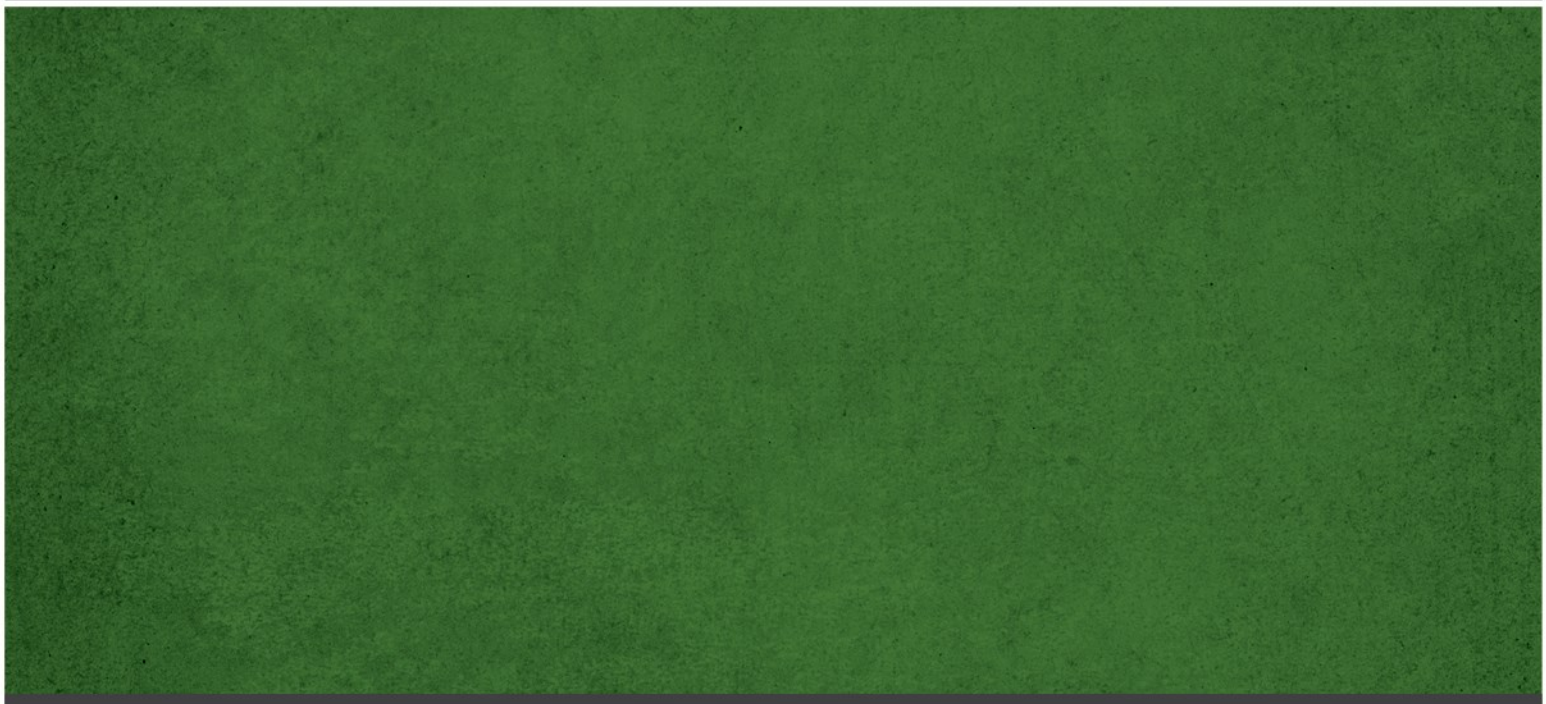
An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Interim Statement on the Use of the rVSVΔG-ZEBOV-GP Vaccine for the Prevention of Ebola Virus Disease



PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :
Déclaration provisoire sur l'utilisation du vaccin rVSVΔG-ZEBOV-GP pour la prévention de la maladie à virus Ebola

This publication can be made available in alternative formats upon request.

Publication date: January 2020

Cat.: HP40-261/2019E-PDF
ISBN: 978-0-660-33149-2
Pub.: 190428

PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

In addition to burden of disease and vaccine characteristics, PHAC has expanded the mandate of NACI to include the systematic consideration of programmatic factors in developing evidence-based recommendations to facilitate timely decision-making for publicly funded vaccine programs at provincial and territorial levels.

The additional factors to be systematically considered by NACI include: economics, ethics, equity, feasibility, and acceptability. Over the coming years NACI will be refining methodological approaches to include these factors. Not all NACI statements will require in-depth analyses of all programmatic factors. As NACI works towards full implementation of the expanded mandate, select statements will include varying degrees of programmatic analyses for public health programs.

PHAC acknowledges that the advice and recommendations set out in this interim statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. As the advice is provided for an ***investigational product that has not yet received regulatory authorization for sale in Canada***, people administering the pre-market vaccine should also be aware of the contents of the pharmacy manual and investigator's brochure provided by the manufacturer. Recommendations for use and other information set out herein may differ from that set out in the pharmacy manual and investigator's brochure of the pre-market vaccine. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

TABLE OF CONTENTS

SUMMARY OF INFORMATION CONTAINED IN THIS NACI INTERIM STATEMENT

The following highlights key information for vaccine providers. Please refer to the remainder of the interim statement for details.

What

Merck's investigational rVSVΔG-ZEBOV-GP vaccine (also referred to as the V920 Ebola Zaire Vaccine and Ervebo) is a live-attenuated, recombinant *vesicular stomatitis virus* (rVSV)-based vector vaccine against *Zaire ebolavirus* (ZEBOV). A limited quantity of this pre-market vaccine is stockpiled in Canada's National Emergency Strategic Stockpile (NESS). *This vaccine does not currently have Health Canada authorization for sale in Canada and has been imported through Health Canada's Special Access Programme.*

Who

This interim advisory committee statement addresses the emergency use of the pre-market rVSVΔG-ZEBOV-GP vaccine stockpiled in the NESS for protection against Ebola virus disease (EVD) caused by ZEBOV infection. The interim recommendations include use in non-pregnant immunocompetent adults; pregnant women; infants, children, and adolescents; and immunocompromised individuals.

How

NACI makes the following interim recommendations for post-exposure prophylaxis against ZEBOV for the pre-market rVSVΔG-ZEBOV-GP vaccine stockpiled in the NESS:

- The vaccine should be offered to non-pregnant immunocompetent adults who have had an exposure to ZEBOV in Canada; and
- The vaccine may be considered for pregnant women, infants, children, adolescents, and immunocompromised individuals who have had an exposure to ZEBOV in Canada.

NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine stockpiled in the NESS may be considered as pre-exposure prophylaxis against ZEBOV for non-pregnant immunocompetent adults in exceptional situations when a dedicated team of healthcare workers is anticipated to provide direct care for a confirmed case with symptomatic ZEBOV infection, if vaccine is available.

Why

EVD is a rare, severe, acute viral illness with a case fatality rate in humans ranging from 25–90%. Although uncertainties around safety, immunogenicity, efficacy, and effectiveness remain, vaccination with the rVSVΔG-ZEBOV-GP vaccine currently offers the best available protection against EVD caused by ZEBOV infection given the potential for severe harm from EVD and few options for reducing case fatality. The rVSVΔG-ZEBOV-GP vaccine has shown few serious adverse events, despite a high degree of reactogenicity, and is immunogenic in non-pregnant immunocompetent adults. The vaccine has been shown to be efficacious in preventing EVD in the context of community outbreaks, if symptoms of EVD did not appear within 10 days of vaccination.

I. INTRODUCTION

Ebola virus disease (EVD) is a rare, severe, acute viral illness in humans and non-human primates caused by ribonucleic acid viruses from the genus *Ebolavirus*, a member of the *Filoviridae* family [1]. Of the five well-described *Ebolavirus* species, four are known to cause illness in humans. The *Zaire ebolavirus* (ZEBOV) is considered the most virulent of these species, having the highest case fatality rate and being responsible for the majority of outbreaks to date.

EVD has an incubation period of 2–21 days, with most cases experiencing onset of symptoms around 4–10 days after exposure. Within 10 days of symptom onset, fatal cases will experience severe symptoms and succumb to the disease. Symptoms usually begin with a sudden onset of flu-like symptoms, such as fever, myalgia, severe headache, and malaise, typically followed by worsening gastrointestinal symptoms and fluid loss. Haemorrhage is a late manifestation and, in recent outbreaks, occurs in fewer than half of cases, usually from the gastrointestinal tract or other mucosa. Case fatality in humans ranges from 25–90%.

Non-fatal cases typically begin recovery 6–11 days after onset of symptoms. Full recovery occurs over a long period of time and is often associated with long-term sequelae. During recovery, *Ebolavirus* can persist in some body fluids such as semen, urine, and breast milk. Follow-up of a cohort of EVD survivors in Liberia has demonstrated persistence of ZEBOV in semen for up to 40 months with a range of 233 to 1178 days and a median of 551 days [2]. Viral relapse can also occur [3].

Infectiousness starts from the time of symptom onset and the risk of transmission is highest when viral load is greatest. Person-to-person transmission can occur through direct physical contact with body fluids from an infected symptomatic person or dead body, or indirectly through physical contact with surfaces and fomites that are contaminated with these fluids. With the exception of the potential for sexual transmission during the convalescent period, *Ebolavirus* has not been demonstrated to spread to others by an asymptomatic person. *Ebolavirus* is not transmitted between humans through casual interactions or airborne transmission, but can be transmitted by aerosol-generating medical procedures.

EVD has generally been geographically limited to outbreak-prone areas of sub-Saharan Africa. Between 1976 and 2012, sporadic cases and outbreaks of EVD were reported in several African countries. During the 2014–2016 West Africa EVD outbreak, the largest recorded outbreak of EVD to date, imported cases were identified in other countries in Africa, Europe, and North America. Limited secondary transmission in the United States and Spain from cases that have travelled from Africa has been reported [4, 5]. There has been an ongoing outbreak of EVD since August 2018 in the Democratic Republic of the Congo (DRC), which is the second largest outbreak at the time of writing. No cases of EVD have been identified in Canada to date.

With the ongoing outbreak of EVD in the DRC, it is possible that Canada will receive an imported case of EVD prior to the authorization of a vaccine for EVD by Health Canada. As part of contingency planning for an imported EVD case, the Public Health Agency of Canada (PHAC) has procured Merck's investigational vaccine for EVD, the rVSVΔG-ZEBOV-GP vaccine (also referred to as the V920 Ebola Zaire Vaccine and Ervebo), for the National Emergency Strategic Stockpile (NESS) through Health Canada's Special Access Programme. On recommendation of the European Medicines Agency (EMA), the European Commission granted a conditional marketing authorization for this vaccine on November 11, 2019 and the World

Health Organization (WHO) prequalified the vaccine (i.e., the vaccine met WHO's standards for quality, safety, and efficacy) on November 12, 2019. The rVSVΔG-ZEBOV-GP vaccine was approved by the United States Food and Drug Administration on December 19, 2019. NACI generally issues guidance only for immunizing agents that have been authorized by Health Canada. However, in this exceptional circumstance, PHAC has requested pre-market guidance from NACI on this investigational product because a limited quantity has been stockpiled in Canada for emergency use.

Merck's rVSVΔG-ZEBOV-GP vaccine is a live-attenuated, recombinant *vesicular stomatitis virus* (rVSV)-based vector vaccine, in which the vaccine vector's envelope glycoprotein (GP) is deleted and replaced with the ZEBOV envelope GP. The vaccine does not contain live ZEBOV. Many clinical trials have been completed using Merck's investigational vaccine, including dose-ranging trials to assess its safety and immunogenicity and a large cluster-randomized trial to evaluate its efficacy during the 2014–2016 West Africa outbreak.

There are several other investigational vaccines for EVD undergoing human trials [(6)], but the rVSVΔG-ZEBOV-GP vaccine is the only one that is currently in widespread use despite its investigational status. The rVSVΔG-ZEBOV-GP vaccine has been available on compassionate grounds for both the 2014–2016 West Africa outbreak and the ongoing outbreak in the DRC. As of November 16, 2019, 253,545 people at risk in the DRC have received the vaccine [(7)].

For the DRC outbreak, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization recommended a "ring vaccination" strategy to protect those at highest risk of EVD in the outbreak [(8)]. Ring vaccination involves contact tracing and vaccination of the contacts of an EVD case and the contacts of those contacts. As the situation in the DRC deteriorated in early 2019, additional vaccination strategies have been recommended for outbreak control [(9)]. These recommendations were devised for the epidemiological and public health situation in Africa and therefore are not directly applicable for the Canadian context.

Further details on EVD, including outbreak updates, can be found on the Government of Canada website.

Guidance objective

The objective of this advisory committee interim statement is to review the safety, immunogenicity, efficacy, and effectiveness evidence available for the rVSVΔG-ZEBOV-GP vaccine and to provide interim guidance on the emergency use of this pre-market vaccine stockpiled in the NESS for the prevention of severe disease in individuals exposed to ZEBOV.

Advice on the following are outside the scope of NACI's mandate and therefore are not addressed in this interim statement:

a) vaccination of travellers to areas outside of Canada that are prone to EVD outbreaks[*];
b) the use of passive immunizing agents such as ZMapp for treating EVD;
c) symptom management and clinical treatment of EVD;
d) stockpile recommendations; and
e) infection prevention and control (IPC) measures for EVD.

[*] The Committee to Advise on Tropical Medicine and Travel (CATMAT) is the external advisory body that assists PHAC with travel health-related advice, including advice on pre-travel vaccinations.

II. METHODS

In brief, the broad stages in the preparation of a NACI advisory committee statement are:

1. Knowledge synthesis;
2. Synthesis of the body of evidence of benefits and harms, considering the quality of the evidence and magnitude of effects observed; and
3. Translation of evidence into a recommendation.

Details regarding NACI's evidence-based process for developing a statement are outlined in Evidence-based Recommendations for Immunization − Methods of the National Advisory Committee on Immunization.

Rapid reviews were conducted on the safety, immunogenicity, efficacy, and effectiveness of the rVSVΔG-ZEBOV-GP vaccine in humans and non-human primates and the effectiveness of the ring vaccination strategy in preventing EVD transmission. The search strategy was developed in consultation with a librarian from the Health Library of Health Canada and PHAC and included two separate searches (search strategies can be found in Appendix A). One search included terms specific to the rVSVΔG-ZEBOV-GP vaccine and the other included terms for ring vaccination. The literature searches were performed in 12 bibliographic databases and one clinical trial database. The searches were restricted to studies published in English or French. No publication date restrictions were applied. The final database search was executed on March 29, 2019 for the rVSVΔG-ZEBOV-GP vaccine and March 14, 2019 for ring vaccination. Hand searches of the reference lists of included articles and relevant reviews were performed. As the rVSVΔG-ZEBOV-GP vaccine has not yet been licensed for use in any jurisdiction at the time of literature review, adverse event reporting for this pre-market vaccine are not expected through passive vaccine safety surveillance systems such as the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) and therefore these surveillance systems were not searched for case reports.

Articles retrieved from the searches were screened by title and abstract. The full text of articles deemed relevant based on inclusion and exclusion criteria, or that had insufficient information to exclude, were retrieved and assessed for eligibility through full-text screening. Study selection was completed independently by two reviewers. Disagreements between the two reviewers were resolved by discussion and reaching a consensus. Data from included studies were extracted into evidence tables. The quality of evidence for individual studies and for the body of evidence was assessed using the criteria outlined by Harris et al. [10]. Data extraction and quality assessment were both completed by one reviewer and verified by a second reviewer. Results from included studies were synthesized narratively in the evidence tables. Geometric mean titre (GMT) values for varying dose levels of the rVSVΔG-ZEBOV-GP vaccine were extracted separately.

Knowledge synthesis was performed by LZ and AK. Proposed recommendations for vaccine use were developed by NACI's EVD Vaccine Working Group and reviewed for input by NACI's Vaccine Safety Working Group, the Canadian Immunization Committee, the Council of Chief Medical Officers of Health, and the EVD-Clinical Treatment Centre Task Group. The manufacturer was invited to present preclinical and clinical data for their vaccine to the EVD Vaccine Working Group on May 7, 2019 and was further consulted to identify additional safety data for the following special populations: pregnant and breastfeeding women, infants, children, adolescents, and immunocompromised individuals. A PHAC technical advisor (LZ) presented

the findings of the knowledge synthesis to NACI on June 6, 2019. The evidence and proposed recommendations were discussed by the NACI EVD Vaccine Working Group in June and July 2019 and the proposed recommendations were deliberated by NACI on July 31, 2019. Given that this is a pre-market vaccine, NACI's Vaccine Safety Working Group was also consulted in June 2019 on the proposed recommendations. Following thorough review of the evidence and assessing the risk-benefit of vaccination with the pre-market vaccine, NACI reached consensus on specific recommendations. As part of the standard pre-release process for NACI statements, the manufacturer was consulted to identify any factual errors contained in the interim statement prior to publication. The descriptions of relevant considerations, rationale, and knowledge gaps on the use of the pre-market rVSVΔG-ZEBOV-GP vaccine are described in the following sections.

III. VACCINE

A flow diagram of the study selection process can be found in Appendix B. After database searching, hand searching, and eligibility screening, 37 studies—26 studies in humans [11-30, 41-44] and 11 studies in non-human primates, including an unpublished study not reported here [31-40]— were included for review. Of the 26 studies in humans, 19 studies reported on unique subjects [12-16, 19-21, 24-29, 41-44] while the remainder offered supplemental data or provided additional analyses. Of these 19 studies, there were seven phase 1 dose-ranging clinical trials [12-16, 19] (five were randomized placebo-controlled [12-16, 19]), one phase 2 randomized controlled trial [20] (the phase 3 component of this study was cancelled due to declining EVD cases), three phase 3 randomized controlled trials [21, 24, 25] (two were cluster-randomized comparing immediate to delayed vaccination [21, 24]), three ring vaccination field studies [26, 27, 44], two prospective cohort studies [29, 41], one cross-sectional survey on safety [42], and two case reports of post-exposure prophylaxis (PEP) following needlestick or sharps injuries [28, 43]. The total vaccinated sample sizes by dose and outcome for the studies conducted in humans are tabulated in Table 1. The majority of subjects received the 2×10^7 plaque-forming unit (PFU) dose, which is the nominal dose of the vaccine deployed for use in the 2014–2016 West Africa outbreak and in the ongoing outbreak in the DRC. Safety information that was presented to the Global Advisory Committee on Vaccine Safety on June 5–6, 2019 [45] are included to supplement the review findings.

Six modelling studies were also identified that modeled the effects of ring vaccination on control of EVD outbreaks in the African context [46-51]. These modeling studies were reviewed by NACI, but are not further discussed in this interim statement as the findings do not directly relate to the Canadian context.

Table 1: Vaccinated sample sizes of studies in humans by dose level of the rVSVΔG-ZEBOV-GP vaccine and outcome*

Dose level (PFU)**	Number of studies reporting on efficacy or effectiveness (vaccinated sample size)	Number of studies reporting on immunogenicity (vaccinated sample size)	Number of studies reporting on safety (vaccinated sample size)
3×10^3	n/a	2 (n=84)	3 (n=104)
3×10^4	n/a	2 (n=84)	2 (n=84)
1×10^5	n/a	1 (n=10)	1 (n=10)
3×10^5	n/a	3 (n=135)	4 (n=145)
5×10^5	n/a	1 (n=10)	1 (n=10)
3×10^6	n/a	6 (n=169)	5 (n=159)
9×10^6	n/a	1 (n=50)	1 (n=50)
1×10^7	n/a	1 (n=35)	1 (n=35)
2×10^7	4 (n=99,049)	8 (n=1652)	13 (n=150,204)***
5×10^7	n/a	1 (n=16)	2 (n=17)
1×10^8	n/a	3 (n=319)	4 (n=341)

Abbreviations: n/a: not available; PFU: plaque-forming unit.

* Total vaccinated sample sizes by dose level and outcome are approximated based on the number of study subjects planned to be given the vaccine. These numbers are based on published articles included for review and therefore may differ from other tabulated sources.

