant to other sites.

9.7 Halting Rules

Halting the study requires immediate discontinuation of study agent administration and suspension of enrollment and randomization until a decision is made whether or not to continue enrollment/randomization and study agent administration. Immediate notification to the FDA is also required.

If any of the following occur, the study may be halted by the CSO:

- A previously unknown SAE, Grade 4 AE, or Grade 4 laboratory event for which no clear alternative explanation other than vaccine exists and which, in the opinion of the CSO, presents a more generalized and serious risk to the study population.
- Any serious safety issue that the principal investigator and/or the CSO determines should halt the study.

The RCHSPP CSO (Medical Monitor/equally qualified designee Medical Monitor) will communicate his/her decision to halt the study to the study principal investigator, the IND Sponsor, and the DSMB.

In addition, either the DSMB (see Section 12) or the FDA may halt the study at any time following review of any safety concerns.

Finally, a local IRB may also halt the study at their site.

9.7.1 Reporting a Study Halt

If a halting rule is identified by the study principal investigator, the CSO and/or the DSMB, a description of the AE(s) or safety issue will be reported by the CSO or designee within 1 business day of sponsor awareness to both the IND Sponsor and the site investigators. The site investigators will notify their local IRBs.

9.7.2 Resumption of a Halted Study

The DSMB will determine, and recommend to the Sponsor, whether it is safe to resume the study. The CSO (Medical Monitor or designee) will notify the site investigators of the sponsor decision on resumption of the study. The site investigators will notify their local IRBs of the decision.

9.8 Withdrawal Criteria for an Individual Subject

An individual subject will be withdrawn for any of the following:

- An individual subject's decision. (The investigator should attempt to determine the reason for the subject's decision.)
- Non-compliance with study procedures to the extent that it is potentially harmful to the subject or to the integrity of the study data.
- The investigator determines that continued participation in the study would not be in the best interest of the subject.

9.8.1 Replacement of Withdrawn Subjects

Subjects who withdraw from the study will not be replaced.

9.9 Safety Oversight

9.9.1 Safety Review and Communications Plan

A Safety Review and Communications Plan (SRCP) has been developed for the protocol. The SRCP is an internal communications document between the principal investigator and the CSO, which delineates the safety oversight responsibilities of the principal investigator, the CSO, and other stakeholders. The SRCP also includes the overall plan for conducting periodic safety surveillance assessments.

9.9.2 Sponsor Medical Monitor

A medical monitor, representing the Study Sponsor (OCRPRO), has been appointed for oversight of safety in this clinical study. The Sponsor Medical Monitor will be responsible for performing safety assessments as outlined in the SRCP.

10 SITE MONITORING PLAN

According to the International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, section 5.18, and FDA 21 CFR 312.50, clinical protocols are required to be adequately monitored by the study sponsor. This study monitoring will be conducted according to the "NIAID Intramural Clinical Monitoring Guidelines." Monitors under contract to the NIAID/OCRPRO will visit the clinical research site to monitor aspects of the study in accordance with the appropriate regulations and the approved protocol. The objectives of a monitoring visit will be: 1) to verify the existence of signed informed consent documents and documentation of the consent process for each monitored subject; 2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs; 3) to compare abstracted information with individual subjects' records and source documents (subjects' charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and 4) to help ensure investigators are in compliance with the protocol. The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections [OHRP]), FDA, and applicable guidelines (ICH GCP) are being followed. During the monitoring visits, the investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The investigator (and/or designee) will make study documents (e.g., consent forms, data abstracts) and pertinent hospital or clinical records readily available for inspection by the local IRB, the FDA, the site monitors, and the NIAID staff for confirmation of the study data.

A specific protocol monitoring plan will be discussed with the principal investigator and study staff prior to enrollment. The plan will outline the frequency of monitoring visits based on such factors as study enrollment, data collection status, and regulatory obligations.

