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Post-exposure prophylactic vaccine candidates for the treatment of human Risk Group 4 pathogen infections

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Abstract

Introduction: The development of therapeutics and vaccines to combat Risk Group 4 pathogens, which are associated with high case-fatality rates, is a high priority. Post-exposure prophylactic vaccines have the potential to bridge classical therapeutic and vaccine applications, but little progress has been reported to date.

Areas covered: This review provides an overview of post-exposure prophylactic vaccine candidates against Risk Group 4 pathogens.

Expert opinion: A few candidate post-exposure prophylactic vaccines protect experimental animals infected with a few Risk Group 4 pathogens, such as filoviruses or hantaviruses, but efficacy of candidate vaccines has not been similarly reported for most other high-consequence pathogens. A major drawback for the further development of existing candidates is the lack of understanding of their mechanisms of action, knowledge of which could help to identify focused paths forward in vaccine development and licensure. These drawbacks to further development ultimately slow progress toward post-exposure prophylactic vaccine licensure.

Keywords

biosafety level 4; BSL-4; post-exposure prophylaxis; Risk Group 4; VSIV; VSV

1. Introduction

The World Health Organization (WHO) defines a Risk Group 4 (RG-4) microorganism as “[a] pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly” and is associated with “high and individual community risk” in part because “effective treatment and preventive

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measures are not usually available” [1]. RG-4 pathogen lists vary slightly from nation to nation. In the US, all RG-4 pathogens are viruses, and research with viable forms of these viruses typically requires maximum containment—biosafety level 4 (BSL-4) or maximum containment—animal biosafety level 4 (ABSL-4) laboratories [1,2] (Table 1), of which only a few exist globally [3].

Viruses under this classification include such high-profile pathogens as Ebola virus (EBOV), Marburg virus (MARV), and Lassa virus (LASV). Countermeasure approaches currently under development include vaccine strategies as pre-exposure prevention and therapeutics as post-exposure prophylaxis (PEP) either to prevent disease after infection or to treat disease early for rapid recovery. However, the number of studies investigating the utility of vaccine approaches for PEP, i.e., after a potential high-consequence viral exposure to prevent disease onset or severity, are relatively few.

Though PEP vaccines have been licensed sparingly by the FDA, the use of PEP vaccines can be very effective especially when routes of pathogen exposure are well documented, such as exposure due to contact with animals known to carry a particular pathogen. Perhaps the most well-known PEP vaccine strategy is deployed after known or potential rabies virus (RABV, *Rhabdoviridae: Lyssavirus*) exposure. RABV passes from infected mammals to humans when animal saliva is introduced through bites or scratches, particularly from dogs and bats [4]. If left untreated, the virus causes rabies, a debilitating encephalitis leading to 40,000–70,000 deaths annually [5,6]. Rabies prevention methods that included the large-scale vaccination of dogs to prevent RABV transmission to humans in the 1950s have been effective in curtailing this disease, at least in the western hemisphere [7]. However, extensive post-exposure studies in animals throughout the 1990s [8–12] prompted the US Centers for Disease Control and Prevention (CDC) to include the recommendation of a PEP vaccination in combination with passive antibody treatment in the event of potential RABV exposure [13]. Since the incorporation of vaccine plus antibody PEP into the treatment regimen and the large-scale vaccination of dogs, rabies cases have dramatically decreased in developed countries: only 33 rabies cases were diagnosed in the US from 2003–2014 [14].

PEP vaccines could also be highly useful after the occurrence of laboratory-acquired infection (LAIs). Stringent safety-related standard operating procedures during work with RG-4 pathogens increasingly limit LAIs; nonetheless, rare infections occur, often with fatal outcomes [15–22]. With an available vaccine in this setting, rapid post-exposure prophylaxis after high risk exposures to RG-4 pathogens may prevent and mitigate disease severity and death.