** Dose values are based on the vaccine potencies reported in the included studies. These dose values may not correspond directly to the potency of the pre-market vaccine product available for use in Canada.

*** The vaccinated sample size for this dose level includes an estimated 130,000 individuals who were vaccinated in the DRC [45].

Most included studies with evaluable study designs according to the Harris et al. criteria [10] received a "good" rating, with the exception of two studies receiving a "fair" rating due to interruptions in study protocol [15, 21]. For all other study designs that were not evaluable with the Harris et al. criteria, no critical flaws were noted besides the intrinsic limitations of those designs.

Extracted study data are presented in the evidence table in Appendix C for human studies and Appendix D for non-human primate studies (data from an unpublished study in non-human primates are not summarized in the evidence table). GMT point estimates and corresponding 95% confidence intervals (95% CI) from the human studies for the varying dose levels of the rVSVΔG-ZEBOV-GP vaccine are summarized in Appendix E. The overall patterns in the data are described for the outcomes of interest in the following sections.

III.1 EFFICACY AND EFFECTIVENESS

Four studies assessed vaccine efficacy or effectiveness in humans in the context of ring vaccination [21, 26, 27, 44]. Two case reports described PEP of healthcare or laboratory workers following high-risk needlestick or sharps injuries [28, 43]. Six studies looking at survival following lethal ZEBOV challenge after pre-exposure prophylaxis (PrEP) [32-36, 40] and two studies looking at survival following PEP after lethal ZEBOV challenge [31, 38] were conducted in non-human primates.

Ring vaccination

Ring vaccination, originally used for smallpox control and eradication, has been used broadly as an outbreak control measure in response to EVD activity. Ring vaccination involves tracking the epidemic and recruiting individuals at increased risk of infection based on their connection to a confirmed case of disease [52]. Ring vaccination typically includes a mix of PEP and PrEP based on confirmed and anticipated (e.g., for healthcare and frontline workers) exposure, respectively, for contacts of cases and contacts of those contacts.

In a phase 3 cluster randomized ring vaccination trial conducted in Guinea during the 2014–2016 West Africa outbreak, vaccine efficacy against EVD occurring 10 or more days after randomization was 100% (95% CI: 77.0–100.0%) comparing all vaccinated contacts and contacts of contacts randomized to receive the vaccine immediately (n=3775) with all contacts and contacts of contacts randomized to receive the vaccine 21 days after randomization and never-vaccinated (n=7995) [21]. The overall vaccine effectiveness in protecting all contacts and contacts of contacts in the randomized clusters (including unvaccinated cluster members; n=4513 immediate and 4529 delayed vaccination) against onset of EVD 10 days or more from randomization was 64.6% (95% CI: -44.2–91.3%). EVD cases occurred at similar attack rates within the first 10 days after randomization regardless of vaccination status; 11 cases among immediately vaccinated adults (0.5%) and 21 cases among all eligible adults assigned to delayed vaccination (0.7%) had onset of symptoms within 10 days of randomization. No cases of EVD occurred 10 days or more after randomization in the immediately vaccinated clusters compared with 16 cases among eligible individuals in delayed clusters. Vaccine effectiveness at 10 days or more post-vaccination against death due to EVD was 100%.

The preliminary estimate of vaccine effectiveness from the ongoing compassionate use ring vaccination program in the DRC (n=93,965 vaccinated) against onset of illness 10 days or more post-vaccination was 97.5% (95% CI: 95.8–98.5%) [44]. There were 71 cases of EVD among vaccinated individuals; 56 developed symptoms within 10 days of vaccination and only nine of these individuals died while 15 individuals developed symptoms 10 days or later following vaccination and none of these individuals died. Vaccine effectiveness at 10 days or more post-vaccination against death due to EVD was also 100% in this study.

Results from these ring vaccination studies suggest that the vaccine was efficacious in preventing EVD, if symptoms of EVD did not appear within 10 days of vaccination. Based on these study findings, 10 days is the time after which vaccinees are assumed to be protected whereas less than 10 days post-vaccination is the period where vaccinees are not protected or partially protected [44]. Correlation between immune response and protection was not investigated in these studies. Ring vaccination was also found to be effective in contributing to outbreak control. However, the relative impact of vaccination on outbreak control compared to other factors (e.g., declining incidence of EVD, other public health measures) was not determined. Furthermore, as these studies were performed during ongoing community-based outbreaks and included contacts who may not have had a high-risk interaction with an index case, the study findings provide evidence of protection but do not differentiate whether it is pre- or post-exposure protection. Two other ring vaccination studies conducted during community-based outbreaks of ZEBOV in Guinea (n=1510 vaccinated) [27] and Liberia (n=210 vaccinated) [26] did not identify secondary cases of EVD occurring among vaccine recipients. These two studies were not designed to assess the impact of vaccination on outbreak control.

The characteristics of the rings, or clusters, that comprise these ring vaccination studies were expectedly heterogeneous: 73–96% of contacts were contacts of contacts (i.e., secondary

contacts), 4–27% of contacts were high-risk contacts (i.e., had close physical contact with an EVD case's body, body fluids, linens, or clothing), 7–20% of contacts were healthcare or frontline workers, median number of days from confirmation of EVD in the index case to vaccination of contacts ranged from 7–15 days, and cluster sizes ranged from several dozen to several hundred people [21, 26, 27, 44]. Pregnant or breastfeeding women and children under six years of age were excluded from receiving the vaccine in these studies. Vaccine efficacy or effectiveness for children and adolescents 6–17 years of age and immunocompromised individuals were not separately reported.

Prophylaxis after needlestick or sharps injury

There are several case reports of PEP following needlestick or sharps injuries. A laboratory worker was vaccinated with a 5×10^7 PFU dose 48 hours after needlestick injury with a syringe containing live ZEBOV [28]. Five healthcare workers were vaccinated with a 1×10^8 PFU dose 1–3 days after potential ZEBOV exposure resulting from sharps injuries sustained in West Africa [43]. These exposures did not result in evidence of infection, but it is not possible to determine whether this was due to vaccine effect or lack of transmission following the needlestick injury.

Efficacy in non-human primates

For PrEP, complete protection was achieved with the vaccine (mostly at the 1×10^7 PFU dose) given 7–28 days before intramuscularly-administered lethal ZEBOV challenge (1000 PFU) [32, 34-36, 40] and partial protection was achieved with the vaccine (5×10^7 PFU dose) given three days before lethal challenge in healthy animals [36]. Partial protection was also achieved with the vaccine (1×10^7 PFU dose) given 31 days before lethal challenge in immunodeficient SHIV-infected animals [33].

For PEP, one study found that 50% of animals survived without showing signs of severe disease after vaccination (2×10^7 PFU dose) within 20–30 minutes of lethal challenge while both controls died [31]. Another study found no difference in survival among vaccinated (2×10^7 PFU dose) or control groups when vaccinated at 1 hour and/or 24 hours after lethal challenge [38].

III.2 IMMUNOGENICITY

Ten studies evaluated immunogenicity following vaccination with the rVSVΔG-ZEBOV-GP vaccine of varying dose levels in humans [12-16, 19, 20, 26, 29] and eight studies assessed immunogenicity following vaccination in non-human primates [31-37, 40]. It is important to note that no immunological correlate of protection has been established for EVD, so it is difficult to interpret immunogenicity findings in the context of disease prevention.

Immunoglobulin G antibody response

The most robustly assessed immunogenicity outcome was the ZEBOV envelope GP-specific immunoglobulin G (IgG) antibody response [12-16, 19, 20, 26, 29]. Most subjects seroconverted (i.e., had a four-fold or greater increase from baseline titre) by day 14 post-vaccination and all subjects seroconverted by day 28 regardless of dose. There was a high degree of inter-individual variability in IgG antibody response regardless of dose. A dose-response relationship was observed with the speed and amplitude of response. However, there appeared to be diminishing marginal antibody response with increasing dose; GMTs were similar at higher

doses due to the wide and overlapping 95% CI, suggesting a plateau of the dose-response curve at higher doses. One trial found a potential age-response relationship, where children and adolescents 6–17 years of age were observed to respond slower than adults [19]. GMTs generally peaked by day 28 and persisted to 1–2 years post-vaccination without significant decline and without significant difference across dose levels. Persistence of IgG antibody response beyond two years after vaccination is unknown. There are ongoing studies looking at antibody persistence up to three [53] or five [54, 55] years following primary vaccination. A protective threshold of IgG antibody response has not been established.

A phase 1 dose-ranging trial looking at a two-dose regimen given on days 0 and 28 found that the second dose was associated with a short-term advantage with respect to the amplitude of response, but there was no significant difference in long-term titres between one- and two-dose regimens [12]. Anamnestic response following a booster dose more than 28 days after the priming dose has not been characterized. There are currently ongoing studies investigating a booster given at 56 days [55] or 18 months [53].

Seroconversion rates at one-month post-vaccination was found to be significantly lower in a small sample of HIV-infected adults (n=13) compared to non-HIV-infected adults (n=383) in Liberia [20]. There is currently a phase 2 randomized controlled trial in progress evaluating the safety and immunogenicity of the vaccine in HIV-infected adults and adolescents at two Canadian sites and two African sites (Burkina Faso and Senegal) [56]. Immunogenicity data for pregnant and breastfeeding women, infants, children under six years of age, and persons with other immunocompromising conditions are not available.

Neutralizing antibody response

Several phase 1 clinical trials also looked at neutralizing antibody responses [12-16, 19]. The neutralizing antibody response appeared to be well-correlated with the IgG response; there was a dose-dependent response, with titres peaking at day 28 post-vaccination, and some evidence of persistence over 6 months–2 years. A neutralizing antibody protective threshold has not been established.

Other immune response outcomes

A few studies were identified that investigated cell-mediated responses and changes to cytokine profiles and circulating host microRNA following vaccination. A dose-dependent CD169 expression was observed, suggesting a dose effect in monocyte activation [15]. Both CD4+ and CD8+ T cells showed increased activity post-vaccination [17]. Circulating follicular T helper cells were correlated with IgG titres [11]. One study found that vaccination led to a skewing in the cytokine profiles that promote humoral immune responses [11]. Another study found a significant induction of cytokines involved in the promotion of cell-mediated response, activation of antigen-presenting cells, and growth and survival of antigen-specific cytotoxic T lymphocytes [17]. Higher doses were found to elicit stronger interlocked cytokine networks compared with lower doses [17]. Vaccination was also found to be accompanied by dose-dependent changes in circulating host microRNA [18]. The importance and impact of these responses have not been elucidated.

Immunogenicity in non-human primates

For PrEP, modest IgG titres were detected in most animals by day 28 post-vaccination (day of lethal ZEBOV challenge) [31-36, 38, 40], including in immunodeficient SHIV-infected animals [33],

whereas neutralizing antibody was not detectable in most animals [31, 35, 36, 40]. A depletion study revealed a minimal role for CD8+ T cell immunity in vaccine-mediated protection [37].

For PEP, IgG titres were detectable between 1–2 weeks after vaccination at 20–30 minutes, 1 hour, or 24 hours after lethal ZEBOV challenge [31, 38].

III.3 SAFETY

Sixteen studies evaluated safety following vaccination with the rVSVΔG-ZEBOV-GP vaccine of varying dose levels in humans [12-16, 19-21, 24-28, 41-43]. Five studies in non-human primates reported clinical symptoms following vaccination [32-36] and one study in non-human primates specifically looked at neurological symptoms following intrathalamic injection of the vaccine or wild-type rVSV [39].

Solicited adverse events

The majority of study subjects vaccinated with the rVSVΔG-ZEBOV-GP vaccine were immunocompetent adults who were not pregnant or breastfeeding. The vaccine is highly reactogenic; over 80% of study subjects were reported by multiple studies as having experienced at least one adverse event [15, 16, 24, 25, 42]. The most frequently reported symptoms were injection site pain, fever, headache, malaise, and myalgia. Although the degree of reactogenicity was high across dose levels, these adverse events were generally transient and mild-to-moderate in intensity. The onset of systemic symptoms typically occurred within three days after vaccination. A phase 1 dose-ranging trial looking at a two-dose regimen given on days 0 and 28 found a lower rate of adverse events after the second dose than after the first dose [12].

Unexpected adverse events

Unexpected adverse events reported in an early clinical trial include arthralgia, arthritis, dermatitis, and vasculitis [15]. Follow up studies, including the large phase 3 ring vaccination trial in Guinea, found arthralgia and arthritis to be less frequent, transient, and of mild-to-moderate intensity [13, 14, 16, 20, 21, 42, 43], but occurring at higher rates compared to placebo [25] or no vaccination [24, 41]. One study found the female sex and a medical history of arthritis as significant risk factors for the development of arthritis post-vaccination, but not treatment dose or age [30]. The median time to onset of arthritis was about 10 days and the mean duration was 6 days in blinded trials, though a few events persisted for months to years [45]. Dermatitis and vasculitis were also infrequently reported, generally mild-to-moderate in intensity, and of short duration [12, 16, 42, 43], and occurred at higher rates compared to placebo [25] or no vaccination [24]. Some dose-ranging studies found that there is likely a trend towards lower reactogenicity with lower doses [13-15], but the unexpected adverse events did not appear to be related to the dose.

Serious adverse events

Serious adverse events were infrequently reported following more than 150,000 vaccinations across all dose levels. In the studies included for review, only two serious adverse events were judged to be vaccine-related (both for the 2×10^7 PFU dose): one febrile reaction and one anaphylaxis [21]. Analysis of double-blinded trials found serious adverse events occurred in 3.4% of vaccine recipients, with the most common event being malaria, compared with 7.8% of

placebo recipients [45]. In over 130,000 vaccinated individuals in the DRC, 228 serious adverse events were identified between August 7, 2018 and June 5, 2019; of these events, only a few, including one case of anaphylaxis, were attributed to the vaccine [45].

Special populations

There are limited safety data in pregnant women, children and adolescents 6–17 years of age, and immunocompromised individuals. In three studies that excluded pregnant and breastfeeding women from vaccination, a small number of enrolled subjects became pregnant within two months after vaccination and very few were pregnant when vaccinated [19, 24, 41, 45]. One randomized trial (n=261) found a higher frequency of pregnancy loss in those who received the vaccine immediately compared with those who received delayed vaccination. The reasons for this observation are unknown. Three studies that included children and adolescents 6–17 years of age (n=537) found an adverse events profile that is similar to adults [19, 21, 27], but with fewer arthralgia events than adults [21, 27]. Two serious adverse events attributed to gastroenteritis and respiratory failure occurred in one of 22 HIV-infected vaccinees [20]. Safety data are currently not available for breastfeeding women, infants, children under 6 years of age, and persons with other immunocompromising conditions.

A phase 2 randomized controlled trial including children with age greater than or equal to 1 year [54] and a phase 2 randomized controlled trial in HIV-infected adults and adolescents with one- and two-dose regimens are in progress [56]. As of June 29, 2019, 34,522 children and adolescents 1–17 years of age have been vaccinated under the WHO compassionate use protocol in the ongoing outbreak in the DRC [7]. In February 2019, the ethics committee of the DRC authorized the expansion of the compassionate use protocol to include vaccination of pregnant and breastfeeding women and children under 1 year of age [8]. In May 2019, authorities in the DRC simplified safety follow-up requirements to passive reporting of serious adverse events by phone and active follow-up of only pregnant women and children under 1 year of age [9]. Specific safety results have not yet been published for these vaccinated individuals; however, no serious safety concerns have been identified so far by WHO or the manufacturer.

Vaccine vector viremia and shedding

Low-level, transient, and dose-dependent rVSV viremia was seen for some subjects on days 1–3 after vaccination, becoming undetectable by days 7–14 [12-16, 20, 28, 43]. Viremia was seen more frequently in children and adolescents compared to adults in one study [19].

Transmissibility of vaccine virus to people outside of the target vaccine population is not known, as no data are available on secondary transmission [45], but is unlikely. Very few vaccinees had measurable shedding of the vaccine virus in urine and saliva [13, 14, 16]. Viral shedding in saliva was seen more frequently in children and adolescents compared to adults [19]. Absent or minimal vaccine virus shedding was observed in oral, nasal, and/or rectal swab samples from animal studies and the wild-type rVSV has naturally low transmissibility [57, 58].

Leukocyte counts

Transient, asymptomatic, dose-related decreases in leukocytes were observed in some subjects and mostly within 2 days post-vaccination [12, 14, 15, 19].

Safety in non-human primates

The rVSVΔG-ZEBOV-GP vaccine appeared to be well-tolerated in non-human primates, showing no evidence of clinical illness in the period following pre-exposure vaccination [32-36]. Intrathalamic injection of the vaccine showed a lack of neurovirulence compared to the wild-type rVSV [39].

IV. PRECAUTIONS

Potential interference with ZMapp

No individuals have received both the rVSVΔG-ZEBOV-GP vaccine and the ZMapp monoclonal antibody cocktail for EVD treatment to date. Therefore, timing of administration and potential interference between these two products are currently unknown. Administration of these products close together may result in decreased effectiveness of the rVSVΔG-ZEBOV-GP vaccine and/or ZMapp because the monoclonal antibody has high affinity for the ZEBOV envelope GP expressed by the vaccine vector and the vaccine virus must replicate over time in order to elicit immune responses.

In the post-exposure setting, expert clinical opinion should be sought when deciding whether ZMapp, the rVSVΔG-ZEBOV-GP vaccine, or a combination of the two is the most appropriate response, taking into account the specifics of the exposure event.

Vaccine virus shedding

Transmission of the vaccine virus has not been reported to date. In clinical trials, very few vaccine recipients had measurable shedding of the vaccine virus in urine and saliva [13, 14, 16] and low-level rVSV viremia observed in some vaccine recipients became undetectable by days 7–14 [12-16, 20, 28, 43]. It is not known if the vaccine virus is secreted in human breast milk. There is no data available regarding the effects of vaccinating breastfeeding women on their infants. Absent or minimal vaccine virus shedding was observed in oral, nasal, and/or rectal swab samples from animal studies and the wild-type rVSV has naturally low transmissibility [57, 58]. Although the risk of transmitting the rVSVΔG-ZEBOV-GP vaccine virus to people outside of the target vaccine population appears to be extremely low, vaccine recipients should be informed that the rVSVΔG-ZEBOV-GP vaccine does not contain live *Ebolavirus*, but is comprised of a live-attenuated recombinant virus, rVSV, that has the theoretical potential to be transmitted to contacts of the vaccinated individual.

Based on expert opinion and taking into consideration the precautions for use made by the EMA [59], individuals vaccinated with the rVSVΔG-ZEBOV-GP vaccine should avoid close contact (including exposure to blood and body fluids) with immunocompromised individuals, pregnant or breastfeeding women, and infants for at least six weeks following vaccination, unless those individuals also have an indication for the rVSVΔG-ZEBOV-GP vaccine.

Similarly, as a precaution, women should avoid breastfeeding and their infants should not have contact with maternal blood and body fluids, where feasible, for at least six weeks following vaccination, unless vaccination with the rVSVΔG-ZEBOV-GP vaccine is also indicated for the infant.

V. INTERIM RECOMMENDATIONS

After careful review of available evidence (see Section III) and considering current knowledge gaps (see Section VI), NACI makes the following interim recommendations on the emergency use of the pre-market rVSVΔG-ZEBOV-GP vaccine stockpiled in the NESS for PEP and PrEP in a Canadian context, recognizing:

- The lack of regulatory approval of the rVSVΔG-ZEBOV-GP vaccine in Canada at the time of writing;
- The limited quantity of this pre-market vaccine available in Canada; and
- The fact that the EVD outbreak in the DRC is a Public Health Emergency of International Concern at the time of writing, and the global rVSVΔG-ZEBOV-GP vaccine supply is being prioritized for those most at risk in Africa where there can be the greatest impact.

As the regulatory, supply, and evidence context for the rVSVΔG-ZEBOV-GP vaccine evolves, NACI will revisit these interim recommendations as needed.

A dose-sparing strategy for the use of the rVSVΔG-ZEBOV-GP vaccine, and associated evidence, may be reviewed and considered by NACI if the need arises.