11 STATISTICAL CONSIDERATIONS

There is uncertainty regarding the durability of the immune response following primary vaccination with the rVSVΔG-ZEBOV-GP vaccine. There is also uncertainty about the magnitude of the difference achieved at 36 months with a booster that is clinically relevant. Thus, sample size has been conservatively estimated.

Data on immunogenicity from the PREVAIL 1 trial conducted in Liberia (N Engl J Med 2017; 377:1438-1447) were used for estimating sample size for PREPARE. In PREVAIL 1, 80% of participants in the rVSVΔG-ZEBOV-GP group had at least a 4-fold increase in titer levels at 12 months. At 24 months, this percentage was 70%. Corresponding percentages for the placebo group at 12 and 24 months were 7%.

Using these data and assuming that approximately 800 participants would be randomized (1:1) in PREPARE at 18 months to boost or no boost with the rVSVΔG-ZEBOV-GP vaccine, power was 90% at the 2-sided 0.05 level of significance to detect an increase of 10% (70% to 80%) with the boost compared to the no boost group in the percentage of responders (≥ 4 fold increase between baseline and 36 months).

As the table below illustrates, geometric mean titers (GMTs) are much greater in PREPARE than in PREVAIL 1 during follow-up. At baseline, levels in PREVAIL 1 are greater than in PREPARE.

Time Point of Serology	PREVAIL 1: N, Mean	PREPARE: N, Mean
Baseline	477, 83	126, 19
Month 1	473, 1000	112, 2750
Month 6	467, 781	86, 2770
Month 12	468, 818	19, 2778
Month 18	NA	12, 2987
Month 24	424, 571	NA

As currently defined, over 90% of PREPARE participants have ≥ 4 fold increase from baseline in titer levels at each follow-up visit (range: 92%-97%).

It is now estimated that approximately 225 participants who have not been previously vaccinated with an Ebola vaccine will enroll in PREPARE and 200 of these participants will agree to be randomized at 18 months.

These preliminary data from PREPARE and the revised estimate of sample size led us to reconsider the primary outcome in PREPARE and sample size/power estimates.

Log-transformed titers at 36 months will be compared for the boost and no boost groups. With 200 participants equally allocated to the boost and no boost group at 18 months, power is 0.80 to detect a 50% higher titer level at 36 months in the boost group compared to the no boost group at the 0.05 (2-sided level of significance) (Clinical Trials 1999; 20:547-554). This sample size estimate assumes the coefficient of variation at 36 months for each group is 1.25 (range from month 1 to month 18 is 0.81 to 2.2). If the no boost group has a titer of 2,500 EU/mL at 36 months, the increase hypothesized corresponds to 1,250 EU/mL (from 2,500 to 3,750 EU/mL). Considering the titer levels for the small number of participants who reported previous vaccination with an Ebola vaccine (p.83), the magnitude of a 50% increase may be higher than 1,250 EU/mL.

The clinical relevance of such an increase remains uncertain. Should information become available on a titer level that affords protection or if another measure is found to be a correlate of protection, sample size assumptions will be reassessed. Power will also be reassessed as more information on the coefficient of variation following the boost becomes available.

SAEs will be collected for all randomized participants through 36 months. SAEs will be classified by system organ class according to MedDRA®. The total number of events and the number of participants with at least one event will be reported. Barnard's test will be used to compare SAEs by randomized treatment group after 36 months of follow-up; time-to-event methods will also be used to compare SAEs over the 36 month follow-up period. Analyses will be carried out for SAEs judged to be related to the vaccine.

Fisher's exact test will be used to compare targeted symptoms in the 2 week diaries collected after the primary and booster vaccinations at Month 1 and Month 19.

Longitudinal mixed models will be used to compare antibody levels collected at multiple follow-up time points during follow-up.. The results of any laboratory tests that are collected in the course of evaluating potential vaccine-related side effects will be graded for severity according to the DAIDS AE Table (http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/daidsaegradingtable.pdf) and the proportion with grade 3 or 4 laboratory abnormalities will be compared.