Here we present a focused review on PEP vaccine candidates targeting RG-4 agents. For most of these pathogens, vaccine development is an active research priority, and many potential pre-exposure vaccine candidates exist [23–28]. Here, we focus on vaccines that have been tested in experimental animal models to establish a therapeutic window for post-exposure administration (Tables 2 and 3). We also provide an overview of vaccines used as PEP in humans during RG-4 pathogen disease outbreaks or in ring vaccinations, as these vaccines may have been administered following an exposure and demonstrated protection (Table 4).

2. PEP vaccine candidates targeting RG-4 pathogens

2.1 Variola virus vaccines

Variola virus (VARV; *Poxviridae: Orthopoxvirus*) causes smallpox, a well-documented human disease associated with numerous pandemics throughout recorded history. Following an initial incubation period ranging from 7–19 days, individuals infected with VARV present with fever, synchronized rash, head and body aches, and vomiting [29]. Early research into medical countermeasures (MCMs) gave rise to the first recorded use of pre-exposure vaccination, described by Edward Jenner in 1801 [30]. Since then, the repertoire of MCMs expanded to more developed pre-exposure and PEP vaccines and therapeutics that eventually eradicated the disease in 1978 [31].

As experimental animal testing was not widely performed in early VARV research, historical data regarding MCMs emerged from studies of vaccines and therapeutics in humans during active outbreaks. Though the efficacy of PEP vaccines against smallpox had been suspected since 1904 [32,33], documented post-exposure use of these vaccines occurred only much later. Post-exposure use of a smallpox vaccine containing the VARV-related vaccinia virus (VACV; *Poxviridae: Orthopoxvirus*) was documented in humans during multiple smallpox outbreaks from 1942–1973 [32,34–45]. Efficacy of PEP vaccination was generally reported as a survival rate or as a rate of development of disease, ranging from 56–100% and 0–75%, respectively. Reported survival and disease development outcomes of PEP vaccination groups were always reportedly better than unvaccinated groups or than the combination of all PEP vaccine-treated and untreated individuals in the outbreak [32,34–45]. However, as these data were collected during active outbreaks and outside a controlled experimental setting, comparison and interpretation of results were often confounded by low subject numbers and poorly defined experimental groups (e.g., chances of differential virus exposure in different contact groups, variable vaccination timing after exposure).

Following the eradication of smallpox and the disposal of most VARV stocks, animal research using surrogate orthopoxviruses, including VACV strain Western Reserve (VACV-WR), monkeypox virus (MPXV), and ectromelia virus Moscow strain (ECTV-Mos) causing mousepox, was performed to further develop MCMs to prepare for possible VARV resurgence. Of the VACV vaccine candidates, only two versions of the live VACV vaccine (VACV-Elstree and modified VACV Ankara [MVA]) have been tested extensively as PEP against these surrogate orthopoxviruses in animal models.

In BALB/c laboratory mice, MVA was 100% efficacious against intranasal (IN) VACV-WR infection (5 mice) [46] and IN ECTV-Mos infection (5 mice) [47] when vaccinated intramuscularly (IM) up to 24 hours post-exposure. Early efficacy fell to 0% (0 of 5 mice) and 80% (4 of 5 mice) when the vaccine was given 48 hours post-exposure for IN VACV-WR and IN ECTV-Mos infection, respectively. Complete PEP vaccine efficacy was also demonstrated with MVA against ECTV-Mos IN infection of TLR9^{-/-} laboratory mice when vaccination occurred by scarification up to 48 hours post-exposure (10 mice) [48]. Similarly, complete protection was observed in ECTV-Mos-infected C57BL/6 laboratory mice when vaccinated by IM with MVA up to 24 hours (6 mice) [47] or after intravenous (IV) administration up to 72 hours post-exposure (5 mice) [49]. IN vaccination of IN ECTV-Mos-

infected C57BL/6 laboratory mice with MVA provided protection to 33% (1 of 3 mice) of animals when vaccination occurred at 48 hours post-exposure [49]. However, MVA did not protect ECTV-Mos-infected A/J laboratory mice (0 of 10 mice) when vaccination was performed by scarification in 0–96 hours post-exposure [50]. The PEP efficacy testing of MVA has yet to be reported in any surrogate nonhuman primate (NHP) models of smallpox.