Exposure definition

For the interim recommendations, exposures[*] to ZEBOV that are considered to pose risk are:

- Unprotected direct physical contact (i.e., through non-intact skin or mucous membranes) with [60, 61]:
  - non-intact skin, mucous membranes, blood, or other body fluids (e.g., stool, emesis, urine, saliva, semen, sweat, breast milk) of a ZEBOV-infected individual;
  - linens or clothing contaminated with ZEBOV-infected blood or body fluids;
  - the dead body of a ZEBOV-infected individual; and/or
  - any other known source of ZEBOV, including contaminated medical instruments, fomites or other contaminated environmental surfaces, laboratory specimens, or animals;
- Unprotected exposure following assistance with the performance of an aerosol-generating medical procedure [62];
- Unprotected sexual contact with an acute or convalescent EVD case (ZEBOV has been demonstrated to persist in semen for up to 40 months [2]) with laboratory-confirmed ZEBOV infection [60]; and/or
- Unprotected handling and/or consumption of ZEBOV-contaminated bush meat products from Africa [63].

[*] In a healthcare or veterinary context, unprotected refers to a lack of the recommended personal protective equipment or a breach in the recommended IPC precautions.

This exposure definition is adapted from CATMAT's Ebola Virus Disease Prevention, Monitoring and Surveillance Recommendations and PHAC's Public Health Management of Cases and Contacts of Ebola Virus Disease in the Community Setting in Canada.

Strength of NACI recommendations

Please note:

- A strong NACI recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present.
- A discretionary NACI recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.

Please see Table 2 for a more detailed explanation of strength of NACI recommendations and grade of the body of evidence. Please see Tables 3 and 4 for details on the ratings of the quality of individual studies.

V.1 POST-EXPOSURE PROPHYLAXIS FOR INDIVIDUALS WHO HAVE HAD AN EXPOSURE TO ZEBOV IN CANADA

Interim recommendation 1a

1a. NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine should be offered as PEP against ZEBOV for non-pregnant immunocompetent adults who have had an exposure to ZEBOV (Strong NACI Recommendation)

- NACI concludes that there is currently fair evidence of safety, immunogenicity, efficacy, and effectiveness to recommend vaccination of non-pregnant immunocompetent adults who have had an exposure to ZEBOV with the rVSVΔG-ZEBOV-GP vaccine (Grade B Evidence).

Summary of evidence and rationale

- The vaccine has shown few serious adverse events, despite a high degree of reactogenicity, and is immunogenic in non-pregnant immunocompetent adults. The vaccine has been shown to be efficacious in preventing EVD in the context of community outbreaks, if symptoms of EVD did not appear within 10 days of vaccination. However, because these efficacy studies were performed during community-based outbreaks of ZEBOV in Africa, they do not provide direct evidence of post-exposure protection.
- The lack of regulatory review and authorization may decrease the acceptability of this pre-market vaccine; however, the potential for severe harm from EVD in those who have had an exposure to ZEBOV and the safety and immunogenicity profile of the vaccine established in non-pregnant immunocompetent adults may improve its acceptability among these individuals.

Interim recommendation 1b

1b. NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine may be considered as PEP against ZEBOV for pregnant women, infants, children, adolescents, and immunocompromised individuals who have had an exposure to ZEBOV (Discretionary NACI Recommendation)

- NACI concludes that there is currently insufficient evidence to recommend vaccination of pregnant women, infants, children, adolescents, and immunocompromised individuals who have had an exposure to ZEBOV with the rVSVΔG-ZEBOV-GP vaccine (Grade I Evidence). Therefore, this interim recommendation is based on expert opinion.

Summary of evidence and rationale

- There are limited safety data for pregnant women, children and adolescents 6–17 years of age, and immunocompromised individuals. One randomized trial found a higher frequency of pregnancy loss in those who received immediate vaccination vs. delayed vaccination. Three studies that included children and adolescents 6–17 years of age found an adverse events profile that is similar to adults, but with fewer arthralgia events than adults. Two serious adverse events attributed to gastroenteritis and respiratory failure occurred in one of 22 HIV-infected vaccinees. Safety data are not currently available for infants and children under 6 years of age.
- There is limited evidence of slower immune response in children 6–17 years of age after vaccination than adults. There is also limited evidence of less optimal immune response in HIV-infected individuals compared with non-HIV-infected individuals. No immunogenicity data are available for pregnant women, infants, and children under 6 years of age.
- Vaccine has been given to these special populations as part of outbreak control measures in the DRC. As of June 29, 2019, 34,522 children and adolescents 1–17 years of age have been vaccinated. In February 2019, the authorities in the DRC authorized the expansion of the compassionate use protocol to include pregnant and breastfeeding women and children under 1 year of age. In May 2019, the authorities simplified safety follow-up requirements to passive reporting of serious adverse events by phone and active follow-up was limited to pregnant women and children under 1 year of age. Specific safety results have not yet been published for these vaccinated individuals; however, no serious safety concerns have been identified so far by WHO or the manufacturer.
- A risk-benefit assessment of this pre-market vaccine, taking into consideration uncertainties in the safety and efficacy of the vaccine, the potential for severe harm from EVD, and the nature and intensity of exposure, should be conducted when deciding whether to vaccinate individuals in these special populations.

Interim recommendation 2

2. When used as PEP against ZEBOV, NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine should be given as expeditiously as possible, targeting within 72 hours of exposure for susceptible, asymptomatic exposed individuals, but may be considered up to 10 days post-exposure, as the incubation period for EVD can range from 2–21 days and vaccination within 10 days of exposure may confer protection (Strong NACI Recommendation)

- NACI concludes that there is currently insufficient evidence to define a vaccination window for effective PEP in preventing severe disease after exposure to ZEBOV (Grade I Evidence). Therefore, this interim recommendation is based on expert opinion.

Summary of evidence and rationale

- The vaccine has been shown to be efficacious in preventing EVD in the context of community outbreaks, if symptoms of EVD did not appear within 10 days of vaccination. The median time from confirmation of EVD in an index case to vaccination of contacts in these studies ranged from 7–15 days. However, because these efficacy studies were performed during community-based outbreaks of ZEBOV in Africa, they do not provide direct evidence of timing for post-exposure protection.
- In studies with non-human primates, partial post-exposure protection against EVD was achieved if vaccinated within 20–30 minutes of intramuscular challenge with a lethal concentration of ZEBOV. No protection against EVD was observed if vaccinated at 1 and/or 24 hours after lethal intramuscular ZEBOV challenge. Data derived from animal studies should be interpreted with caution when used to inform clinical decision making since time-to-death is shorter and mortality rate is higher following intramuscular infection, likely shortening the window of efficacy of post-exposure vaccination compared to mucosal infection. Several instances of PEP given within 3 days of a needlestick or sharps injury have been reported. A laboratory worker was vaccinated with a 5×10^7 PFU dose 48 hours after a needlestick injury with a syringe containing ZEBOV. Five healthcare workers were vaccinated with a 1×10^8 PFU dose 1–3 days after sharps injuries in West Africa. There was no evidence that these exposures resulted in infection but it is not possible to determine whether this was due to vaccine effect or lack of transmission following the needlestick injury.
- Expert clinical opinion should be emergently sought in the management of individuals who are potentially exposed to ZEBOV from a needlestick injury, as the window for effective PEP after intramuscular exposure to ZEBOV is unknown, but likely to be small, and the vaccine may not be immediately available for administration. The risk of severe disease from intramuscular exposure to ZEBOV (e.g., needlestick injury from a ZEBOV-contaminated needle and syringe) is greater than mucosal exposure (e.g., unprotected direct physical contact through non-intact skin or mucous membranes with non-intact skin, mucous membranes, blood, or other body fluids of a ZEBOV-infected individual).
- Common systemic reactions following vaccination include fever, headache, malaise, and myalgia, resembling the early symptoms of EVD. However, typical onset of vaccine reactions is expected within 3 days after vaccination compared with onset of clinical symptoms 4–10 days after exposure to ZEBOV. Therefore, clinical management of reported illness among individuals who have had an exposure to ZEBOV should take into consideration vaccination status, timing of symptom onset relative to vaccination, and presence of any symptoms typically associated with EVD but not with vaccination (e.g., sore throat, nausea and vomiting, diarrhea, haemorrhaging) to mitigate unnecessary referrals to EVD treatment units. Antipyretics have been used for the

management or prevention of post-vaccination fever without identified safety concerns [21], but the use of antipyretics may mask early EVD symptoms.

Interim recommendation 3

3. NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine may be considered as PEP against ZEBOV for individuals who have received a previous dose of the pre-market rVSVΔG-ZEBOV-GP vaccine more than 18 months prior to a current exposure to ZEBOV (Discretionary NACI Recommendation)

- NACI concludes that while there is currently fair evidence of immunogenicity up to two years post-vaccination (Grade B Evidence), there is insufficient evidence to define a serological threshold of protection against ZEBOV or to suggest a need for re-vaccination (Grade I Evidence). Therefore, this interim recommendation is based on expert opinion.

Summary of evidence and rationale

- GMTs of IgG antibody to the ZEBOV envelope GP reported in clinical trials generally peaked by day 28 and persisted to two years post-vaccination without significant decline. Immune correlates of protection and the relative importance of IgG antibody response have not yet been established. Long-term vaccine efficacy has not been demonstrated. There is limited evidence that the rate of adverse events following a second dose given at 28 days post-vaccination is lower than after the first dose. Due to the potential for severe harm from EVD and the uncertainty around the durability and thresholds of vaccine protection, re-vaccination with the rVSVΔG-ZEBOV-GP vaccine may be considered as a precaution after an exposure to ZEBOV occurring more than 18 months after a previous dose of the rVSVΔG-ZEBOV-GP vaccine.
- Expert clinical opinion should be sought when deciding whether to re-vaccinate an individual who has previously received another vaccine for EVD with the rVSVΔG-ZEBOV-GP vaccine.

Interim recommendation 4

4. When used as PEP against ZEBOV, NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine should not be given simultaneously with other live or inactivated vaccines due to the potential for immune interference and the need to be able to monitor for potential symptoms of EVD and rVSVΔG-ZEBOV-GP vaccine adverse events without potential confounding from other vaccine adverse events (Strong NACI Recommendation)

- NACI concludes that there is currently insufficient evidence to recommend concurrent administration of the pre-market rVSVΔG-ZEBOV-GP vaccine with other vaccines (Grade I Evidence). Therefore, this interim recommendation is based on expert opinion.

Summary of evidence and rationale

- Although live-attenuated or inactivated vaccines given by the parenteral route may generally be administered concurrently with other vaccines without concern, there is no data available on the concurrent administration of the rVSVΔG-ZEBOV-GP vaccine with other vaccines. Given the potential for immune interference and the need to be able to monitor for potential symptoms of EVD and rVSVΔG-ZEBOV-GP vaccine adverse

events without potential confounding from other vaccine adverse events, the pre-market rVSVΔG-ZEBOV-GP vaccine should not be given as PEP against ZEBOV simultaneously with other live or inactivated vaccines in this exceptional situation. Other live-attenuated or inactivated vaccines should be administered at a minimal interval of four weeks after vaccination with the rVSVΔG-ZEBOV-GP vaccine. However, given the potential for severe harm from EVD, vaccination with the rVSVΔG-ZEBOV-GP vaccine should not be delayed even if it is within four weeks of a previous vaccine.
- Considering the ethical principles of beneficence and non-maleficence, delaying any other vaccines to prioritize the pre-market rVSVΔG-ZEBOV-GP vaccine for individuals who have had an exposure to ZEBOV is acceptable and ethically justifiable.

V.2 POST-EXPOSURE PROPHYLAXIS FOR INDIVIDUALS WHO HAVE HAD AN OCCUPATIONAL EXPOSURE TO ZEBOV IN CANADIAN HEALTHCARE OR LABORATORY SETTINGS

Interim recommendation 5a

5a. NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine should be offered as PEP against ZEBOV for non-pregnant immunocompetent adults who have had an occupational exposure to ZEBOV in Canadian healthcare or laboratory settings (Strong NACI Recommendation)

- NACI concludes that there is currently fair evidence of safety, immunogenicity, efficacy, and effectiveness to recommend vaccination of non-pregnant immunocompetent adults who have had an occupational exposure to ZEBOV in Canadian healthcare or laboratory settings with the rVSVΔG-ZEBOV-GP vaccine (Grade B Evidence).

Summary of evidence and rationale

- The vaccine has shown few serious adverse events, despite a high degree of reactogenicity, and is immunogenic in non-pregnant immunocompetent adults. The vaccine has been shown to be efficacious in preventing EVD in the context of community outbreaks, if symptoms of EVD did not appear within 10 days of vaccination. However, because these efficacy studies were performed during community-based outbreaks of ZEBOV in Africa, they do not provide direct evidence of post-exposure protection.
- Expert clinical opinion should be emergently sought in the management of individuals who are potentially exposed to ZEBOV from a needlestick injury. Appropriately implemented IPC measures, such as using personal protective equipment and following correct donning and doffing procedures, offer feasible and effective methods of protection against EVD infection. However, due to the nature of the work, there exists a small risk of needlestick injury among healthcare workers providing direct care to EVD cases and laboratory workers handling ZEBOV. The risk of severe disease from intramuscular exposure to ZEBOV (e.g., needlestick injury from a ZEBOV-contaminated needle and syringe) is greater than mucosal exposure (e.g., unprotected direct physical contact through non-intact skin or mucous membranes with non-intact skin, mucous membranes, blood, or other body fluids of a ZEBOV-infected individual).
- The lack of regulatory review and authorization may decrease the acceptability of this pre-market vaccine. However, given the potential for severe harm from EVD in those who have had an exposure to ZEBOV and the safety and immunogenicity profile of the vaccine for non-pregnant immunocompetent adults, offering the pre-market rVSVΔG-ZEBOV-GP vaccine to these individuals is acceptable and ethically justifiable.

Interim recommendation 5b

5b. NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine may be considered as PEP against ZEBOV for pregnant or immunocompromised individuals who have had an occupational exposure to ZEBOV in Canadian healthcare or laboratory settings (Discretionary NACI Recommendation)

- NACI concludes that there is currently insufficient evidence to recommend vaccination of pregnant and immunocompromised individuals who have had an occupational exposure to ZEBOV in Canadian healthcare or laboratory settings with the rVSVΔG-ZEBOV-GP vaccine (Grade I Evidence). Therefore, this interim recommendation is based on expert opinion.

Summary of evidence and rationale

- Safety data are limited for pregnant and immunocompromised individuals. One randomized trial found a higher frequency of pregnancy loss in those who received immediate vaccination vs. delayed vaccination. Two serious adverse events attributed to gastroenteritis and respiratory failure occurred in one of 22 HIV-infected vaccinees.
- There is limited evidence of less optimal immune response in HIV-infected individuals compared with non-HIV-infected individuals. No immunogenicity data are available for pregnant women.
- Vaccine has been given to these special populations, as well as infants, children, and adolescents, as part of outbreak control measures in the DRC. In February 2019, the authorities in the DRC authorized the expansion of the compassionate use protocol to include pregnant and breastfeeding women and children under 1 year of age. In May 2019, the authorities simplified safety follow-up requirements to passive reporting of serious adverse events by phone and active follow-up was limited to pregnant women and children under 1 year of age. Specific safety results have not yet been published for these vaccinated individuals; however, no serious safety concerns have been identified so far by WHO or the manufacturer.
- Expert clinical opinion should be emergently sought in the management of individuals who are potentially exposed to ZEBOV from a needlestick injury. Appropriately implemented IPC measures, such as using personal protective equipment and following correct donning and doffing procedures, offer feasible and effective methods of protection against EVD infection. However, due to the nature of the work, there exists a small risk of needlestick injury among healthcare workers providing direct care to EVD cases and laboratory workers handling ZEBOV. The risk of severe disease from intramuscular exposure to ZEBOV (e.g., needlestick injury from a ZEBOV-contaminated needle and syringe) is greater than mucosal exposure (e.g., unprotected direct physical contact through non-intact skin or mucous membranes with non-intact skin, mucous membranes, blood, or other body fluids of a ZEBOV-infected individual).
- A risk-benefit assessment of this pre-market vaccine, taking into consideration uncertainties in the safety and efficacy of the vaccine, the potential for severe harm from EVD, and the nature and intensity of exposure, should be conducted when deciding whether to vaccinate individuals in these special populations.

Interim recommendations 2 through 4 also apply to individuals who have had an occupational exposure to ZEBOV in Canadian healthcare or laboratory settings.

V.3 PRE-EXPOSURE PROPHYLAXIS

Advice on PrEP for travellers is not provided in this interim statement on the emergency use of the pre-market rVSVΔG-ZEBOV-GP vaccine stockpiled in the NESS.

Interim recommendation 6

6. NACI recommends that the pre-market rVSVΔG-ZEBOV-GP vaccine may be considered as PrEP against ZEBOV for non-pregnant immunocompetent adults in exceptional situations when a dedicated team of healthcare workers is anticipated to provide direct care for a confirmed case with symptomatic ZEBOV infection, if vaccine is available (Discretionary NACI Recommendation)

- NACI concludes that there is currently fair evidence of safety, immunogenicity, efficacy, and effectiveness to recommend vaccination of non-pregnant immunocompetent adults at risk of exposure to ZEBOV (Grade B Evidence) and insufficient evidence of long-term protection beyond two years post-vaccination (Grade I Evidence). Therefore, this interim recommendation is based on expert opinion.

Summary of evidence and rationale

- The vaccine has shown few serious adverse events, despite a high degree of reactogenicity, and is immunogenic in non-pregnant immunocompetent adults. The vaccine has been shown to be efficacious in preventing EVD in the context of community outbreaks, if symptoms of EVD did not appear within 10 days of vaccination. However, because these efficacy studies were performed during community-based outbreaks of ZEBOV in Africa, they do not provide direct evidence of pre-exposure protection. GMTs of IgG antibody to the ZEBOV envelope GP reported in clinical trials generally peaked by day 28 and persisted to two years post-vaccination without significant decline. Long-term vaccine efficacy is unknown.
- Although the acceptability of this narrow interim recommendation for PrEP may be low among healthcare workers who perceive themselves to be at risk of exposure to ZEBOV, wider PrEP against ZEBOV is currently not feasible or recommended at this time in Canada based on the limited availability of the pre-market vaccine in Canada and globally and the potentially large number of Canadian healthcare workers who may have some perceived risk of exposure to ZEBOV (there have been no cases of EVD in Canada to date).
- Appropriately implemented IPC measures, such as using personal protective equipment and following correct donning and doffing procedures, offer feasible and effective methods of protection against EVD infection and should be followed as the situation dictates, regardless of vaccination status.
- Vaccine-derived adverse events may mimic early EVD symptoms; therefore, clinical management of reported illness among vaccinated individuals who have had an exposure to ZEBOV should take into consideration vaccination status, timing of symptom onset relative to vaccination, and presence of any symptoms typically associated with EVD but not with vaccination.

VI. KNOWLEDGE GAPS

After careful review of available evidence, NACI has identified the need for further research to address current knowledge gaps where data are absent or limited. NACI recognizes that there are studies already in progress that may address many of these gaps but the findings of these studies were not yet available at the time of review. Identified knowledge gaps include:

- Immune correlates of protection have not been established.
- The window of vaccination for effective PEP is unknown.
- The degree of post-exposure protection (e.g., decreasing infectiousness and clinical illness in individuals that had already acquired infection) is unknown.
- Cross-protective efficacy against other *Ebolavirus* species or *Marburg virus* in humans is unknown, though the vaccine is unlikely to protect against these other viruses of the *Filoviridae* family due to significant differences in viral antigens.
- Safety and immunogenicity data for children and adolescents 6–17 years of age and immunocompromised individuals are limited. Safety data are limited and immunogenicity data are not available for pregnant women. Safety and immunogenicity data are not available for breastfeeding women, infants, and children under 6 years of age.
- Transmissibility of the vaccine virus is unknown, including whether the vaccine virus is secreted in human breast milk.
- Persistence of immune response beyond two years after vaccination is unknown.
- Long-term vaccine efficacy is unknown.
- Anamnestic response following a booster dose more than 28 days after the priming dose has not been characterized.
- Interference with ZMapp or other passive immunizing agents against EVD is unknown.
- Safety of concurrent administration with other vaccines is unknown.