Subgroup analyses for the primary endpoint, SAEs and other safety data, will be performed to determine whether the effect of the booster differs qualitatively across various baseline-defined subgroups. Subgroup analyses will be performed by age, gender, site, and type of "at risk" occupation. An overall test of heterogeneity will provide evidence of whether the magnitude of the booster's efficacy/safety estimates vary across these baseline subgroups.

Analyses will also be carried out comparing the participants who are eligible and consent to be randomized at Month 18 with those who are not eligible and/or do not consent.

12 INDEPENDENT DATA AND SAFETY MONITORING BOARD

Data and Safety Monitoring Board (DSMB)

The NIAID Intramural DSMB includes independent experts that do not have direct involvement in the conduct of the study and have no significant conflicts of interests as defined by NIAID policy. After completion of all study visits in 2023, the Board stopped active monitoring of the protocol but the study teams plans to submit a copy of the final publication preprint to them as a courtesy when it becomes available in August 2024. Currently under discussion by the study team is whether there might be added value in further modifying the protocol and consent to invite participants in the un-boosted group to return both to assess long-term antibody levels as well as to possibly undergo a delayed homologous booster dose. No decision has been made as yet in this regard but, were this to happen, willing participants would be reconsented to this new phase. The team would then request that the Board resume review of the study data to continue their oversight of the safety, efficacy, study progress, and conduct of this new phase of the study. At that time, the study team would resume the following practices: All SAEs, all UPs, and all IND Safety Reports would be reported by the PI to the DSMB at the same time they are submitted to the IRB or IND Sponsor. The PI would notify the DSMB of any cases of intentional or unintentional unblinding as soon as possible. The PI would

notify the Board at the time pausing or halting criteria are met and obtain a recommendation concerning continuation, modification, or termination of the study. The PI would submit the written DSMB summary reports with recommendations to the IRB(s).

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Informed Consent Process

Informed consent is a process where information is presented to enable persons to voluntarily decide whether or not to participate as a research subject. It is an ongoing conversation between the human research subject and the researchers which begins before consent is given and continues until the end of the subject's involvement in the research. Discussions about the research will provide essential information about the study and include: purpose, duration, experimental procedures, alternatives, risks, and benefits. Subjects will be given the opportunity to ask questions and have them answered.

The subjects will sign the informed consent document prior to undergoing any research procedures. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The researcher will document the signing of the consent form in the subject’s medical record. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.2 Non–English-Speaking Participants

Refer to site-specific procedures in the appendices for any special provisions pertaining to enrollment of non–English-speaking participants.

13.3 Subject Confidentiality

All records will be kept confidential to the extent provided by federal, state, and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. Records will be kept locked and all computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, NIAID, the IND Sponsor, or OHRP.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Capture and Management

Study data will be maintained on CRFs and/or in an electronic database and collected directly from subjects during study visits and telephone calls, or will be abstracted from subjects’ medical records. Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary to confirm the data abstracted for this study. Data collection and entry will be performed by authorized individuals. The investigator is responsible for assuring that the data collected are complete, accurate, and recorded in a timely manner.

14.2 Record Retention

The investigator is responsible for retaining all essential documents listed in the ICH GCP guidelines. Study records will be maintained by the principal investigator for a minimum of

5 years and in compliance with institutional, IRB, state, and federal medical records retention requirements, whichever is longest. All stored records will be kept confidential to the extent required by federal, state, and local law.

Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator will provide written notification of such intent to OCRPRO/NIAID with the name of the person who will accept responsibility for the transferred records and/or their new location. Destruction or relocation of research records will not proceed without written permission from OCRPRO/NIAID.