VACV-Elstree proved to be an efficacious PEP vaccine in ECTV-Mos-infected BALB/c laboratory mice when vaccination occurred by scarification 24 hours post-exposure (83%, 5 of 6 mice). IM VACV-Elstree was also efficacious in these animals at a lower dose up to 24 hours post-exposure (90%, 9 of 10 mice) and at a higher dose up to 72 hours, regardless of whether infectious virus (80%, 4 of 5 mice) or ultraviolet-inactivated virus (80%, 4 of 5 mice) was used [47]. Though VACV-Elstree did not protect VACV-WR-infected BALB/c laboratory mice (0 of 5 mice) up to 24 hours post-exposure, [46] VACV-Elstree is the only candidate vaccine to have at least limited efficacy in NHPs, protecting 17% (1 of 6) of crab-eating macaques (*Macaca fascicularis* Raffles, 1821) against a lethal monkeypox virus infection at 24 hours post-exposure [51].

Though these PEP vaccines have been extensively studied in human clinical settings and in surrogate animal models of smallpox, only one study evaluated a determinate of PEP vaccine protection, interferon gamma [52]. In this study, the v50 B13RM γ vaccine, a recombinant VACV (v50) in which the B13R serpin site is replaced by mouse interferon, M γ , given to laboratory C57BL/6 mice IN 24 hours following exposure to VACV-WR provided 100% protection (sample size undeclared). However, administration of the same vaccine without the M γ replacement, v50 B13R, provided 17% protection (sample size undeclared). Similarly, administration of v50 B13RM γ or v50 B13R to laboratory C57BL/6 mice by FP injection 24 hours following exposure to ECTV-Mos protected 83% (25 of 30) or 50% (15 of 30) of mice, respectively [52]. Thus, this study suggests the importance of vaccines expressing interferon gamma in providing protection against VACV and ECTV in surrogate laboratory mouse models.

2.2 Filovirus vaccines

2.2.1 Ebola virus vaccines—Ebola virus (EBOV; *Filoviridae: Ebolavirus*) causes Ebola virus disease (EVD), which frequently results in lethal outcomes [53]. Historically, EVD was rarely encountered, caused only dozens to a few hundred human infections, and was limited to Middle Africa [54]. An extensive EVD outbreak began in Western Africa in 2013 and resulted in 28,652 infections and 11,325 deaths (case fatality rate [CFR] = 40%) that distributed to over 15 countries by the end of the outbreak in 2016 [55,56]. This outbreak moved filovirus research and MCM development to the forefront of RG-4 pathogen investigations as judged by the sheer number of PubMed-listed publications compared to all other RG-4 pathogens. Furthermore, the WHO officially recognized EBOV as one of a few RG-4 pathogens that ought to be studied with priority [57].

Pteropodid bats are under suspicion as EBOV reservoir host(s). However, infectious EBOV has not yet been found in any bat, and the transmission route from bats to humans is even less clear [58]. Consequently, PEP vaccines cannot yet be applied to treat humans after potential reservoir exposure. However, PEP vaccines have significant potential in research,

field laboratory, and clinical settings where accidental EBOV exposures and/or infections can occur [59,60].