TABLES

Table 2: NACI recommendations: strength of recommendation and grade of evidence

Strength of NACI recommendation	Grade of evidence
Based on factors not isolated to strength of evidence (e.g., public health need)	**Based on assessment of the body of evidence**
Strong "should/should not be offered" • Known/anticipated advantages outweigh known/anticipated disadvantages ("should"); or • Known/Anticipated disadvantages outweigh known/anticipated advantages ("should not") • Implication: A strong recommendation applies to most populations/individuals and should be followed unless a clear and compelling rationale for an alternative approach is present	A – good evidence to recommend
	B – fair evidence to recommend
	C – conflicting evidence, however other factors may influence decision-making
	D – fair evidence to recommend against
	E – good evidence to recommend against
	I – insufficient evidence (in quality or quantity), however other factors may influence decision-making
Discretionary "may be considered" • Known/Anticipated advantages closely balanced with known/anticipated disadvantages; or uncertainty in the evidence of advantages and disadvantages exists • Implication: A discretionary recommendation may be considered for some populations/individuals in some circumstances. Alternative approaches may be reasonable.	A – good evidence to recommend
	B – fair evidence to recommend
	C – conflicting evidence, however other factors may influence decision-making
	D – fair evidence to recommend against
	E – good evidence to recommend against
	I – insufficient evidence (in quality or quantity), however other factors may influence decision-making

Table 3: Ranking individual studies: levels of evidence based on research design

Level	Description
I	Evidence from randomized controlled trial(s).
II-1	Evidence from controlled trial(s) without randomization.
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group using clinical outcome measures of vaccine efficacy.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

Table 4: Ranking individual studies: quality (internal validity) rating of evidence

Quality rating	Description
Good	A study (including meta-analyses or systematic reviews) that meets all design- specific criteria* well.
Fair	A study (including meta-analyses or systematic reviews) that does not meet (or it is not clear that it meets) at least one design-specific criterion* but has no known "fatal flaw".
Poor	A study (including meta-analyses or systematic reviews) that has at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations.

* General design-specific criteria are outlined in Harris et al. [10].

LIST OF ABBREVIATIONS

CATMAT	Committee to Advise on Tropical Medicine and Travel
CI	Confidence interval
DRC	Democratic Republic of the Congo
EMA	European Medicines Agency
EU	ELISA unit
EVD	Ebola virus disease
GMT	Geometric mean titre
GP	Glycoprotein
HIV	*Human immunodeficiency virus*
IgG	Immunoglobulin G
IPC	Infection prevention and control
NACI	National Advisory Committee on Immunization
NESS	National Emergency Strategic Stockpile
PEP	Post-exposure prophylaxis
PHAC	Public Health Agency of Canada
PFU	Plaque-forming unit
PrEP	Pre-exposure prophylaxis
rVSVΔG-ZEBOV-GP	Recombinant *vesicular stomatitis virus-Zaire ebolavirus*
SAGE	Strategic Advisory Group of Experts on Immunization
SHIV	*Simian-human immunodeficiency virus*
WHO	World Health Organization

ACKNOWLEDGMENTS

This statement was prepared by L Zhao, A Killikelly, M Tunis, M Patel, G Poliquin, S Deeks, and C Quach on behalf of the NACI EVD Vaccine Working Group and was approved by NACI.

NACI gratefully acknowledges the contribution of M-A Beaulieu, A Coady, P Deb-Rinker, L Gamble, A House, S Ismail, M Laplante, M Matthieu-Higgins, K Young, the NACI Vaccine Safety Working Group, the Canadian Immunization Committee, the Council of Chief Medical Officers of Health, and the EVD-Clinical Treatment Centre Task Group.

NACI EVD Vaccine Working Group

Members: C Quach (Chair), S Deeks (Vice-Chair), Y-G Bui, R Harrison, M Libman, and S Vaughan

Ex-officio representatives: J Anderson (National Defence and the Canadian Armed Forces), J Courtemanche (Centre for Emergency Preparedness and Response, PHAC), R Pless (Biologics and Genetic Therapies Directorate, Health Canada), G Poliquin (National Microbiology Laboratory, PHAC), and J Sciberras (Vice President's Office, Infectious Disease Prevention and Control Branch, PHAC)

NACI

Members: C Quach (Chair), S Deeks (Vice-Chair), N Dayneka, P De Wals, V Dubey, R Harrison, K Hildebrand, M Lavoie, C Rotstein, M Salvadori, B Sander, N Sicard, and S Smith.

Former NACI members: W Vaudry (Vice-Chair)

Liaison representatives: J Brophy (Canadian Association for Immunization Research and Evaluation), LM Bucci (Canadian Public Health Association), E Castillo (Society of Obstetricians and Gynaecologists of Canada), A Cohn (Centers for Disease Control and Prevention, United States), J Emili (College of Family Physicians of Canada), K Klein (Council of Chief Medical Officers of Health), D Moore (Canadian Paediatric Society), M Naus (Canadian Immunization Committee), and A Pham-Huy (Association of Medical Microbiology and Infectious Disease Canada)

Former liaison representatives: T Cole (Canadian Immunization Committee) and C Mah (Canadian Public Health Association)

Ex-officio representatives: J Gallivan (Marketed Health Products Directorate, HC), E Henry (Centre for Immunization and Respiratory Infectious Diseases [CIRID], PHAC), M Lacroix (Public Health Ethics Consultative Group, PHAC), J Pennock (CIRID, PHAC), R Pless (Biologics and Genetic Therapies Directorate, Health Canada), G Poliquin (National Microbiology Laboratory, PHAC), C Rossi (National Defence and the Canadian Armed Forces), and T Wong (First Nations and Inuit Health Branch, Indigenous Services Canada).

Former ex-officio representatives: K Barnes (National Defence and the Canadian Armed Forces)

REFERENCES

1. Malvy D, McElroy AK, de Clerck H, Günther S, van Griensven J. Ebola virus disease. Lancet. 2019;393(10174):936-48.
2. PREVAIL III Study Group. A longitudinal study of Ebola sequelae in Liberia. N Engl J Med. 2019;380(10):924-34.
3. Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. Lancet. 2016;388(10043):498-503.
4. Liddell AM, Davey RT, Mehta AK, Varkey JB, Kraft CS, Tseggay GK, et al. Characteristics and clinical management of a cluster of 3 patients with Ebola virus disease, including the first domestically acquired cases in the United States. Ann Intern Med. 2015;163(2):81-90.
5. Parra JM, Salmerón OJ, Velasco M. The first case of Ebola virus disease acquired outside Africa. N Engl J Med. 2014;371(25):2439-40.
6. World Health Organization. Ebola vaccine candidates [Internet]. 2019. Available from: https://www.who.int/blueprint/priority-diseases/key-action/ebola-vaccine-candidates/en/.
7. World Health Organization. Ebola Virus Disease: Democratic Republic of the Congo: External Situation Report 68 [Internet]. 2019. Available from: https://www.who.int/publications-detail/ebola-virus-disease-democratic-republic-of-congo-external-situation-report-68-2019.
8. World Health Organization. SAGE Interim Recommendations on Vaccination against Ebola Virus Disease (EVD): February 20, 2019 [Internet]. 2019. Available from: https://www.who.int/immunization/interim_ebola_recommendations_feb_2019.pdf.
9. World Health Organization. Interim Recommendations on Vaccination against Ebola Virus Disease (EVD): 7 May 2019 [Internet]. 2019. Available from: https://www.who.int/immunization/policy/position_papers/interim_ebola_recommendations_may_2019.pdf.
10. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3):21-35.
11. Farooq F, Beck K, Paolino KM, Phillips R, Waters NC, Regules JA, et al. Circulating follicular T helper cells and cytokine profile in humans following vaccination with the rVSV-ZEBOV Ebola vaccine. Sci Rep. 2016;6:27944.
12. Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, Hu Z, et al. A recombinant vesicular stomatitis virus Ebola vaccine. N Engl J Med. 2017;376(4):330-41.
13. ElSherif MS, Brown C, MacKinnon-Cameron D, Li L, Racine T, Alimonti J, et al. Assessing the safety and immunogenicity of recombinant vesicular stomatitis virus Ebola vaccine in healthy adults: a randomized clinical trial. CMAJ. 2017;189(24):E819-27.
14. Heppner Jr DG, Kemp TL, Martin BK, Ramsey WJ, Nichols R, Dasen EJ, et al. Safety and immunogenicity of the rVSVΔ G-ZEBOV-GP Ebola virus vaccine candidate in healthy adults: a phase 1b randomised, multicentre, double-blind, placebo-controlled, dose-response study. Lancet Infect Dis. 2017;17(8):854-66.

15. Huttner A, Dayer J, Yerly S, Combescure C, Auderset F, Desmeules J, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. Lancet Infect Dis. 2015;15(10):1156-66.
16. Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dahlke C, Fernandes JF, et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe. N Engl J Med. 2016;374(17):1647-60.
17. Dahlke C, Kasonta R, Lunemann S, Krähling V, Zinser ME, Biedenkopf N, et al. Dose-dependent T-cell dynamics and cytokine cascade following rVSV-ZEBOV immunization. EBioMedicine. 2017;19:107-18.
18. Fischer T, Spohn M, Olearo F, Zinser M, Kasonta R, Stubbe H, et al. Dynamic changes of circulating miRNAs induced by the Ebola virus vaccine VSV-EBOV. Vaccine. 2018;36(46):7083-94.
19. Agnandji ST, Fernandes JF, Bache EB, Mba RMO, Brosnahan JS, Kabwende L, et al. Safety and immunogenicity of rVSVΔG-ZEBOV-GP Ebola vaccine in adults and children in Lambaréné, Gabon: A phase I randomised trial. PLoS Med. 2017;14(10):e1002402.
20. Kennedy SB, Bolay F, Kieh M, Grandits G, Badio M, Ballou R, et al. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. N Engl J Med. 2017;377(15):1438-47.
21. Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). Lancet. 2017;389(10068):505-18.
22. Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet. 2015;386(9996):857-66.
23. Conteh M, Goldstein ST, Wurie HR, Gidudu J, Lisk DR, Carter RJ, et al. Clinical surveillance and evaluation of suspected Ebola cases in a vaccine trial during an Ebola epidemic: the Sierra Leone trial to introduce a vaccine against Ebola. J Infect Dis. 2018;217(suppl_1):S33-9.
24. Samai M, Seward JF, Goldstein ST, Mahon BE, Lisk DR, Widdowson M, et al. The Sierra Leone trial to introduce a vaccine against Ebola: an evaluation of rVSVΔ G-ZEBOV-GP vaccine tolerability and safety during the West Africa Ebola outbreak. J Infect Dis. 2018;217(suppl_1):S6-S15.
25. Halperin SA, Arribas JR, Rupp R, Andrews CP, Chu L, Das R, et al. Six-month safety data of recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine in a phase 3 double-blind, placebo-controlled randomized study in healthy adults. J Infect Dis. 2017;215(12):1789-98.
26. Bolay FK, Grandits G, Lane HC, Kennedy SB, Johnson MP, Fallah MP, et al. PREVAIL I cluster vaccination study with rVSVΔG-ZEBOV-GP as part of a public health response in Liberia. J Infect Dis. 2019;219(10):1634-41.
27. Gsell P, Camacho A, Kucharski AJ, Watson CH, Bagayoko A, Nadlaou SD, et al. Ring vaccination with rVSV-ZEBOV under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report. Lancet Infect Dis. 2017;17(12):1276-84.

28. Günther S, Feldmann H, Geisbert TW, Hensley LE, Rollin PE, Nichol ST, et al. Management of accidental exposure to Ebola virus in the biosafety level 4 laboratory, Hamburg, Germany. J Infect Dis. 2011;204(suppl_3):S785-90.

29. Huttner A, Agnandji ST, Combescure C, Fernandes JF, Bache EB, Kabwende L, et al. Determinants of antibody persistence across doses and continents after single-dose rVSV-ZEBOV vaccination for Ebola virus disease: an observational cohort study. Lancet Infect Dis. 2018;18(7):738-48.

30. Halperin SA, Das R, Onorato MT, Liu K, Martin J, Grant-Klein RJ, et al. Immunogenicity, Lot Consistency, and Extended Safety of rVSVΔG-ZEBOV-GP Vaccine: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study in Healthy Adults. J Infect Dis. 2019. In press.

31. Feldmann H, Jones SM, Daddario-DiCaprio KM, Geisbert JB, Ströher U, Grolla A, et al. Effective post-exposure treatment of Ebola infection. PLoS Pathog. 2007;3(1):e2.

32. Geisbert TW, Daddario-DiCaprio KM, Geisbert JB, Reed DS, Feldmann F, Grolla A, et al. Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses. Vaccine. 2008;26(52):6894-900.

33. Geisbert TW, Daddario-DiCaprio KM, Lewis MG, Geisbert JB, Grolla A, Leung A, et al. Vesicular stomatitis virus-based Ebola vaccine is well-tolerated and protects immunocompromised nonhuman primates. PLoS Pathog. 2008;4(11):e1000225.

34. Geisbert TW, Geisbert JB, Leung A, Daddario-DiCaprio KM, Hensley LE, Grolla A, et al. Single-injection vaccine protects nonhuman primates against infection with Marburg virus and three species of Ebola virus. J Virol. 2009;83(14):7296-304.

35. Jones SM, Feldmann H, Ströher U, Geisbert JB, Fernando L, Grolla A, et al. Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses. Nat Med. 2005;11(7):786.

36. Marzi A, Robertson SJ, Haddock E, Feldmann F, Hanley PW, Scott DP, et al. EBOLA VACCINE. VSV-EBOV rapidly protects macaques against infection with the 2014/15 Ebola virus outbreak strain. Science. 2015;349(6249):739-42.

37. Marzi A, Engelmann F, Feldmann F, Haberthur K, Shupert WL, Brining D, et al. Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. Proc Natl Acad Sci U S A. 2013;110(5):1893-8.

38. Marzi A, Hanley PW, Haddock E, Martellaro C, Kobinger G, Feldmann H. Efficacy of vesicular stomatitis virus–Ebola virus postexposure treatment in rhesus macaques infected with Ebola virus Makona. J Infect Dis. 2016;214(suppl_3):S360-6.

39. Mire CE, Miller AD, Carville A, Westmoreland SV, Geisbert JB, Mansfield KG, et al. Recombinant vesicular stomatitis virus vaccine vectors expressing filovirus glycoproteins lack neurovirulence in nonhuman primates. PLoS Negl Trop Dis. 2012;6(3):e1567.

40. Qiu X, Fernando L, Alimonti JB, Melito PL, Feldmann F, Dick D, et al. Mucosal immunization of cynomolgus macaques with the VSVΔG/ZEBOVGP vaccine stimulates strong Ebola GP-specific immune responses. PloS One. 2009;4(5):e5547.

41. Juan-Giner A, Tchaton M, Jemmy J, Soumah A, Boum Y, Faga EM, et al. Safety of the rVSV ZEBOV vaccine against Ebola Zaire among frontline workers in Guinea. Vaccine. In press.

42. Kasereka MC, Sawatzky J, Hawkes MT. Ebola epidemic in war-torn Democratic Republic of Congo, 2018: Acceptability and patient satisfaction of the recombinant Vesicular Stomatitis Virus–Zaire Ebolavirus Vaccine. Vaccine. 2019;37(16):2174-8.

43. Wong KK, Davey RT, Hewlett AL, Kraft CS, Mehta AK, Mulligan MJ, et al. Use of postexposure prophylaxis after occupational exposure to Zaire Ebolavirus. Rev Infect Dis. 2016;63(3):376-9.

44. World Health Organization. Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: an example of integration of research into epidemic response [Internet]. 2019. Available from: https://www.who.int/csr/resources/publications/ebola/ebola-ring-vaccination-results-12-april-2019.pdf.

45. World Health Organization. Weekly Epidemiological Record, 2019, vol. 94, 28. Wkly Epidemiol Rec. 2019;94(28):309-16.

46. Ajelli M, Merler S, Fumanelli L, Pastore y Piontti A, Dean NE, Longini IM, et al. Spatiotemporal dynamics of the Ebola epidemic in Guinea and implications for vaccination and disease elimination: a computational modeling analysis. BMC Med. 2016;14(1):130.

47. Bodine EN, Cook C, Shorten M. The potential impact of a prophylactic vaccine for Ebola in Sierra Leone. Math Biosci Eng. 2018;15(2):337-59.

48. Chowell G, Kiskowski M. Modeling ring-vaccination strategies to control Ebola virus disease epidemics. In: Mathematical and Statistical Modeling for Emerging and Re-emerging Infectious Diseases. Cham: Springer; 2016. p. 71-87.

49. Kucharski AJ, Eggo RM, Watson CH, Camacho A, Funk S, Edmunds WJ. Effectiveness of ring vaccination as control strategy for Ebola virus disease. Emerg Infect Dis. 2016;22(1):105-8.

50. Merler S, Ajelli M, Fumanelli L, Parlamento S, Pastore y Piontti A, Dean NE, et al. Containing Ebola at the source with ring vaccination. PLoS Negl Trop Dis. 2016;10(11):e0005093.

51. Wells C, Yamin D, Ndeffo-Mbah ML, Wenzel N, Gaffney SG, Townsend JP, et al. Harnessing case isolation and ring vaccination to control Ebola. PLoS Negl Trop Dis. 2015;9(5):e0003794.

52. World Health Organization. Ebola virus disease: frequently asked questions [Internet]. 2018. Available from: https://www.who.int/ebola/drc-2018/faq-vaccine/en/.

53. National Institute of Allergy and Infectious Diseases (NIAID). Immunogenicity of Recombinant Vesicular Stomatitis Vaccine for Ebola-Zaire (rVSV[Delta]G-ZEBOV-GP) for Pre-Exposure Prophylaxis (PREP) in People at Potential Occupational Risk for Ebola Virus Exposure [Internet]. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT02788227.

54. University of Oxford. Partnership for Research on Ebola VACcinations (PREVAC) [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03140774.

55. University of Oxford. Persistence of the Immune Response After Immunisation With Ebola Virus Vaccines (PRISM) [Internet]. 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT03140774.

56. Dalhousie University. African-Canadian Study of HIV-Infected Adults and a Vaccine for Ebola - ACHIV-Ebola [Internet]. 2017. Available from: https://clinicaltrials.gov/ct2/show/NCT03031912.

57. de Wit E, Marzi A, Bushmaker T, Brining D, Scott D, Richt JA, et al. Safety of recombinant VSV-Ebola virus vaccine vector in pigs. Emerg Infect Dis. 2015;21(4):702-4.

58. Geisbert TW, Feldmann H. Recombinant vesicular stomatitis virus–based vaccines against Ebola and Marburg virus infections. J Infect Dis. 2011;204(suppl_3):S1075-81.

59. European Medicines Agency. Annex I: Summary of Product Characteristics [Internet]. 2019. Available from: https://ec.europa.eu/health/documents/community-register/2019/20191111146469/anx_146469_en.pdf.

60. Public Health Agency of Canada. Public Health Management of Cases and Contacts of Ebola Virus Disease in the Community Setting in Canada [Internet]. 2018. Available from: https://www.canada.ca/en/public-health/services/diseases/ebola/health-professionals-ebola/interim-guidance-public-health-management-cases-contacts-ebola-community-setting-canada.html.

61. Public Health Agency of Canada. Infection Prevention and Control Expert Working Group: Advice on Infection Prevention and Control Measures for Ebola Virus Disease in Healthcare Settings [Internet]. 2015. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/viral-haemorrhagic-fevers/infection-prevention-control-expert-working-group-advice-on-infection-prevention-control-measures-ebola-virus-disease-healthcare-settings-1.html.

62. Osterholm MT, Moore KA, Kelley NS, Brosseau LM, Wong G, Murphy FA, et al. Transmission of Ebola viruses: what we know and what we do not know. MBio. 2015;6(2):e00137-15.