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Appendix A. NIAID-Specific Procedures: Revised 1 September 2020

1 Participation of NIH Employees

NIH employees may participate in this study, with the following conditions:

- Neither participation nor refusal to participate in this protocol will have any effect on the subject's employment or work situation.
- The NIH information sheet regarding NIH employee research participation will be distributed to all potential subjects who are NIH employees.
- The employee subject's privacy and confidentiality will be preserved in accordance with NIH Clinical Center and NIAID policies, which define the scope and limitations of the protections.
- For NIH employee subjects, consent will be obtained by an individual independent of the employee's team. Those in a supervisory position to any employee and co-workers of the employee will not obtain consent.
- The protocol study staff will be trained annually on obtaining potentially sensitive and private information from co-workers or subordinates. This training will be reinforced as needed, at weekly team meetings.
- The Protocol and/or Site PI: Because there is at least some preclinical, NHP, and limited clinical experience to suggest that the vaccine may have some prophylactic value in preventing EVD after a serious exposure to EBOV, the protocol and/or site PI may enroll in this trial if he/she otherwise qualifies occupationally for the inclusion criteria listed for the protocol. Specifically, the reason that he/she wishes to participate is that they are currently, or shortly plan to be, in a clinical or laboratory occupation for which there is a reasonable chance of EBOV exposure in the course of those duties, and they wish to afford themselves of the possible protective benefits of pre-exposure immunization. They must meet all of the other inclusion criteria specified in the protocol. In addition to the provisions listed above in regard to handling of confidential employee information and protection of privacy, enrollment of the PI in the trial must conform to HRPP SOP 14: Research Involving NIH Staff as Subjects, specifically Section 14F.7.
- Informed consent of the protocol and/or site PI can be obtained by a nonsupervisory co-worker who is qualified based upon knowledge and expertise to do so if 1) this process is IRB approved in advance, and 2) involves a member of the staff already authorized to perform informed consent of other study participants.

1.1 Special Consideration for participants from the NIH Subsites including NIAID Rocky Mountain Lab, Hamilton, MT (RML) and Galveston National Lab at University of Texas, Galveston, TX (UTMB), University of Nebraska Medical Center (UNMC), and Boston Medical Center (BMC):

1.2

- Due to changes in funding the sites listed above will not participate as stand-alone sites for the PREPARE protocol but instead their eligible staff will be enrolled as volunteers at the NIH Clinical Center. Eligible Clinicians, Scientists, Veterinarians, and Vet Techs, and Field Personnel will travel to the NIH Clinical

Center for Day 0/Vaccination. Followup serum samples will then be drawn at the local Occupational Medicine Clinic or Quest Lab as appropriate. NIH Subsites will be trained in storing/shipping of samples by the Frederick Lab Trainers.

- Unless the participant or OMS staff has specific clinical concerns, Months 1-12 and 19-36 for these participants may be phone assessments with the Study Team at NIH in Bethesda following serum sample and site assessment at their respective OMS clinics.
- All participants can be randomized as early as Month 17 in order to be given sufficient time to plan for travel to the Clinical Center and to avoid unnecessary travel inconvenience and expense. Only those participants randomized to receive a booster dose will travel to the Clinical Center. Those randomized to 'no booster' will have all remaining serum samples drawn at their respective OMS as above.

2 IRB Reporting Procedures

Assessment of Safety

AEs and other reportable events are defined in Policy 801: Reporting Research Events.

Reporting Procedures

Unanticipated problems, non-compliance, and other reportable events will be reported to the NIAID IRB according to Policy 801.

https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs

3 Additional Assessment of Long-term Durability of Immune Response

Participants in the primary cohort of the study will be invited to re-enroll in order to assess long-term immunogenicity beyond the original Month 36 endpoint. Approximately 30 participants at the NIH Clinical Center site will be invited to re-enroll in the study in order to have a single blood draw performed to generate serum that will be evaluated by either the FANG or the Quanterix assay for current anti-GP antibody titer levels. As an additional option participants will also be asked to donate PBMCs at this blood draw to facilitate further evaluation of the B-cell response to the study vaccine as a complement to ongoing studies.