The most extensively studied EBOV PEP vaccine is based on a recombinant vesicular stomatitis Indiana virus (VSIV; *Rhabdoviridae: Lyssavirus*) that expresses EBOV glycoprotein (GP_{1,2}) instead of the VSIV glycoprotein (G). This vaccine has been recently approved by the US Food and Drug Administration as a pre-exposure vaccine. When administered as PEP as late as 24 hours following an otherwise lethal EBOV injection, this vaccine (typically referred to as VSV G/ZEBOV-GP) protected 60% (3 of 5), 100% (n=5), and 100% (n=5) of domesticated guinea pigs (*Cavia porcellus* Linnaeus, 1758), golden hamsters (*Mesocricetus auratus* Waterhouse, 1839), and laboratory mice, respectively [61,62]. NHP studies have produced similar results, protecting 67% (2 out of 3) of rhesus monkeys (*Macaca mulatta* Zimmermann, 1780) when administered 24 hours following an otherwise lethal EBOV injection [63]. However, disease progression in the NHP model is generally faster than in humans and is almost always 100% lethal [64,65]. Therefore, the treatment efficacy window of recombinant VSIV (rVSIV) used as PEP in humans may differ from the therapeutic window reported in NHP models.

Additional studies have also assessed the efficacy of combinatorial candidate vaccines using the rVSIV vector to protect against multiple, unrelated viruses. These studies include a dual EBOV/Andes virus (ANDV; *Hantaviridae: Orthohantavirus*) vaccine with 40% protection (2 of 5) of golden hamsters when given 24 hours after EBOV exposure [62] and a dual EBOV/influenza A virus (FLUAV; *Orthomyxoviridae: Alphainfluenzavirus*) vaccine with 90% protection in (9 of 10) BALB/c laboratory mice when given up to 30 minutes after exposure [66].

In addition to *in vivo* PEP assessment in animal models, candidate vaccines have also been used for emergency situations in humans. rVSIV-based PEP vaccine has been used multiple times subsequent to accidental injury by a potentially EBOV-contaminated needles, and all of the treated individuals survived (8 of 8 humans). However, whether survival was influenced by VSV G/ZEBOV-GP treatment is unclear as evidence of actual EBOV infection could not be established for any of these individuals [16,67–69].

Additionally, a ring vaccination trial was completed in Guinea and Sierra Leone to assess VSV G/ZEBOV-GP's protective efficacy during the 2013–2016 EVD outbreak. In this trial, 98 clusters encompassing 4,160 to-be-vaccinated individuals who had contact with an EVD index case or who were contacts of those contacts were randomly assigned to immediate (51 clusters) and delayed (47 clusters) vaccination groups. Delayed vaccination groups received the vaccine 21 days following enrollment. Investigators observed no cases of EVD 10 days or more following vaccination in the immediate vaccination group as opposed to 16 EVD cases affecting 7 delayed vaccination clusters [70]. Though this trial had a few notable weaknesses, including a lack of baseline blood draws for serology to confirm EBOV exposure in presumably protected individuals and lack of individual randomization [71–74], these findings add to the evidence base supporting deployment of the rVSIV vaccine in pre- and post-exposure settings.

Additionally, this vaccine was used as PEP to treat 26 healthcare workers assessed as high risk of exposure to EBOV after treating a healthcare worker with reactivation of EVD in 2015. Whereas all treated individuals did not develop EVD, none of the exposed individuals became infected with EBOV, making a conclusion as to PEP vaccine efficacy difficult [75]. In the ongoing EVD outbreak in the Democratic Republic of the Congo [76], a similar ring vaccination strategy has been used; very likely a subset of the over 257,607 individuals vaccinated so far represent contacts who have already been infected [76–79]. In those individuals, confirmed development of infection and/or impact of the vaccination on disease severity or clinical phenotype is of great interest but has yet to be reported [80].

Other PEP candidate vaccines of note include a human adenovirus 5 (Ad5)-vectored vaccine also expressing EBOV GP_{1,2}, and a non-infectious EBOV virion-like particle (VLP) vaccine consisting of core EBOV components (in particular matrix protein VP40 and GP_{1,2}) [81,82]. Although published data are not available on attempted ring vaccinations using either of these candidate vaccines, PEP efficacy has been tested *in vivo*. Investigators found that 67% (6 of 9) and 25% (1 of 4) of crab-eating macaques were protected from otherwise lethal EBOV infection when the Ad5-vectored vaccine was administered 30 minutes or 24 hours post-exposure, respectively [81]. Similar findings were reported for the EBOV VLP vaccine in laboratory mice, as 100% of animals were protected when the vaccine was given 24 hours post-exposure [82]. As this degree of PEP is similar to previously published data on the VISV-vectored vaccine, the Ad5-vectored and VLP vaccines may also be considered PEP candidates for human use.