63. Canadian Food Inspection Agency. Statement on Imported Bush Meat from Africa [Internet]. 2014. Available from: http://www.inspection.gc.ca/food/archived-food-guidance/meat-and-poultry-products/imports/imported-bush-meat-from-africa/eng/1414092166342/1414092167045.

64. Lai L, Davey R, Beck A, Xu Y, Suffredini AF, Palmore T, et al. Emergency postexposure vaccination with vesicular stomatitis virus–vectored Ebola vaccine after needlestick. JAMA. 2015;313(12):1249-55.

APPENDIX A: SEARCH STRATEGY AND RESULTS

Search strategy for rVSV-ZEBOV vaccine in Medline, Embase, Global Health, Scopus, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database

#	Searches
1	(rVSV-ZEBOV or VSVDG-ZEBOV or VSV-EBOV or V920).mp.
2	(recombinant vesicular stomatitis virus zaire ebola virus or Recombinant vesicular stomatitis virus Zaire Ebolavirus).mp.
3	or/1-2
4	ebola*.mp.
5	(Merck or National Microbiology Laboratory or "Public Health Agency of Canada" or PHAC or Newlink).mp.
6	and/4-5
7	or/3,6
8	remove duplicates from 7

Search strategy for rVSVΔG-ZEBOV-GP vaccine in Scopus

(((TITLE-ABS-KEY (rvsv-zebov OR vsvdg-zebov OR vsv-ebov OR v920)) OR (TITLE-ABS-KEY (recombinant AND vesicular AND stomatitis AND virus AND zaire AND ebola AND virus OR recombinant AND vesicular AND stomatitis AND virus AND zaire AND ebolavirus))) OR ((TITLE-ABS-KEY (merck OR "National Microbiology Laboratory" OR "Public Health Agency of Canada" OR phac OR newlink)) AND (TITLE-ABS-KEY (ebola*)))) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "French"))

Search strategy for rVSVΔG-ZEBOV-GP vaccine in ClinicalTrials.gov

rvsv-zebov | Ebola Virus Disease or Ebola; V920 | Ebola Virus Disease or Ebola; vsvdg-zebov | Ebola Virus Disease or Ebola; vsv-zebov Ebola Virus Disease or Ebola; vsv-ebov | Ebola Virus Disease or Ebola; or recombinant vesicular | Ebola Virus Disease or Ebola above

Search strategy for ring vaccination in Medline, Embase, Global Health, Scopus, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, NHS Economic Evaluation Database

#	Searches
1	((ring or rings) adj5 (immunis* or immuniz* or vaccin* or innoculat*)).mp.
2	remove duplicates from 1
3	limit 2 to (english or french) [Limit not valid in CDSR,ACP Journal Club,DARE,CCA,CLCMR,CLEED; records were retained]

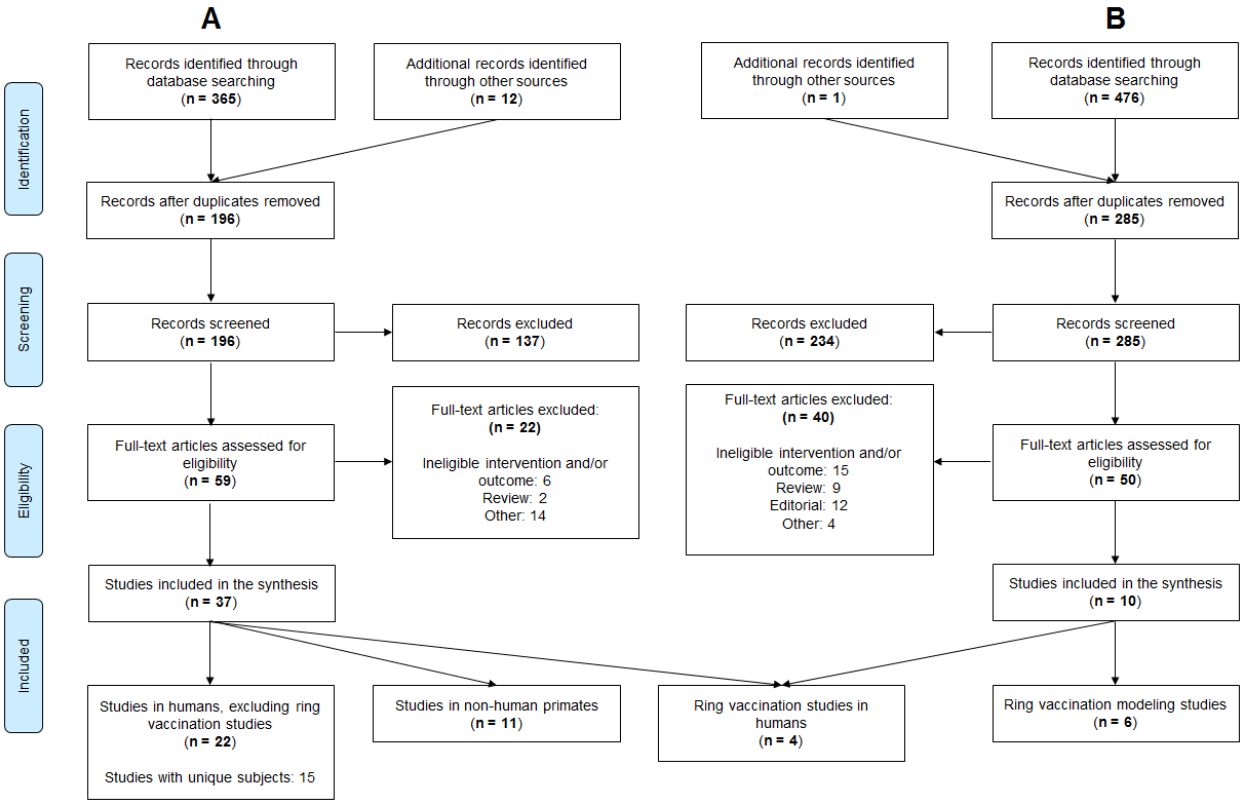
Search strategy for ring vaccination in Scopus

TITLE-ABS-KEY ((RING OR RINGS) W/5 (IMMUNIS* OR IMMUNIZ* OR VACCIN* OR INNOCULAT*)) AND (LIMIT-TO (LANGUAGE , "ENGLISH") OR LIMIT-TO (LANGUAGE , "FRENCH"))

Search strategy for ring vaccination in ClinicalTrials.gov

Ring Vaccine; Ring Vaccination; Ring Immunization; or Ring Inoculation

APPENDIX B: FLOW DIAGRAM OF THE STUDY SELECTION PROCESS FROM THE (A) RVSVΔG-ZEBOV-GP VACCINE AND (B) RING VACCINATION SEARCHES



APPENDIX C: SUMMARY OF EVIDENCE RELATED TO THE SAFETY, IMMUNOGENICITY, EFFICACY, AND EFFECTIVENESS OF THE RVSVΔG-ZEBOV-GP VACCINE IN HUMANS

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
Phase 1 clinical trials					
Citation Regules et al. 2017 (12) Farooq et al. 2016 (11) (additional analysis) **Study ID** V920-001 (NCT02269423); V920-002 (NCT02280408)	**Design** Phase 1, double-blind, dose-escalation, randomized, placebo-controlled trial (multi-centre) **Location** United States **Funding** Industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 3×10^6 PFU • 2×10^7 PFU • 1×10^8 PFU Saline placebo	**Population definition** Healthy adults 18–65 years of age. Exclusion criteria included pregnant or lactating women, individuals with HIV, those with a history or predisposition to VSV or filovirus exposure, and those with clinically significant medical conditions. **Sample size** Total: 78 • 3×10^6 PFU: 20 (10 received a second dose at day 28) • 2×10^7 PFU: 20 (10 received a second dose at day 28) • 1×10^8 pfu: 20 (10 received a second dose at day 28)	**Immunogenicity** • Seroconversion rates at day 14 post-vaccination for GP-specific IgG antibodies (≥4-fold increase from baseline value) were observed in 80% (n=16), 95% (n=19), and 90% (n=18) of subjects who received the 3×10^6 PFU, 2×10^7 PFU, and 1×10^8 PFU doses. All subjects seroconverted by day 28. Subjects who received the higher doses (2×10^7 and 1×10^8 PFU) had higher GMTs than subjects who received the lower dose (3×10^6 PFU). GMTs peaked at day 28 for the 2×10^7 PFU dose and at day 56 for the $3x10^6$ and 1×10^8 PFU doses. There was no significant difference in GMTs between those who received the 2×10^7 and 1×10^8 PFU doses. All dose groups had comparable titres by day 180. • Subjects in all dose groups who received a second dose had increasing GMTs from day 28–56. Subjects in the lowest dose group	I Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			• Placebo: 18 Second dose was given to subjects at 1 study site only. **Baseline characteristics** Similar across groups. Mean age of 35.8 years. 29% female.	who received 1 dose had decreasing GMTs from day 28–84. At day 180, there was no significant difference in GMTs between groups that received a second dose of vaccine and those that received a single dose. • There was a dose-dependent response in neutralizing antibody titres that paralleled the trend for IgG titres, including a peak at day 28 and decrease/plateau as of day 180. Neutralizing antibody titres were similar for the higher dose groups (2×10^7 and 1×10^8 PFU). **Safety** • Mild-to-moderate injection site pain was observed in the majority of subjects. Systemic reactogenicity was transient and mild-to-moderate in severity in the majority of vaccinated subjects. There was no association between vaccine dose and the frequency or severity of adverse events. • Fever was observed in 33% (n=20) of vaccinated subjects and fever onset and frequency did not appear to be dose-dependent. Fever typically developed 12–24 hours post-vaccination and resolved by the end of 1 day post-vaccination. Other commonly reported systemic	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				symptoms include headache, myalgia, and fatigue with typical onset of 12–24 hours post-vaccination. • Oral ulcers developed in 5 vaccine recipients 4–16 days post-vaccination. • Arthralgia was reported by 31.7% (n=19) of vaccinated subjects with most occurring within a week post-vaccination. No clinical cases of arthritis were diagnosed. • Transient mild-to-moderate lymphopenia occurred in 40% (n=24) of vaccinated subjects with abatement by day 3 post-vaccination as well as mild-to-moderate neutropenia in 23% (n=14) of vaccinated subjects with abatement within 2–4 days post-vaccination. • All subjects had detectable rVSV viremia on day 1 or 3 confirmed by PCR, becoming undetectable by day 14 post-vaccination in all subjects. • No SAEs were reported.	
Citation ElSherif et al. 2017 (13) **Study ID** V920-003 (NCT02374385)	**Design** Phase 1, observer-blind, dose-ranging, randomized, placebo-	**Vaccine** rVSVΔG-ZEBOV-GP: • 1×10^5 PFU • 5×10^5 PFU • 3×10^6 PFU	**Population definition** Healthy adults 18–65 years of age. Exclusion criteria included pregnant or lactating women,	**Immunogenicity** • Seroconversion rates at 14 days post-vaccination for GP-specific IgG antibodies (≥4-fold increase from baseline value without elevated titre at baseline) were significantly higher in rVSVΔG-ZEBOV-GP vs. placebo	I Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
	controlled trial (single centre) **Location** Canada **Funding** No industry funding	Saline placebo	immunocompromised individuals, those with a history or predisposition to VSV or filovirus exposure, and those with underlying medical conditions. **Sample size** Total: 40 • 1×10^5 PFU: 10 • 5×10^5 PFU: 10 • 3×10^6 PFU: 10 • Placebo: 10 **Baseline characteristics** Similar across groups. Mean age of 35.6 years. 60% female among all vaccines.	recipients (83.7% vs. 2.8%, p<0.001); seroconversion rates remained significantly higher in the rVSVΔG-ZEBOV-GP group at 12 months post-vaccination (79.5% vs. 6.8%, p<0.001). GMTs increased over time up to day 180 post-vaccination for the 1×10^5 and 5×10^5 PFU doses and peaking at day 28 post-vaccination for the 3×10^6 PFU dose; a faster response was seen for the higher dose. Titres remained comparable across all doses at day 180 and were significantly higher than placebo. • Seroconversion at 28 days post-vaccination was observed for most individuals (even vaccinees of the lowest doses). Seroconversion rates were similar between IgG and neutralizing antibodies, but dose response was not evident for neutralizing antibodies. **Safety** • Solicited adverse events were mild to moderate with headache being the most frequent systemic reaction. Onset of these symptoms ranged from the day of vaccination to 14 days post-vaccination, lasting 1–9 days. Mild-to-moderate injection-site pain was also more common in vaccinees compared to placebo	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				recipients and was more frequent with increasing dose. Arthralgia and myalgia within 14 days post-vaccination were frequent, of mild-to-moderate intensity, and were more frequent with increasing dose. • Unsolicited adverse events were reported by 60% of vaccine recipients, but were mostly mild to moderate, except a report of severe arthralgia that started at day 18 post-vaccination and lasted 1 day. No cases of arthritis were observed. • rVSV viremia in the blood was detected in 2 subjects receiving 3×10^6 PFU by day 2 post-vaccination and 60% (n=18) of vaccinated subjects at day 3 post-vaccination, with the greatest frequency in the highest dose group. Blood viremia was not detected at 7 days post-vaccination. No virus shedding was detected in saliva or urine. • No vaccine-related SAEs were reported.	
Citation Heppner et al. 2017 (14) **Study ID** V920-004 (NCT02314923)	**Design** Phase 1b, double-blind, dose-response, randomized, placebo-	**Vaccine** rVSVΔG-ZEBOV-GP: • 3×10^3 PFU • 3×10^4 PFU • 3×10^5 PFU • 3×10^6 PFU	**Population definition** Healthy adults 18–60 years of age. Exclusion criteria included pregnant or lactating women and	**Immunogenicity** • Seroconversion against GP-specific IgG was achieved in most vaccine recipients at day 28 post-vaccination, even at the lowest doses, with titres peaking at day 56 or 84 (titres were not checked at day 84 for $\geq9\times10^6$	I Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
	controlled trial (multi-centre) **Location** USA **Funding** Industry funding	• 9×10^6 PFU • 2×10^7 PFU • 1×10^8 PFU Saline placebo	individuals with immunodeficiency, including HIV infection. **Sample size** Total: 513 (2 cohorts) • 3×10^3 PFU: 64 • 3×10^4 PFU: 64 • 3×10^5 PFU: 64 • 3×10^6 PFU: 80 • 9×10^6 PFU: 50 • 2×10^7 PFU: 50 • 1×10^8 PFU: 50 • Placebo: 90 **Baseline characteristics** Similar across groups. Mean age of 37.1 years. 47.4% female among all vaccinees.	PFU dose groups) and persisting with minimal change to day 360. Dose response was observed with the highest titres at day 28 post-vaccination in the 1×10^8 and 2×10^7 PFU dose groups (no statistically significant difference between these dose groups) and the lowest titres in the 3×10^3 and 3×10^4 PFU dose groups. Time to onset of the immune response was dose-related, with seroconversion rates lower in the low-dose groups than in the high-dose groups. • IgG and neutralizing antibodies were both dose-related, strongly correlated at day 28, and persisted for 1 year. **Safety** • Most common adverse events occurred in the first day post-vaccination and were of mild-to-moderate intensity, of short duration, and dose dependent. The most common local adverse events at the 2×10^7 PFU dose within 14 days post-vaccination were arm pain (57.4%) and local tenderness (59.6%). The most common systemic adverse events at this dose within 14 days post-vaccination were headache (46.8%), fatigue (38.3%), myalgia (34.0%), subjective fever (29.8%),	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				shivering or chills (27.7%), sweats (23.4%), joint aches and pain (19.1%), objective fever (14.9%), and joint tenderness or swelling (14.9%). • Self-limited post-vaccination arthritis occurred in 4.5% of vaccine recipients vs. 2.1% of placebo recipients with median onset on day 12 and duration of 8 days for vaccinees and no apparent dose relationship, but the risk of post-vaccination arthralgia increased with age. Post-vaccination dermatitis occurred in 5.7% of vaccine recipients vs. 3.2% of placebo recipients and was self-limited. Mouth ulcers and mucosal lesions were detected in 1.9% of vaccine recipients vs. 1.1% of placebo recipients. • Transient dose-related decreases from baseline were noted in vaccinees for lymphocytes and neutrophils at day 7, normalizing by day 28. • Low-level, transient, and dose-dependent viremia occurred in 19.6% of vaccine recipients and mostly within 2 days post-vaccination. Of these, only 1 vaccinee had detectable shedding of viral RNA in urine and saliva. • No vaccine-related SAEs were	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				reported.	
Citation Huttner et al. 2015 (15) Agnandji et al. 2016 (16) (supplemental data) Huttner et al. 2018 (29) (supplemental data) **Study ID** V920-005 (NCT02287480)	**Design** Phase 1/2, double-blind, dose-finding, randomized, placebo-controlled trial (single centre) **Location** Switzerland **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 3×10^5 PFU (low dose) • 1×10^7 PFU (high dose) • 5×10^7 PFU (high dose) Saline placebo	**Population definition** Healthy adults aged 18–65 years of age. Exclusion criteria included pregnant or lactating women and those who are not immunocompetent. **Sample size** Total: 115 • 3×10^5 PFU: 51 (13 open-label) • 1×10^7 PFU: 35 (19 open-label) • 5×10^7 PFU: 16 • Placebo: 13 **Baseline characteristics** Similar across groups. Mean age of 36 years. 46% female overall.	**Immunogenicity** • Seropositivity rates on day 28 for GP-specific IgG antibodies (titre ≥50) were similar for low-dose (94%) and high-dose (100%) recipients, but with significantly lower IgG GMTs (fold-increase of about 3) observed in low-dose vs. high-dose recipients (p=0.002). Time to onset of the immune response was dose-related. GP-specific antibodies increased significantly at day 28 and peaked at day 84 post-vaccination. The 5×10^7 PFU dose elicited a higher GMT at day 84 than the 1×10^7 PFU dose but the 95% CI were wide and overlapping. Antibody persistence was correlated with time (higher at 1 year than at 2 years follow up) and with dose (100% of participants given a 1×10^7 or 5×10^7 PFU dose retained antibodies after 2 years, whereas only 89% of 3×10^5 PFU recipients remained positive over the same interval). • Neutralizing antibody titres increased significantly by 28 in all dose groups with seropositivity of 64–71%. By day 180, titres fell significantly in all dose groups, with seropositivity dropping to 27–31%. Neutralizing antibody	I Fair (open-label vaccinations and study interruption leading to withdrawals)