Inasmuch as participation in this long term blood draw is voluntary and the numbers of participants falling into the two original study arms (i.e. booster dose at Month 18 versus no booster dose) may or may not be balanced, there are no plans to undertake formal statistical analysis of these late titers in comparison to the Month 0-36 titers previously measured and analyzed. However, participants will be informed of their individual titer results, and those with particularly low titer levels may wish to consult with the Occupational Medical Service as to whether a booster dose of *Ervebo* may be indicated in advance of the next outbreak of EVD or as pre-exposure prophylaxis in advance of BioSafety Level 4 work involving EVOD.

Appendix B: List of Proposed Study Sites and Points of Contact

Proposed Study Site	Point of Contact	Contact Information
NIH Clinical Center, Bethesda, MD	Richard T. Davey, Jr., M.D.	rdavey@niaid.nih.gov 301-496-8029 301-728-0851
NIAID Rocky Mountain Laboratory (NIH Clinical Center subsite)	James Schmitt,M.D.	schmittj@mail.nih.gov 301-496-4411
University of Texas Medical Branch, Galveston, TX (FWA00002729) (NIH Clinical Center subsite)	Susan McClellan, MD, MPH	sumclell@utmb.edu Galveston National Laboratory University of Texas Medical Branch Galveston, TX 77555-0610 (409) 747-0236
University of Nebraska Medical Center, Omaha, NE (FWA#00002939) (NIH Clinical Center subsite)	Angela Hewlett, MD	alhewlett@unmc.edu 985400 Nebraska Medical Center Omaha, NE 68198-5400 (402) 559-8650
Boston Medical Center/Boston University (FWA#00000301) (NIH Clinical Center subsite)	Nahid Bhadelia, MD	nbhadeli@bu.edu National Emerging Infectious Diseases Laboratories, Boston University, Boston, MA 02118 (617) 414-5201
The Hope Clinic of the Emory Vaccine Center, Emory University Atlanta, GA (FWA00005792) and Centers for Disease Control and Prevention	Nadine Rouphael, MD	nroupha@emory.edu The Hope Clinic of the Emory Vaccine Center, Emory University 500 Irvin Court, Suite 200 Decatur, GA 30030 404-712-1435
Public Health Agency of Canada, Winnipeg	Guillaume Poliquin, MD	guillaume.poliquin@phac-aspc.gc.ca 204-789-7054 539 John Buhler Research Center 715 McDermitt Avenue Winnipeg, Manitoba R3E 3P4

17 January 2019

Appendix C: Protocol Modifications Applicable Exclusively to Staff Traveling to an area of current Ebola outbreak

On 8 May 2018, the Ministry of Health and Population (MoHP) of the Democratic Republic of Congo (DRC) confirmed an outbreak of Ebola Virus Disease (EVD) in the Bikoro area of Equateur Province, which lies in Northwest DRC, following confirmation by the Institut National de Recherche Biomédicale (INRB), Kinshasa. As of 17 January 2019, there have been 680 cases reported, including 410 deaths. Five health zones, Bikoro, Iboko, the provincial capital Mbandaka, Ingende, and Ntondo, are now suspected to be affected; however, no cases in Ntondo and Ingende have yet been identified. WHO has developed a plan to provide a rapid localized control of EVD in Bikoro. Partners engaged in the response to date include MSF, IFRC, UNICEF, CDC and USAID. The immediate actions are to establish an outbreak response platform, implement surge capacity and develop a communications strategy. The WHO is supporting the MoHP in coordinating the overall response and is establishing an Incident Management System (IMS). The WHO is also preparing to conduct EVD preparedness and readiness activities in nine neighboring countries: Angola, Burundi, Central African Republic, Congo, Rwanda, South Sudan, Tanzania, Uganda, and Zambia. The CDC is working with MSF, DRC MoHP, INRB, and WHO to identify priority areas for support.