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				responses were less durable than IgG response. No dose response was seen. **Safety** • Solicited reactogenicity, unsolicited events, or both within 14 days post-injection were noted in 88% (n=45) of low-dose recipients vs. 98% (n=50) of high-dose and 15% (n=2) of placebo recipients (p=0.141). Most events were mild or moderate and their incidence and intensity did not differ significantly between low-dose and placebo recipients. Local pain, subjective and objective fever, and myalgia were significantly less common and less intense in low-dose vs. high-dose recipients. Onset of reactogenicity was significantly later in low-dose vs. high-dose recipients. Duration of reactogenicity was similar between low-dose and high-dose vaccine recipients (median of 1 day with IQR of <24 hours to 3 days). • Lymphocyte, neutrophil, and platelet counts decreased between days 1 and 3 after injection. The decreases were significantly milder in low-dose vs. high-dose vaccinees. • rVSV viremia was minimal, mostly resolved by day 7, and significantly reduced in low-dose vs. high-dose	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				recipients. • Arthralgia was experienced by 25% (n=13) of low-dose recipients after a median of 10 days post-vaccination compared with 22% (n=11) of high-dose recipients. Arthritis was associated with increasing age in low-dose but not in high-dose recipients. Pain lasted a median of 18 days and was mainly of mild-to-moderate intensity. • Dermatitis developed in 54% (n=7) of low-dose recipients with arthritis vs. 27% (n=3) of high-dose recipients with arthritis. • Vasculitis developed in 1 each of low-dose and high-dose recipients. • No SAEs were reported.	
Citation Agnandji et al. 2016 (16) Dahlke et al. 2017 (17) (additional analysis) Fischer et al. 2018 (18) (additional analysis) **Study ID** V920-006	**Design** Phase 1, open-label, dose-escalation, non-randomized, non-controlled trial (single centre) **Location** Germany	**Vaccine** rVSVΔG-ZEBOV-GP: • 3×10^5 PFU • 3×10^6 PFU • 2×10^7 PFU	**Population definition** Healthy adults aged 18–55 years of age. Exclusion criteria included pregnant or lactating women and individuals with immunosuppressive or deficient condition. **Sample size** Total: 30 • 3×10^5 PFU: 10	**Immunogenicity** • All vaccinees were seropositive by day 28. A significant increase in GP-specific IgG antibodies was observed after any vaccine dose at day 28, peaking at day 28, and persisting with a non-significant decline to day 180 post-vaccination. • Neutralizing antibody response was similar in trend as the IgG response: a dose-related increase on day 28 and persistence until day 180 with a non-significant decline.	II-1 Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
(NCT02283099)	**Funding** No industry funding		• 3×10^6 PFU: 10 • 2×10^7 PFU: 10 **Baseline characteristics** Similar across groups. Mean age of 38.8 years. 66.7% female overall.	**Safety** • Adverse events were experienced by 97% (n=29) of subjects. The majority of adverse events were mild and all adverse events were transient (median duration of 2.14 days) and peaking at 1–2 days post-vaccination. No significant dose effect was detected. Most frequent adverse events were pain at injection site, myalgia, and headache. • Fever, rVSV viremia, and lymphopenia were observed in the higher dose groups, but not in the lowest dose group. • 4 subjects experienced unsolicited adverse events (3 among the lowest dose group): 3 cases of arthralgia and 1 case of oligoarthritis – all were transient and of mild-to-moderate intensity. • No vaccine-related SAEs were reported.	
Citation Agnandji et al. 2017 [19] **Study ID** V920-007 (PACTR-201411000919191)	**Design** Phase 1, open label, dose-finding, randomized trial (single centre)	**Vaccine** rVSVΔG-ZEBOV-GP: • 3×10^3 PFU • 3×10^4 PFU • 3×10^5 PFU • 3×10^6 PFU • 2×10^7 PFU	**Population definition** Healthy individuals 6–50 years of age. Exclusion criteria included pregnant or lactating women and individuals with immunodeficiency,	**Immunogenicity** *Adults* • 11% (13/114) of adults had GP-specific IgG antibody titres >200 EU/mL at baseline and 27% (31/115) had titres >500 EU/mL at baseline. These vaccinated individuals had significantly higher antibody	I Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
	Location Gabon **Funding** No industry funding	Saline placebo	including HIV infection. **Sample size** Total: 115 adults and 40 children (6–12 years) and adolescents (13–17 years) • 3×10^3 pfu: 20 adults • 3×10^4 pfu: 20 adults • 3×10^5 pfu: 20 adults • 3×10^6 pfu: 39 adults • 2×10^7 pfu: 16 adults and 40 children and adolescents **Baseline characteristics** Similar across groups. Mean age of 23–28 years for adults, 15 years for adolescents, and 9 years for children. 18.3% female among vaccinees.	concentrations than adults without baseline GP-specific antibodies at day 56 post-vaccination at some doses. • 70–100% vaccinated with doses ≥3×10^4 PFU reached ≥4-fold increase of GP-specific GMT by day 28, with titres peaking at day 56 and persisting higher than baseline up to 180 days post-vaccination. Highest titres were observed with the 2×10^7 PFU dose regardless of baseline antibody status. *Children and adolescents* • 0% and 7% of children and adolescents, respectively, were seropositive for GP-specific IgG antibodies at baseline. As in adults, those with pre-existing immunity had higher responses to the vaccine at days 28 and 56 post-vaccination. • 95% of children and 100% of adolescents who received a 2×10^7 PFU dose reached ≥4-fold increase of GP-specific GMT by day 28, with titres peaking at 180 days post-vaccination. *All vaccinees* • In vaccinees with detectable pre-vaccination ZEBOV GP-specific IgG antibody titres, a vaccine dose as low	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				as 3×10^4 PFU induced high antibody titres. • Highest titres of neutralizing antibodies were observed at day 28 with the 2×10^7 PFU dose. Children had higher neutralizing antibody titres compared with adolescents or adults. **Safety** *Adults* • Headaches, fatigue, pain at injection site, gastrointestinal symptoms, and subjective fever were the most frequently reported, and of these, most were of mild-to-moderate intensity. Frequency of events was similar across doses up to day 28. • Monocytes increased and lymphocytes decreased in the first week post-vaccination in a dose-dependent fashion. • No vaccine-related SAEs were reported. *Pregnant women* • 3 women became pregnant after vaccination and their neonates had no safety complications. *Children and adolescents* • Headaches, fatigue, pain at injection site, gastrointestinal symptoms, and subjective fever were most frequently	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				reported. All symptoms were of mild-to-moderate intensity. • Monocytes and lymphocytes increased between days 2–7 and leukocytes decreased in the first week post-vaccination. Leukocytes gradually restored to baseline values by day 28 and lymphocytes rapidly restored to baseline values by day 7. • No vaccine-related SAEs were reported. *All vaccinees* • Children and adolescents had significantly higher rVSVΔG-ZEBOV-GP RNA copy numbers in plasma at day 2 post-vaccination compared to adults. A considerably higher proportion of children and adolescents had detectable viral shedding in saliva.	
Citation Agnandji et al. 2016 (16) **Study ID** V920-008 (NCT02296983)	**Design** Phase 1, open-label, dose-escalation, non-randomized, non-controlled trial	**Vaccine** rVSVΔG-ZEBOV-GP: • 3×10^6 PFU • 1×10^7 PFU	**Population definition** Healthy adults 18–55 years of age. Exclusion criteria included pregnant or lactating women. **Sample size** Total: 40 • 3×10^6 PFU: 20	**Immunogenicity** • GP-specific IgG antibodies were detected in all vaccine recipients at day 28 post-vaccination for the 3×10^6 PFU dose, peaking at day 28, and persisting to day 180 without significant decline. GP-specific antibodies were detected at day 180 post-vaccination for the 2×10^7 PFU dose (day 28 was not presented). The 2×10^7 PFU dose elicited a higher	II-3 Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
	Location Kenya **Funding** No industry funding		• 2×10^7 PFU: 20 **Baseline characteristics** Similar across groups with the exception of race. Mean age of 42–43 years. 25% female among vaccinees.	GMT at day 180 than the 3×10^6 PFU dose. **Safety** • 85% of the 3×10^6 PFU dose vaccine recipients reported any adverse event within 14 days post-vaccination, with most events being mild or moderate. Common symptoms included pain at injection site, objective fever, myalgia, and headache. • 4 moderate arthralgia events were observed in the first week post-vaccination (20% of vaccine recipients) and 1 arthritis event was observed in the second week post-vaccination among recipients of the 3×10^6 PFU dose. Oral vesicles were not observed for this dose group. • Low-level viremia was detected in most subjects between 1–3 days post-vaccination, with higher copies detected for the higher dose. Most resolved by day 7. • No vaccine-related SAE was observed.	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
Phase 2/3 clinical trials					
Citation Kennedy et al. 2017 (20) **Study ID** V920-009 ("PREVAIL"; NCT02344407)	**Design** Phase 2/3, double-blind, randomized, placebo-controlled trial (single centre) **Location** Liberia **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU ChAd3-EBO-Z (chimpanzee adenovirus 3-based vaccine) Saline placebo	**Population definition** Adults 18 years of age and older. Exclusion criteria included pregnant or breastfeeding women and individuals with a history of EVD infection. **Sample size** Total: 1500 • rVSVΔG-ZEBOV-GP: 500 • ChAd3-EBO-Z: 500 • Placebo: 500 **Baseline characteristics** Similar across groups. Median age of 30 years. 36.6% female overall.	**Immunogenicity** • Seroconversion rates at 1 month post-vaccination for GP-specific IgG antibodies (≥4-fold increase from baseline value without elevated titre at baseline) were significantly higher in rVSVΔG-ZEBOV-GP vs. placebo recipients (83.7% vs. 2.8%, p<0.001). Seroconversion rate remained significantly higher in the rVSVΔG-ZEBOV-GP group at 12 months post-vaccination (79.5% vs. 6.8%, p<0.001). GMT was highest at 1 month post-vaccination, declined at 6 months, and persisted to 12 months. *HIV-infected individuals* • Seroconversion rates at 1 month post-vaccination for GP-specific IgG antibodies were significantly lower in HIV-infected (n=13) vs. non-HIV-infected rVSVΔG-ZEBOV-GP recipients (61.9% vs. 84.7%, p<0.01). **Safety** • Injection site reactions were reported in 30.9% of those in the rVSVΔG-ZEBOV-GP group and 6.8% of those in the placebo group (p<0.001). The most common events were headache (31.9%), fever (30.5%), muscle pain (26.9%), and fatigue (15.4%).	I Good (phase 3 component could not be conducted due to the rapid decline in EVD cases)

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				Solicited events were reported more often at week 1 compared to placebo ($p<0.001$), but did not differ significantly at month 1. • Joint pain did not significantly differ between the rVSVΔG-ZEBOV-GP and placebo groups. • Plasma rVSVΔG-ZEBOV-GP RNA was detected in 2 of 8 subjects and none of those who received ChAd3-EBO-Z or placebo. • Within 1 month after vaccination, 20 subjects had an SAE, including 6 (1.2%) in the rVSVΔG-ZEBOV-GP group vs. 8 (1.6%) in the placebo group ($p=0.68$). 70% of SAEs were attributed to malaria. *HIV-infected individuals* • Of 22 HIV-infected individuals who received the vaccine, two serious adverse events that were attributed to gastroenteritis and respiratory failure occurred in one subject.	
Citation Henao-Restrepo et al. 2017 (21) Henao-Restrepo et al. 2015 (22) (interim findings)	**Design** Phase 3, open-label, cluster-randomized ring vaccination trial (multi-	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU	**Population definition** Contacts and contacts of contacts of confirmed EVD cases (a cluster or "ring"). Contacts were defined as individuals who	**Ring vaccination characteristics** • Mean time from symptom onset in index cases to ring inclusion ranged from 7.3–10.9 days with median cluster sizes of 80–105 people. More than 80% of contacts and contacts of contacts were defined as contacts of contacts and 15% of immediately	I Fair (non-randomized clusters offering immediate vaccination

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
Study ID V920-010 ("Ebola ça suffit"; PACTR-201503001057193)	centre) **Location** Guinea and Sierra Leone **Funding** No industry funding		lived in the same household, visited or were visited by the index case after the onset of symptoms, provided the index case with unprotected care, or prepared the body for the traditional funeral ceremony. These contacts included high-risk contacts who were in close physical contact with the patient's body or body fluids, linens, or clothing. Contacts of contacts were the neighbours of the index case to the nearest appropriate geographical boundary plus the household members of any high-risk contacts living away from the index cases' residence. Exclusion criteria included pregnant and	vaccinated and 9% of delayed or never vaccinated were high-risk contacts. **Effectiveness** • Vaccine efficacy of immediate compared to delayed ring vaccination (including never-vaccinated) against confirmed EVD ≥10 days post-vaccination was 100% (95% CI: 77.0–100.0%). No EVD cases occurred in 3775 individuals receiving immediate vaccination ≥10 days post-vaccination (through the 84 day follow up period) while 34 cases occurred in 7995 individuals assigned to delayed vaccination. EVD cases occurred in the first 10 days after randomization at similar attack rates (0.3–0.8%) regardless of vaccination status or study eligibility. Because no EVD cases occurred ≥10 days post-vaccination in the immediately vaccinated group, the vaccine effectiveness during this time period against death due to EVD was 100%. • Vaccine effectiveness in protecting all contacts and contacts of contacts in the randomized clusters (immediate vs. delayed vaccination and including unvaccinated cluster members) against confirmed EVD ≥10 days post-vaccination was 64.6% (95% CI:	and expansion of study eligibility to include children were implemented later into the study period)

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			breastfeeding women, severely ill, those <18 years of age (vaccination was later offered to children 6–17 years of age), and those with a history of EVD. **Sample size** Total: 117 clusters with 5837 vaccinated subjects (194 vaccinated individuals were children 6–17 years of age) • Immediate vaccination: 70 clusters (51 randomized and 19 non-randomized) • Delayed vaccination (21 days after enrolment): 47 clusters **Baseline characteristics** Broadly comparable among index cases and contacts and	-44.2–91.3%), with a vaccination rate of 65.6% among eligible contacts and contacts of contacts. **Safety** • 53.9% of individuals reported at least one adverse event in the 14 days post-vaccination. Nearly all events were mild or moderate, with headache (25.4%), fatigue (18.9%), and muscle pain (13.1%) being the most commonly reported. Arthralgia was reported by 17.9% of vaccinated subjects with a mean duration of 2 days and resolved spontaneously without sequelae. • 2 SAEs were judged to be vaccine-related (1 febrile reaction and 1 anaphylaxis) and 1 possibly related (influenza-like illness). All 3 recovered without sequelae. *Children* • In the 3 days post-vaccination, of 97 reported solicited adverse events in children, the most common were headache (52.6%), fatigue (11.3%), and injection pain (9.3%), whereas for adults the most common were headache (25.0%), fatigue (19.0%), and muscle pain (13.2%). Arthralgia was reported by 2.2% of vaccinated children and 18.5% of vaccinated	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			contacts of contacts. Median age of 35 years. 53% female assigned to immediate vaccination and 66% female assigned to delayed vaccination.	adults with a mean duration of 2 days.	
Citation Samai et al. 2018 (24) Conteh et al. 2018 (23) (supplemental data) **Study ID** V920-011 ("STRIVE"; NCT02378753)	**Design** Phase 2/3, open-label, randomized trial (multi-centre) **Location** Sierra Leone **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU	**Population definition** Healthcare and frontline Ebola response workers ≥18 years of age. Exclusion criteria included pregnant or breastfeeding women and individuals with immunodeficiency, including HIV infection. **Sample size** Total: 8651 in main study and 436 in safety sub-study • Immediate vaccination (within 7 days of enrolment): 4319 • Delayed vaccination (18–	**Safety** • 91.2% of safety sub-study vaccine recipients reported systematic adverse events within 7 days of vaccination compared with 35.5% of unvaccinated subjects. Vaccine recipients were more likely to experience fever, feverishness, fatigue, feeling unwell, muscle pain, joint pain, chills, headache, nausea, abdominal pain, rash, and skin vesicles, with most of these events occurring within 1–2 days of vaccination, being of mild-to-moderate severity, and resolving within 5 days. • Between 5–28 days post-vaccination, vaccinated subjects were significantly more likely than unvaccinated subjects to report joint pain (16.7% vs. 4.8%) and rash (7.8% vs. 1.7%). Vaccinated subjects were significantly more likely to report skin vesicles (2.0% vs. 0%) and oral	I Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			24 weeks after enrolment): 4332 **Baseline characteristics** Similar between main study and safety sub-study. Median age of 30.7 years. 36.9% female among vaccinated.	ulcers (2.0% vs. 0%) in the second week post-vaccination. • No vaccine-related SAEs were reported in the main study. *Pregnant women* • 104 gestations in 103 women (43 vaccinated and 60 unvaccinated) occurred within 2 months after vaccination or enrolment. Among those with known birth outcomes, pregnancy losses were comparable between vaccinated and unvaccinated women. No congenital anomalies were diagnosed among 38 infants who were followed up for 28 days and in a neonatal death. A WHO report published on July 12, 2019 provided additional safety data for pregnant women in this study: among 261 pregnant women who received the vaccine, the frequency of pregnancy loss was higher in the group receiving immediate vaccination compared with the group receiving delayed vaccination. The reasons for the difference are unknown.	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
Citation Halperin et al. 2017 (25) Halperin et al. 2019 (30) (supplemental data) **Study ID** V920-012 (NCT02503202)	**Design** Phase 3, double-blind, randomized, placebo-controlled trial (multi-centre) **Location** Canada (1 site), Spain (1 site), and the United States (40 sites) **Funding** Industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU • 1×10^8 PFU Saline placebo	**Population definition** Healthy adults 18–65 years of age. Exclusion criteria included pregnant or breastfeeding women and those who have impaired immunological function, including HIV infection. **Sample size** Total: 1197 • 2×10^7 PFU: 798 (3 consistency lots) • 1×10^8 PFU: 266 • Placebo: 133 **Baseline characteristics** Similar across groups. Mean age of 41 years. 52.1% female among vaccinees.	**Immunogenicity** • Seroconversion rates for GP-specific IgG antibodies (≥2-fold increase from baseline value and antibody titre ≥200 EU/mL, or ≥4-fold increase from baseline value) were >94% in each vaccine group by day 28 post-vaccination and >88% by month 24 post-vaccination. GP-specific IgG antibodies increased significantly at day 28 and persisted through 24 months without significant decline in any vaccine group. Geometric mean fold rises of ≥58-fold-rise from baseline were observed across vaccine groups and were durable over 24 months (≥43-fold-rise at all timepoints and in all vaccine groups) • Neutralizing antibody titres increased by day 28 post-vaccination in all vaccine groups, peaked at 18 months, and did not decrease at 24 months. Seroresponse rates for neutralizing antibodies (≥4-fold increase from baseline value) remained high (≥82%) across timepoints and in all vaccine groups. **Safety** • At least one adverse event was reported by 81–85% of vaccinated subjects compared with 44% of placebo recipients. Most events were	I Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				of mild-to-moderate intensity and resolved within 1 week. The most common events were fever, headache, and arthralgia. • Higher rates of rash were observed in the 2×10^7 PFU dose group (3.8%) and 1×10^8 PFU group (3.8%) compared to the placebo group (1.5%), but the differences between groups were not statistically significant. Rash had a median onset of 7.5 days and a median duration of 6 days. • Arthralgia and arthritis were reported at a statistically significantly higher rate in the vaccine groups than in the placebo group. 17.1% of vaccinees developed arthralgia. Arthralgia had a median onset of 2 days and a median duration of 3 days. 5.1% of vaccinees developed arthritis, with a median onset of 11 days and a median duration of 7 days. Arthritis was more commonly reported in vaccinees 46–65 years of age compared with vaccinees 18–45 years of age. The median duration of arthritis was 7 and 5 days for the 2×10^7 PFU and 1×10^8 PFU dose groups respectively. These events were mild-to-moderate in intensity, with severe arthralgia reported by 0.8% (2×10^7 PFU) and 3.1% (1×10^8 PFU) of participants and	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				severe arthritis reported by 0.4% of participants (all vaccine groups combined). Female sex and a medical history of arthritis were identified as potential risk factors for the development of arthritis post-vaccination, while treatment dose, body mass index, age, and race were not significant risk factors. • 21 SAEs and 2 deaths were reported within 6 months post-vaccination; all were assessed by investigators as unrelated to the vaccine. During 24 months post-vaccination, 35 (4.4%) participants in the 2×10^7 PFU dose group, 8 (3.1%) participants in the 1×10^8 PFU dose group and 4 (3.0%) participants in the placebo group reported SAEs, all considered not related to the vaccine. There were no discontinuations due to adverse events.	
Observational studies					
Citation Bolay et al. 2019 [26]	**Design** Ring vaccination study from November 19 to December 11, 2015	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU	**Population definition** Close contacts and contacts of the close contacts of an EVD cluster case (2 male siblings and their father) who were 6 years of age and older and consented to	**Ring characteristics** • Of the 650 identified close contacts and contacts of close contacts, 57 were healthcare workers and 4 were patients seen at the hospital at the time EVD was diagnosed in cases. 32% of close contacts and contacts of close contacts consented to vaccination. 3.3% reported contact	III

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
	Location Liberia **Funding** No industry funding		vaccination. Exclusion criteria included pregnant and breastfeeding women, children under 6 years of age, and those with a history of EVD. Close contacts were defined as those who lived in the same households as the cases, those who had visited the cases since the onset of their illnesses, and those who were in close physical contact with the cases' body or body fluids, linens, clothing, or dishes. These contacts included people who lived in the households in a ring around the family with EVD, healthcare workers at the associated Ebola treatment unit, and patients being cared for at the same	with body fluids, 92.4% reported contact with close contacts, and 7.1% reported being healthcare workers at a facility visited by one of the cases. The median number of days from laboratory confirmation of EVD in the index until vaccination of contacts was 15 days (range of 4–22 days). **Effectiveness** • No additional EVD cases were identified during the 1–6 month follow-up of the outbreak response. **Immunogenicity** • A significant increase in GP-specific IgG antibody titres was observed at 1 month post-vaccination (median fold-increase of 8.6). **Safety** • At least one adverse event was reported by 56% (n=106) of subjects. The most common solicited events were headache (40%), fever (31%), fatigue (13%), muscle pain (13%), and joint pain (10%). Most events were mild (90%). • No SAEs were reported.	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			hospital of the treatment unit. **Sample size** Total: 210 of 650 (32%) of enumerated contacts and contacts of contacts were vaccinated. **Baseline characteristics** Median age of 33 years. 14% female.		
Citation Gsell et al. 2017 [27]	**Design** Ring vaccination study from March 17 to April 21, 2016 **Location** Guinea **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU	**Population definition** Close contacts and contacts of the close contacts of the EVD index case. Contacts were individuals who visited or were visited by the index case after the onset of symptoms; had lived in the same household; or were in close physical contact with the patient's body, body fluids, linens, or clothing within the last 21	**Ring characteristics** • 20% of vaccinees were 6–17 years of age and 20% were frontline workers. The delay from onset to confirmation of the index case ranged from 4–7 days, with the exception of a case diagnosed on the day of onset. Mean time from ring inclusion to vaccination ranged from 0.5–5.0 days. Mean cluster size was 414 people (range of 75–715). 73–96% of contacts and contacts of contacts were defined as contacts of contacts and 4–27% of contacts and contacts of contacts were defined as high-risk contacts.	III

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			days. Contacts of contacts were defined as neighbours, family, or extended family members who lived within the nearest geographical boundary of all contacts, and the household members of any high-risk contacts. High-risk contacts were defined as in the Ebola ça suffit trial and included contacts who had either touched body fluids, linens, clothing, or dishes; had been in direct physical contact; or had slept and ate in the same household as the index case. Exclusion criteria included pregnant and breastfeeding women, children under 6 years	**Effectiveness** • No secondary cases of EVD occurred among the vaccine recipients within 10 days or 10 or more days post-vaccination (through the 21 day follow up period). All subsequent cases of EVD were individuals who were not counted as part of the rings as contacts of contacts or were infected before the outbreak was identified. **Safety** • 17% of 303 children 6–17 years of age and 36% of 1207 adults reported at least one adverse event following vaccination. All events reported by children were mild and 98% of events reported by adults were mild. Most adverse events occurred between 31 minutes and 3 days post-vaccination. Adults most commonly reported headache (15%), muscle pain (13%), myalgia (13%), fatigue (10%), and arthralgia (7%). Children aged 6–17 years of age most commonly reported headache (12%), muscle pain (4%), and myalgia (3%). Children reported fewer arthralgia events than adults; arthralgia was reported by 1 vaccine recipient aged 6–17 years (<1%) compared to 7% of adult vaccine recipients.	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			of age, severely ill or immunocompromised individuals, or those who had a history of anaphylaxis following vaccination. **Sample size** Total: 1510 of 1659 (91%) of enumerated contacts and contacts of contacts were vaccinated (303 vaccinated individuals were children 6–17 years of age). **Baseline characteristics** 20–48% female.	• No vaccine-related SAEs were reported	
Citation Günther et al. 2011 (28) **Design** Case report **Location** Germany **Funding** No industry funding		**Vaccine** rVSVΔG-ZEBOV-GP: • 5×10^7 PFU	**Case description** Female laboratory worker who received rVSVΔG-ZEBOV-GP PEP (48 hours post-exposure) after a needlestick injury in a biosafety level 4 laboratory.	**Effectiveness** • Subject did not have laboratory evidence of ZEBOV infection. **Safety** • Vaccine recipient developed fever and myalgia on day 1 post-vaccination with temperature returning to normal on the same day. • rVSV viremia was detected on days 1 and 2 post-vaccination.	III

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
Citation Huttner et al. 2018 (29) **Study ID** V920-005/-007/-008 (NCT02933931)	**Design** Prospective cohort study **Location** Gabon, Geneva, and Kenya **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 3×10^5 PFU • 3×10^6 PFU • 1×10^7 PFU • 5×10^7 PFU	**Population definition** Participants of 3 phase 1 clinical trials who were vaccinated once in 2014–2015 with rVSVΔG-ZEBOV-GP vaccine, did not receive further rVSVΔG-ZEBOV-GP vaccination, and had no suspected or documented clinical exposure to Ebola virus throughout the study period. **Sample size** Total: 217 from the original phase 1 trials • Gabon: 75 • Geneva: 102 • Kenya: 40	**Immunogenicity** • Seropositivity (GP-specific IgG titre ≥58.84 EU/mL) was 94% at day 28 post-vaccination (100% for doses ≥3×10^6 PFU). Vaccine dose influenced early (day 28) antibody response. • At 1 year and 2 years post-vaccination, seropositivity remained high and dose dependency was lost. Seropositivity in recipients of ≥3×10^6 PFU dose of vaccine persisted to 1 year (Gabon and Kenya groups) or 2 years (Geneva group) post-vaccination at 100%, whereas delayed seropositivity response was observed in some recipients of the lower 3×10^5 PFU dose. • GMT peaked between 1–3 months post-vaccination, then declined until month 6, and then plateaued between 6 and 12 months (up to 2 years in the Geneva group for high dose recipients) across all doses and sites. In the Geneva group, lower 2 year titres than 1 year titres were observed for recipients of the low dose vaccine (GMT ratio: 0.61, $p<0.0001$). • Lower GMTs at day 28 in subjects given the low dose of vaccine (3×10^5 PFU) were due to a slow response in some individuals and the higher	II-2 Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				doses (≥3×10^6 PFU) induced a more prompt and stronger response. Complete loss of antibody detection was rare after 6 months, occurring in 9% of subjects given the low dose.	
Citation Juan-Giner et al. (in press) [41] **Study ID** V920-010 (Sub-study of "Ebola ça suffit"; PACTR-201503001057193)	**Design** Prospective cohort study (multi-centre) **Location** Guinea **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU	**Population definition** Adult personnel working in health services, including Ebola treatment centres, Ebola outreach, and non-Ebola related health services. Frontline workers who refused vaccination were eligible as controls. Exclusion criteria included previous EVD infection or recent exposure, self-reported clinically important immunodeficiency, history of anaphylaxis to a vaccine or vaccine component, severe illness, pregnancy, and fever.	**Safety** • 74.7% of vaccinated subjects reported an adverse event within 14 days post-vaccination. The most frequently reported events were headache, fatigue, arthralgia, myalgia, and subjective fever. Most events were mild to moderate in intensity and of short duration (lasted a median of 2 days and for most, disappeared within 3–4 days). • Most events were reported within 3 days post-vaccination, with only 13.3% of vaccinated subjects reporting an event starting after the 3 day follow-up visit. The most frequent combination of symptoms reported during the first 3 days post-vaccination were fatigue and headache (31.6% of subjects), and were frequently accompanied by arthralgia (37.4%), myalgia (33.2%), and fever (32.7%). Fever was most common within 48 hours post-vaccination. Local reaction, fatigue, headache, arthralgia, myalgia, and subjective fever occurring within the	II-2 Good

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
			Sample size Total: 2016 vaccinated individuals and 99 unvaccinated controls **Baseline characteristics** Controls were younger and more likely to be female and work in a health centre. Mean age of 33.4 years for vaccinees and 28.3 years for non-vaccinees. 25% females among vaccines and 37.4% females among non-vaccinees.	first 3 days post-vaccination were statistically significantly different in the vaccinated group compared to the unvaccinated group; other symptoms and symptoms occurring after 3 days post-vaccination were not significantly different between the vaccinated and unvaccinated groups. • A total of 8 SAEs were detected among participants between days 2–250 post-vaccination. No vaccine-related SAEs were reported. *Pregnant women* • 12 gestations in 11 vaccinated women occurred within 14–160 days after vaccination (mean of 14.2 weeks). Among the 12 pregnancies, there were no congenital anomalies. 1 woman who was vaccinated 34 days after her last menstruation had a miscarriage. The woman became pregnant 4 months later and gave birth to a healthy baby. A stillbirth occurred at term in a woman vaccinated 37 days after her last menstruation; the woman had a stillbirth 2 years prior.	

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
Citation Kasereka et al. 2019 [42]	**Design** Cross-sectional survey **Location** DRC **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP (dose not specified in the article, but assumed to be 2×10^7 PFU given the study context)	**Population definition** Convenience sample of vaccine recipients and unvaccinated community members 18 years of age and older. **Sample size** Total: 186 • Vaccinated: 90 **Baseline characteristics** Significant differences in rural/urban setting, education, and occupation comparing vaccinees to non-vaccinees.	**Safety** • At least one adverse event was reported by 83% (n=75) of vaccinees. The most common events were headache (69%), fatigue (43%), pain at injection site (43%), and myalgia (24%). Nausea, fever, arthralgia, diarrhea, generalized rash, and vomiting were reported by 4–9% of subjects.	III
Citation Wong et al. 2016 [43] Lai et al. 2015 [64] (supplemental data)	**Design** Case series **Location** West Africa and medically evacuated to the United States within 2–3 days after injury.	**Vaccine** rVSVΔG-ZEBOV-GP: • 1×10^8 PFU TKM-100802 (RNA interfering antiviral)	**Case description** Healthcare workers who received PEP (1–3 days post-exposure) after potential ZEBOV exposure in West Africa. **Sample size** Total: 6 • rVSVΔG-ZEBOV-GP for PEP: 5	**Effectiveness** • Subjects did not have laboratory evidence of ZEBOV infection. No sharps were known to be contaminated with ZEBOV. **Safety** • All subjects experienced transient adverse events within 1 day post-vaccination, with fever, headache, and nausea being the most commonly reported adverse events.	III

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
	Funding No industry funding			Fever began 12–24 hours after vaccination. Diarrhea was reported in 2 subjects. Arthralgia, vomiting, and rash were each reported by 1 subject. Pain at injection site was reported by 3 subjects. All symptoms resolved by day 21 after potential exposure to ZEBOV. • rVSV viremia was detected in 3 subjects.	
Citation World Health Organization 2019 (44)	**Design** Ring vaccination study from August 1, 2018 to March 25, 2019 **Location** DRC **Funding** No industry funding	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU	**Population definition** Contacts and contacts of contacts of an index case. **Sample size** 91,492 of 100,754 (90.8%) contacts and contacts of contacts of 951 confirmed and probable EVD cases were vaccinated. **Baseline characteristics** Median age of 28 years for both index cases and vaccinees. 53% female among index cases and 42% female among vaccinees.	**Ring characteristics** • 679 rings were defined around 776 cases. Due to feasibility and acceptability limitations, rings were not possible around 175 cases. The mean time from symptom onset to confirmation of EVD in the index case was 6 days and the mean time from symptom onset to the start of ring vaccination was 7 days. Rings had a median of 104 people (range of 59 to 157). 73% of the enumerated ring were contacts of contacts with 9% of the members of the ring being high-risk contacts. **Effectiveness** • The estimated vaccine efficacy for those with onset of illness 10 days or more post-vaccination was 97.5% (95% CI: 92.4–99.1%) and for those with EVD regardless of timing of	III

Study	Study design	Intervention*	Population	Summary of key findings	Level & quality of evidence
				onset of illness was 88.1% (95% CI: 79.9–92.9%). • 9 deaths occurred among 56 cases with onset of symptoms 0–9 days after vaccination and no deaths occurred among people where the illness onset occurred 10 or more days post-vaccination. Therefore, the vaccine effectiveness at 10 or more days post-vaccination against EVD-related death was 100% (95% CI: 90.3–100%).	

Abbreviations: CI: confidence interval; DRC: Democratic Republic of the Congo; EU: ELISA unit; EVD: Ebola virus disease; GMT: geometric mean titre; GP: glycoprotein; HIV: *human immunodeficiency virus*; IgG: immunoglobulin G; IQR: interquartile range; PCR: polymerase chain reaction; PEP: post-exposure prophylaxis; PFU: plaque-forming unit; RNA: ribonucleic acid; rVSV: recombinant *vesicular stomatitis virus*; rVSVΔG-ZEBOV-GP: recombinant *vesicular stomatitis virus-Zaire ebolavirus*; SAE: severe adverse event; ZEBOV: *Zaire ebolavirus*.

* The rVSVΔG-ZEBOV-GP vaccine is also referred to as V920 Ebola Zaire Vaccine.

APPENDIX D: SUMMARY OF EVIDENCE RELATED TO THE SAFETY, IMMUNOGENICITY, EFFICACY, AND EFFECTIVENESS OF THE RVSVΔG-ZEBOV-GP VACCINE IN NON-HUMAN PRIMATES

Study	Intervention*	Population	Summary of key findings
Citation Feldmann et al. 2007 [31]	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU rVSV control vaccines (*Marburg virus* or *Lassa virus* GP): • 2×10^7 PFU **Time of administration** Post-exposure: 20–30 min after lethal ZEBOV challenge **Route of administration** IM	10 healthy adult rhesus macaques were challenged by IM inoculation with 1000 PFU of ZEBOV (Mayinga), of which 8 received rVSVΔG-ZEBOV-GP vaccine after lethal challenge and 2 served as experimental controls (1 received an rVSV vaccine expressing *Marburg virus* GP and the other an rVSV vaccine expressing *Lassa virus* GP).	• 4 out of 8 animals survived without showing signs of severe disease after vaccination within 20–30 min of lethal ZEBOV challenge. rVSVΔG-ZEBOV-GP vaccine recipients that succumbed to EVD between days 8–10 following ZEBOV challenge developed plasma ZEBOV viremia on day 6 whereas low-level, transient plasma viremia was seen in animals that survived. 1 animal that had cleared the ZEBOV infection by day 10 died on day 18 due to complications from *Streptococcus pneumoniae*. rVSV viremia was detected in most vaccinated animals on day 3 post-vaccination and did not correlate with survival. • Low IgM antibody titres were detected on days 6–14, moderate IgG antibody titres on days 10–22, and neutralizing antibody titres (1:80) on days 14–37 after challenge in survivors of the ZEBOV challenge and the animal that survived until day 18. Humoral immune responses could not be detected in any of the non-survivors. • A slight decline in circulating CD4+ and CD8+ T cell counts on day 6 after challenge was detected in most animals regardless of intervention or outcome. NK and B cells increased on day 6 regardless of intervention or outcome, with a decline in B cells on day 10.

Study	Intervention*	Population	Summary of key findings
Citation Geisbert et al. 2008 [32]	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU rVSV control vaccine (*Marburg virus* GP): • 2×10^7 PFU **Time of administration** Pre-exposure: 28 days before lethal aerosol ZEBOV challenge **Route of administration** IM	6 male cynomolgus macaques, of which 3 were vaccinated with rVSVΔG-ZEBOV-GP and 3 were vaccinated with the control vaccine, were challenged with an aerosol exposure to 1000 PFU of ZEBOV. The findings for 6 other monkeys used for a *Marburg virus* challenge are not summarized here.	• Control animals started to show clinical signs of disease and high ZEBOV plasma titres on day 6 after challenge and succumbed to ZEBOV infection on days 6, 7, and 8. None of the 3 rVSVΔG-ZEBOV-GP-vaccinated animals became sick from the ZEBOV challenge and all 3 animals survived. A transient low level rVSV viremia was detected on day 2 after vaccination in plasma from 4 of 6 rVSVΔG-ZEBOV-GP-vaccinated animals. rVSV was not detected in swab samples of any animal. • By day of ZEBOV challenge (28 days post-vaccination), all rVSVΔG-ZEBOV-GP-vaccinated animals had developed modest IgG antibody titres against ZEBOV GP and these titres increased after ZEBOV challenge. • No evidence of IFN-γ or TNF-α production in CD4+ or CD8+ T cells was found before or after ZEBOV challenges in any of the animals. • No animals showed any signs of clinical symptoms after vaccination. • Tissue viremia from aerosol challenge mimicked patterns found in IM challenge.
Citation Geisbert et al. 2008 [33]	**Vaccine** rVSVΔG-ZEBOV-GP: • 1×10^7 PFU Saline placebo **Time of administration** Pre-exposure: 31 days before lethal ZEBOV challenge	Of 9 adult rhesus macaques with clinical evidence of SHIV infection (reduced CD4+ T cell counts and SHIV viremia in 4 of 9), 6 received the rVSVΔG-ZEBOV-GP vaccine and 3 receive placebo. All vaccine recipients and 2 controls were challenged with an IM	• 4 of the 6 rVSVΔG-ZEBOV-GP-vaccinated SHIV-infected animals and both placebo control animals started to show clinical signs of disease on day 6 after challenge. Disease progressed in 2 of the rVSVΔG-ZEBOV-GP-vaccinated SHIV-infected animals and both of the placebo control animals; these 2 rVSVΔG-ZEBOV-GP-vaccinated animals died on days 9 and 13 and the placebo control animals died on days 9 and 10. Animals that did not survive had the lowest CD4+ counts, suggesting that CD4+ T cells may play a role in mediating protection

Study	Intervention*	Population	Summary of key findings
	Route of administration IM	inoculation of 1000 PFU of ZEBOV (heterologous Kikwit) 31 days later.	against ZEBOV. Vaccination led to transient rVSV viremia detected on day 2 post-vaccination, with no shedding of vaccine virus. • None of the 6 rVSVΔG-ZEBOV-GP-vaccinated animals developed IgG antibody titres against ZEBOV GP by the day of ZEBOV challenge. 2 animals developed modest IgG antibody titres by day 15 after challenge (day 46 after vaccination) and a third animal developed a titre by day 28 after challenge (day 59 after vaccination). • No animals showed any evidence of clinical illness or overt fever during the 31 day post-vaccination period.
Citation Geisbert et al. 2009 [34]	**Vaccine** Blended rVSV vaccine containing 3×10^7 PFU total: • 1×10^7 PFU of ZEBOV GP • 1×10^7 PFU of *Marburg virus* GP • 1×10^7 PFU of *Sudan ebolavirus* GP. rVSVΔG-ZEBOV-GP: • 3×10^7 PFU rVSV control vaccine (non-filovirus GP): • 3×10^7 PFU	20 cynomolgus macaques were randomized into 5 experimental groups. Of interest, 1 group (n=3) received the blended vaccine and was challenged with an IM inoculation of 1000 PFU of ZEBOV 28 days later. 1 control animal that was vaccinated with the non-filovirus-containing rVSV vector was also challenged with ZEBOV 28 days later. Other vaccinated animals were challenged with *Marburg virus*, *Sudan ebolavirus*, and *Cote d'Ivoire ebolavirus*.	• All 3 animals vaccinated with the blended vaccine containing rVSVΔG-ZEBOV-GP survived challenge with ZEBOV. The control animal died on day 8 after challenge with ZEBOV. rVSV RNA was detected only at day 2 post-vaccination in 1 animal. • All animals developed modest IgG titres against ZEBOV by day of challenge (day 28 post-vaccination). • No animal showed any evidence of clinical illness as a result of vaccination. • The 1 animal vaccinated with rVSVΔG-ZEBOV-GP and challenged with *Sudan ebolavirus* had *Sudan ebolavirus* viremia on day 6 and succumbed to infection on day 10.