Because of this outbreak, a coordinated response by USG agencies, non-governmental partners, and various international health groups is already underway. Although the full scope of this initiative is still unfolding at present, it is anticipated that domestic US and Canadian government and non-government health care workers, laboratory staff, logistics coordinators, European and other international health care staff, and other staff will need to be deployed to the affected region(s) in Africa. However, because of the unanticipated emergence and rapidity of this latest outbreak, some at-risk personnel otherwise eligible for enrollment in the PREPARE protocol – i.e., a group who potentially may derive the greatest benefit from pre-exposure prophylaxis with the study product - may not meet all of the current eligibility criteria. Specifically, in order to limit elements that conceivably could blunt or otherwise affect the overall antibody response to the Merck vaccine (both primary and booster), the protocol currently excludes concomitant or closely-spaced immunization with other vaccine products: that is, participants may not have received vaccination with a killed vaccine within 14 days of the Merck product, or within 30 days for those who have received a live virus vaccination. Unfortunately, it appears likely that some of the staff being considered for imminent deployment, or those whose deployment status and dates of departure are uncertain, must also often receive other vaccinations (e.g., tetanus, Yellow Fever, hepatitis A and B, typhoid, etc.) on relatively short notice that are felt necessary to

offer them optimal protection against pathogens other than Ebola virus to which they might also be exposed while serving in DRC or, potentially, in other affected regions of Africa. For this special group of protocol enrollees for whom an alternative or staggered vaccination schedule is not feasible, and while acknowledging that the full breadth of their antibody response to the Merck vaccine could be adversely affected by this change, the protocol eligibility criteria are being revised as follows:

- Exclusively for at-risk staff being considered for deployment within 30 days of enrollment for whom the benefit-risk assessment is favorable as judged by the investigator, we will remove the restriction against concomitant receipt of killed vaccine and live viral vaccines within 14 and 30 days, respectively, of immunization with the Merck vaccine.
- Participants will be informed that we do not know what effect the removal of this restriction may have on their anti-GP antibody titers if they receive other vaccines in close proximity to the study vaccine.
- Females of reproductive potential (as defined in the main protocol) are specifically exempt for 30 day pre-dose contraception if, in the view of the investigator, they provide a reliable history of meeting the inclusion requirement as follows at the time of dosing and have a negative pregnancy test on the day of immunization:
    - abstinence from potentially reproductive sexual contact [i.e. has NOT engaged in heterosexual intercourse where both partners are capable of reproduction] for the 30 days pre-exposure to study vaccine
- If participants <u>are</u> to receive another live viral vaccine (e.g., Yellow Fever vaccine), whenever possible that vaccine should be administered on the same day as the Merck vaccine.
- All other vaccines (killed) can either be administered on the same day as the Merck vaccine or on any other day prior to deployment.
- Every effort will be made to continue the full set of safety assessments defined post-immunization in the protocol, although the data capture means (e.g. REDCap) to do so may need adjustment to the field conditions associated with deployment.
- This provision for exemption to the full eligibility criteria will continue until the current outbreak in DRC or in other affected regions is declared to be contained and/or no other staff deployments are under consideration, whichever comes first, but may be applied for future similar outbreaks as necessary.
- Due to the unpredictable nature of deployments under field conditions, it is possible that some participants may not be able to comply fully with the protocol-defined schedule of study assessments and blood draws, although every reasonable effort should be made to do so.
- In the final statistical analysis plan to be developed for the primary and secondary outcomes of the study, appropriate consideration will be given as to whether the safety and immunogenicity data pertaining to this special group of enrollees should be handled separately from those data collected for other study

participants. Immunogenicity following co-administration of rVSVΔG-ZEBOV-GP vaccine (V920) with vaccines commonly administered to travelers and relief workers (e.g. tetanus, Yellow Fever, hepatitis A, etc.) will be described. Potential enrollees not qualifying for these special exemptions during this time period must continue to meet all eligibility criteria as defined in the main body of the protocol.

- Finally, participants exempted from these concomitant vaccine restrictions during their primary immunization with the Merck vaccine will not be exempted from these restrictions at the time of eligibility determination for their randomized booster dose, assuming no similar outbreak conditions exist at that time to justify that exemption.