Study	Intervention*	Population	Summary of key findings
	Time of administration Pre-exposure: 28 days before lethal challenge **Route of administration** IM		
Citation Jones et al. 2005 [35]	**Vaccine** rVSVΔG-ZEBOV-GP: • 1×10^7 PFU rVSV control vaccine (*Marburg virus* GP): • 5×10^7 PFU **Time of administration** Pre-exposure: 28 days before lethal ZEBOV challenge **Route of administration** IM	6 healthy adult cynomolgus macaques, of which 4 were vaccinated with rVSVΔG-ZEBOV-GP and 2 with the control vaccine were challenged with an IM inoculation of 1000 PFU of ZEBOV (Kikwit) 28 days after vaccination. 6 other monkeys were challenged with the *Marburg virus*.	• All animals vaccinated with rVSVΔG-ZEBOV-GP showed no signs of clinical illness after a homologous ZEBOV challenge. rVSVΔG-ZEBOV-GP-vaccinated animals that were heterologously challenged with *Marburg virus* showed first signs of clinical illness by day 4. Control-vaccinated animals started to show clinical signs of disease on day 3 after challenge with ZEBOV. Mild rVSV viremia was detected on day 2 after vaccination and was transient. • By day 28 post-vaccination, all rVSVΔG-ZEBOV-GP-vaccinated animals had developed low- to moderate-level IgG antibody titres against ZEBOV GP. Neutralizing antibody titres were not detectable before challenge but became positive 14 and 28 days after challenge. • After vaccination, none of the animals showed any signs of clinical symptoms. • IFN-γ and TNF-α were not detectable before ZEBOV challenge, but responded positively after challenge. • All rVSVΔG-ZEBOV-GP-vaccinated animals surviving homologous challenge were heterologously challenged with *Sudan ebolavirus* (Gulu strain). 3 animals died on days 6/7 after re-challenge with evident *Sudan ebolavirus* viremia.

Study	Intervention*	Population	Summary of key findings
			The *Sudan ebolavirus* macaque challenge model was not uniformly lethal.
Citation Marzi et al. 2015 [36]	**Vaccine** rVSVΔG-ZEBOV-GP: • 5×10^7 PFU rVSV control vaccine (*Marburg virus* GP): • 5×10^7 PFU **Time of administration** Pre-exposure: 28, 21, 14, 7 or 3 days before lethal ZEBOV challenge **Route of administration** IM	15 cynomolgus macaques, of which 2 or 3 were randomized to receive the rVSVΔG-ZEBOV-GP vaccine at 28, 21, 14, 7, or 3 days before challenge, were challenged with an IM inoculation of 1000 PFU of ZEBOV (Makona). 3 animals received the control vaccine.	• All control and 1 day 3-vaccinated animals developed severe Ebola haemorrhagic fever and were euthanized 5–8 days after challenge. 2 other day 3-vaccinated animals developed mild or moderate symptoms of disease and survived, with 1 clearing ZEBOV infection by day 9 and the other with no detectable ZEBOV viremia. Animals vaccinated with rVSVΔG-ZEBOV-GP at days 28, 21, 14, and 7 before challenge did not develop any clinical signs of disease, showed no ZEBOV viremia, and all survived. • At the time of challenge, animals in the day 28, 21, and 14 vaccination groups showed potent ZEBOV GP-specific IgG responses. Titres of animals in the day 7 and 3 vaccination groups approximated baseline levels at time of challenge. Only the day 28, 21, and 14 vaccinated animals had neutralizing antibodies at the time of challenge, with increased neutralizing antibody titres in serum of all surviving animals. • Normal behaviour with no detectable adverse effects was observed after vaccination. • All controls showed marked increases of IL-1β, IL-6, IL-15, IFN-γ, IL-10 and MCP-1 after challenge, consistent with cytokine storm indicative of severe or lethal Ebola haemorrhagic fever. Vaccinated animals in the day 28, 21, 14, and 7 groups showed low-to-undetectable levels of these cytokines and chemokines, reflecting effective control of ZEBOV replication. Animals in the day 3 group showed intermediate levels of these cytokines and

Study	Intervention*	Population	Summary of key findings
			chemokines on days 3, 6, and 9 after challenge, with 1 animal in this group succumbing to infection showing similar levels as the control animals while both survivors converting at day 14 to levels seen in other vaccinated groups.
Citation Marzi et al. 2013 [37]	**Vaccine** rVSVΔG-ZEBOV-GP: • 1×10^7 PFU rVSV control vaccine (*Marburg virus* GP): • 1×10^7 PFU **Time of administration** Pre-exposure: 35 or 28 days before lethal ZEBOV challenge **Route of administration** IM	A cohort of 20 male cynomolgus macaques, of which 16 were vaccinated with rVSVΔG-ZEBOV-GP and 4 were vaccinated with the control vaccine, were challenged on day 28 after vaccination with an IM inoculation of 1000 PFU of ZEBOV (Kikwit). Of the 16 vaccinated with rVSVΔG-ZEBOV-GP, 4 were non-depleted controls, 4 were CD4+ T cell depleted before and during vaccination, 4 were CD8+ T cell depleted before and during vaccination, and 4 were CD20+ B cell depleted before and during vaccination. A second cohort of 6 animals, of which 5 received the rVSVΔG-ZEBOV-GP vaccine and 1 received the control vaccine, were challenged on day 35. In this second cohort, 4 animals were depleted of	• Following ZEBOV challenge, both CD4+ T cell-depleted and control animals succumbed to disease by day 5–8 after challenge. Survival of the CD8+ depleted animals suggesting a minimal role for CD8+ T cells in vaccine-mediated protection. Survival of the CD20+ B-cell-depleted animals suggests issues with their model depletion system. ZEBOV GP-specific IgG antibodies were not detected in animals succumbing to infection. Depletion of CD4+ T cells before and during vaccination impaired CD4+ T cell help during a B cell/antibody-mediated response causing complete lack of GP-specific antibodies, indistinguishable from control animals, resulting in eventual death. Depletion of CD4+ T cells during challenge resulted in survival of animals, indicating a minimal role for CD4+ T cell immunity, vs. T cell help in a humoral response, in rVSV-mediated protection. The robust IgG response in CD20+ B cell-depleted animals suggests that the depletion in secondary lymphoid tissues was most likely incomplete. With the exception of the CD4+ T cell-depleted group, all animals vaccinated with rVSVΔG-ZEBOV-GP generated a robust neutralizing antibody response on day of challenge (day 28 post-vaccination).

Study	Intervention*	Population	Summary of key findings
		CD4+ T cells at time of challenge and 2 were non-depleted controls that received either the rVSVΔG-ZEBOV-GP vaccine or rVSV control vaccine.	
Citation Marzi et al. 2016 (38)	**Vaccine** rVSVΔG-ZEBOV-GP: • 2×10^7 PFU (1-dose) • 1×10^7 PFU (2-dose) rVSV control vaccine (*Marburg virus* GP): 1×10^7 PFU (2-dose) **Time of administration** Post-exposure: 1 or 24 hours after lethal ZEBOV challenge **Route of administration** IM	15 adult rhesus macaques were challenged by IM inoculation with 1000 PFU of ZEBOV (Makona), of which 3 received a full dose of rVSVΔG-ZEBOV-GP vaccine at 1 hour after lethal challenge, 3 received a full dose at 24 hours, 3 received a half dose at 1 hour and 24 hours, 3 received the control vaccine at 1 hour and 24 hours, and 3 controls were not vaccinated.	• There was no significant difference in survival among all groups by day 10: all unvaccinated controls, 1 animal vaccinated at 1 hour, 1 animal vaccinated at 24 hours, and 2 animals vaccinated at both 1 and 24 hours were euthanized due to signs of symptoms consistent with Ebola haemorrhagic fever. Another animal vaccinated at 1 hour was euthanized at day 28 having survived the acute phase of Ebola disease but had developed neurological symptoms and pneumonia. All other animals vaccinated with rVSVΔG-ZEBOV-GP survived. Overall, rVSVΔG-ZEBOV-GP-vaccinated animals showed a 44% survival rate. rVSV RNA was detected in all vaccinated animals as early as 12 hours after vaccination and persisted until at least day 3 after ZEBOV infection, with none being detected by day 6. Protection from the control vaccine was similar (2 of 3 survived following challenge). • ZEBOV GP-specific IgM antibody responses were undetectable or very low over the first 9 days after ZEBOV challenge and were not different between survivors and non-survivors. By day 9, IgM levels increased in survivors at about the same time serum IgG could be detected. • IFN-α was at low levels in all animals up to 3 days after challenge and increased to higher levels with

Study	Intervention*	Population	Summary of key findings
			no significant difference between groups. By day 6 after challenge, IFN-α decreased in survivors (possibly due to controlling of ZEBOV infection) and increased in non-survivors and unvaccinated controls. IFN-γ production was low in all animals until day 6 after challenge, remaining low in survivors, and significantly increased for non-survivors and unvaccinated controls.
Citation Mire et al. 2012 (39)	**Vaccine** rVSVΔG-ZEBOV-GP: • 1×10^7 PFU rVSV control vaccine (*Marburg virus* GP or wild-type): • 1×10^7 PFU Vehicle control of clarified, heat-inactivated Vero cell culture supernatant **Route of administration** Intrathalamic injection	21 healthy male cynomolgus macaques were inoculated intrathalamically with rVSVΔG-ZEBOV-GP vaccine (n=7), rVSV vaccine containing *Marburg virus* GP (n=7), wild-type rVSV (n=3), or vehicle control (n=4).	• 2 of 3 animals given the wild-type rVSV showed severe neurological symptoms whereas animals receiving vehicle control, rVSVΔG-ZEBOV-GP or rVSV vaccine containing *Marburg virus* GP did not develop these symptoms. Major lesions in neural tissues were identified by histological analysis for all 3 animals given the wild-type rVSV, but no significant lesions were observed in the filovirus vaccine or vehicle control groups.
Citation Qiu et al. 2009 (40)	**Vaccine** rVSVΔG-ZEBOV-GP: • 1×10^7 PFU rVSV control vaccine (*Marburg virus* GP): • 1×10^7 PFU	12 adult cynomolgus macaques, of which 10 were vaccinated with rVSVΔG-ZEBOV-GP orally (n=4), intranasally (n=4), or IM (n=2) and 2 were vaccinated with the control vaccine, were challenged	• All animals vaccinated with rVSVΔG-ZEBOV-GP showed no signs of clinical illness after ZEBOV challenge. Controls showed symptoms associated with ZEBOV haemorrhagic fever and were euthanized on day 6. • Potent antibody responses were detected in all rVSVΔG-ZEBOV-GP-vaccinated animals

Study	Intervention*	Population	Summary of key findings
	Time of administration Pre-exposure: 28 days before lethal ZEBOV challenge **Route of administration** IM, oral, or intranasal	with IM inoculation with 1000 PFU of ZEBOV (Kikwit) 28 days after vaccination.	independent of route of administration. Between days 14–21 post-vaccination, all rVSVΔG-ZEBOV-GP-vaccinated animals developed high levels of IgA, IgM, and IgG against ZEBOV GP. Neutralizing antibody titres were low, though detectable post-vaccination. • Relatively stable or mild increase of CD3+, CD4+, and CD8+ T cell counts were seen after challenge for all vaccination routes, while controls demonstrated typical lymphocyte loss. All 3 routes of vaccination induced the production of both IL-2 and IFN-γ and long-term memory responses.

Abbreviations: GP: glycoprotein; IgG: immunoglobulin G; IgM: immunoglobulin M; IM: intramuscular; PFU: plaque-forming unit; rVSV: recombinant *vascular stomatitis virus*; rVSVΔG-ZEBOV-GP: recombinant *vesicular stomatitis virus-Zaire ebolavirus*; SHIV: *simian-human immunodeficiency virus*; ZEBOV: *Zaire ebolavirus.*

* The rVSVΔG-ZEBOV-GP vaccine is also referred to as V920 Ebola Zaire Vaccine.

APPENDIX E: GEOMETRIC MEAN TITRES REPORTED IN INCLUDED STUDIES IN HUMANS BY DOSE LEVEL OF THE RVSVΔG-ZEBOV-GP VACCINE

Study	n	Post-vaccination geometric mean titre point estimate, EU/mL (95% confidence interval)*								
		Day 0	Day 7	Day 14	Day 28	Day 56	Day 84	Day 180	Year 1	Year 2
3×10^3 PFU										
Agnandji et al. 2017 [19]	20	**24** (9–60)	-	-	**81** (35–184)	**43** (14–131)	-	-	-	-
Heppner et al. 2017 [14]	64	-	**54.1** (48.4–60.6)	**96.6** (70.9–131.8)	**921.0** (629.4–1347.5)	**1162.3** (819.3–1650.7)	**1314.7** (896.2–1928.6)	**959.5** (680.0–1354.0)	**941.7** (628.5–1411.1)	-
3×10^4 PFU										
Agnandji et al. 2017 [19]	20	**23** (9–63)	-	-	**489** (264–908)	**633** (305–1314)	-	-	-	-
Heppner et al. 2017 [14]	64	-	**58.1** (51.3–65.8)	**150.9** (109.5–207.8)	**866.2** (616.5–1217.1)	**1015.6** (739.4–1394.9)	**1099.7** (794.1–1522.1)	**709.9** (515.2–978.1)	**789.4** (538.2–1157.9)	-
1×10^5 PFU										
ElSherif et al. 2017 [13]	10	-	-	**96.8** (36.9–253.7)	**636.2** (258.6–1565.2)	**824.9** (341.7–1991.4)	**993.6** (469.6–2102.1)	**1169.7** (586.4–2333.2)	-	-
3×10^5 PFU										
Agnandji et al. 2017 [19]	20	**33.7** (27.6–41.1)	-	-	**540.2** (254.4–1146.7)	**809.9** (355.3–1846.1)	**654.0** (333.1–1283.9)	**375.2** (189.9–741.2)	**602.3** (357.9–1013.7)	-
Heppner et al. 2017 [14]	64	-	**53.9** (49.1–59.2)	**140.6** (104.5–189.3)	**1131.4** (847.1–1511.1)	**1405.0** (1037.1–1903.5)	**1449.2** (1059.4–1982.4)	**927.4** (670.5–1282.6)	**975.2** (659.9–1441.1)	-
Huttner et al. 2015 [15]	51	**30.0** (28.9–31.1)			**267.4** (175.3–407.9)		**824.9** (576.7–1179.9)	**583.9** (407.5–836.5)	**618.2** (412.0–927.6)	**440.8** (297.8–652.5)

Study	n	Post-vaccination geometric mean titre point estimate, EU/mL (95% confidence interval)*								
		Day 0	Day 7	Day 14	Day 28	Day 56	Day 84	Day 180	Year 1	Year 2
5×10^5 PFU										
ElSherif et al. 2017 [13]	10	-	-	**110.5** (34.0–359.1)	**603.5** (286.0–1273.5)	**792.8** (279.1–2252.2)	**876.7** (410.1–1874.3)	**928.1** (481.4–1789.4)	-	-
3×10^6 PFU										
Agnandji et al. 2016 [16]	10	**25.0** (-)	-	-	**1392.9** (893.7–2170.8)	-	-	**903.9** (506.7–1612.2)	-	-
Agnandji et al. 2016 [16]	20	**34.0** (25.1–46.2)	-	-	**1005.2** (655.2–1542.1)	**1054.9** (721.6–1542.3)	**1018.9** (711.0–1460.2)	**756.9** (520.1–1101.5)	**667.9** (484.7–920.2)	-
Agnandji et al. 2017 [19]	39	**40.6** (29.2–56.5)	-	-	**1245.0** (778.4–1991.2)	**1330.7** (829.7–2134.1)	**994.0** (629.0–1571.0)	**684.6** (479.6–977.2)	**616.1** (441.3–860.1)	-
ElSherif et al. 2017 [13]	10	-	-	**187.3** (126.0–278.4)	**1321.3** (830.2–2102.9)	**1152.6** (771.3–1722.5)	**992.6** (583.3–1689.1)	**895.7** (437.2–1835.1)	-	-
Heppner et al. 2017 [14]	80	-	**54.9** (50.4–59.8)	**249.2** (197.1–315.0)	**1376.7** (1063.7–1781.7)	**1547.4** (1207.8–1982.6)	**1600.0** (1224.7–2090.2)	**1087.6** (831.4–1422.7)	**1201.4** (908.0–1589.7)	-
Regules et al. 2017 [12]	10*	-	-	**283** (150–534)	**1300** (831–2034)	**2599** (1537–4395)	**2263** (1485–3449)	**2786** (1248–6218)	-	-
9×10^6 PFU										
Heppner et al. 2017 [14]	50	-	**56.7** (45.3–70.9)	**241.6** (160.4–364.1)	**919.0** (660.0–1279.6)	**1029.3** (743.8–1424.4)	-	**786.6** (555.6–1113.6)	**942.7** (644.8–1378.4)	-
1×10^7 PFU										
Huttner et al. 2015 [15]	35	**32.6** (28.2–37.7)	-	-	**821.2** (579.7–1163.5)	-	**1332.1** (955.9–1856.5)	**747.6** (539.1–1036.9)	**1005.7** (697.4–1450.4)	**761.3** (516.2–1122.8)

Study	n	Post-vaccination geometric mean titre point estimate, EU/mL (95% confidence interval)*								
		Day 0	Day 7	Day 14	Day 28	Day 56	Day 84	Day 180	Year 1	Year 2
2×10^7 PFU										
Agnandji et al. 2016 [16]	10	**30.8** (23.0–41.1)	-	-	**1969.8** (1249.6–3105.2)	-	-	**1600.0** (974.3–1612.2)	-	-
Agnandji et al. 2016 [16]	20	**29.4** (29.4–29.4)	-	-	**785.3** (571.8–1078.7)	**944.6** (625.8–1425.7)	**946.8** (695.5–1288.9)	**877.9** (625.7–1231.9)	**1083.1** (766.8–1529.8)	-
Agnandji et al. 2017 [19]	56	**69.1** (39.7–120.2)	-	-	**1503.0** (943.6–2394.0)	**2589.5** (1625.2–4126.0)	**1825.7** (1133.6–2940.2)	**1514.4** (972.1–2359.3)	**1433.3** (571.8–3592.7)	-
Bolay et al. 2019 [26]	210	**161** (-)	-	-	**1357** (1122–1641)	-	-	-	-	-
Halperin et al. 2017 [25]	796	**<36.1** (<36.1–<36.1)	-	-	**1262.0** (1168.9–1362.6)	-	-	**1113.4** (1029.5–1204.0)	**1078.4** (960.6–1210.7)	**1029.9** (916.3–1157.5)
Heppner et al. 2017 [14]	50	-	**54.8** (48.9–61.5)	**426.0** (286.8–632.8)	**1624.3** (1146.4–2301.5)	**1805.0** (1356.6–2401.6)	-	**1520.9** (1151.3–2009.1)	**1387.9** (1050.6–1833.6)	-
Kennedy et al. 2017 [20]	500	-	**83** (76–89)	-	**1000** (910–1099)	-	-	**781** (721–847)	**818** (752–889)	-
Regules et al. 2017 [12]	10**	-	-	**857** (502–1465)	**4079** (2601–6396)	**3733** (2085–6682)	**2743** (1634–4604)	**2540** (1196–5396)	-	-
5×10^7 PFU										
Huttner et al. 2015 [15]	16	**31.9** (28.4–36.0)	-	-	**1383.0** (996.0–1920.4)	-	**1993.7** (1547.9–2567.8)	**865.7** (630.6–1188.6)	**1037.9** (804.2–1339.6)	**707.8** (546.6–916.4)

Study	n	Post-vaccination geometric mean titre point estimate, EU/mL (95% confidence interval)*								
		Day 0	Day 7	Day 14	Day 28	Day 56	Day 84	Day 180	Year 1	Year 2
1×10^8 PFU										
Halperin et al. 2017 [25, 30]	264	**<36.1** (<36.1–<36.1)	-	-	**1291.9** (1126.9–1481.2)	-	-	**1189.5** (1036.7–1364.9)	**1135.5** (934.8–1379.3)	**1123.2** (923.1–1366.5)
Heppner et al. 2017 [14]	45	-	**65.0** (51.3–82.3)	**475.7** (344.8–656.2)	**1837.9** (1366.3–2472.3)	**2078.9** (1655.7–2610.4)	-	**1927.0** (1419.6–2615.8)	**1786.5** (1345.4–2372.4)	-
Regules et al. 2017 [12]	10**	-	-	**888** (448–1760)	**4079** (2740–6070)	**4525** (1933–10597)	**3940** (1501–10343)	**2786** (1169–6638)	-	-

Abbreviations: EU: ELISA unit; n: sample size; PFU: plaque-forming unit.
* Immunogenicity findings correspond to ELISA for *Zaire ebolavirus* envelope glycoprotein-specific immunoglobulin G antibodies.
** Vaccinees who did not receive a second dose of rVSVΔG-ZEBOV-GP vaccine at day 28 after the first dose.