Mechanistic correlates of protective immunity after use of these candidate PEP vaccines are yet to be defined. Negative control treatment, for instance with a rVSIV candidate vaccine expressing MARV GP_{1,2}, conferred similar levels of protection to rhesus monkeys following an otherwise lethal EBOV exposure as the homotypic rVSIV vaccine expressing EBOV GP_{1,2} [63]. Though EBOV and MARV are relatively closely related, cross-protection has rarely been reported. These results suggest that innate immune activation due to the rVSIV backbone may play a larger role in immediate post-exposure protection than viral antigen (GP_{1,2})-specific responses. On the other hand, a negative MARV VLP control candidate vaccine elicited no protection from a lethal EBOV exposure in laboratory mice, suggesting that protection may be antigen-specific and/or animal model-specific [82]. Therefore, whether innate immune activation or an antigen-specific response is the most important aspect of a PEP treatment is still up for debate.

2.2.2 Marburg virus vaccines—Marburg virus (MARV; *Filoviridae: Marburgvirus*) causes Marburg virus disease (MVD) [53], with cases recorded predominantly in Middle and Eastern Africa. The MVD CFR is extremely high (from 1967 to present: mean ≈80.6%) [54]. In part due to this CFR, MARV research was an integral part in the Soviet Union's biological weapons research program [83]. Like EBOV, MARV is a WHO Blueprint of Priority Diseases pathogen [57]. In nature, MARV is maintained in juvenile Egyptian rousettes (*Roussettus aegyptiacus* Geoffroy, 1810). Human transmission possibly occurs when humans are in direct contact with these cave-dwelling, frugivorous bats or their excreta or secreta [58,84,85].

Only the rVSIV vector has been efficacious as PEP against MVD. This rVSIV-based candidate vaccine is almost identical in composition to VSV G/ZEBOV-GP, except that the EBOV GP_{1,2}-encoding gene is replaced with that encoding MARV GP_{1,2}, strain Musoke (MARV-Musoke). Vaccination protected 100% (5 of 5) of rhesus monkeys when administered 20–30 minutes following IM exposure to 1000 PFU of MARV-Musoke [86]. More recently, the same vaccination strategy protected 83% (5 of 6) and 33% (2 of 6) of rhesus monkeys when administered 24 hours or 48 hours following a 1000 PFU MARV-Musoke exposure, respectively [87]. Lower protection was elicited with varying exposure doses of a different MARV variant, Angola (MARV-Angola). Only 25% (1 of 4) and 75% (3 of 4) of rhesus monkeys were protected when the candidate vaccines were given 30 minutes subsequent to a MARV-Angola exposure dose of 1000 or 50 PFU, respectively [88].

After MARV exposure, the available data suggest that an antigen-specific response may be required to elicit effective PEP protection after all. When a rVSIV-vectored EBOV vaccine was administered 20–30 minutes post-exposure to MARV, no NHP (n = 3) was protected [86]. A similar lack of protection from MARV was noted with a rVSIV-vectored LASV vaccine given 24 (n=1) or 48 (n=1) hours post-exposure [87].

2.2.3 Sudan virus vaccines—Sudan virus (SUDV; *Filoviridae: Ebolavirus*) is relatively closely related to EBOV and causes Sudan virus disease (SVD), with outbreaks encountered less frequently than EVD but with an equally concerning high CFR (since 1976: average CFR of SVD $\approx$ 53.7%) [54]. In contrast to EBOV and MARV, no evidence supports the identity of a SUDV natural reservoir. Thus, PEP candidate vaccine development is primarily aimed at protecting SUDV laboratory researchers, field researchers, and health-care workers.

As in the case of MARV, the rVSIV vector (expressing SUDV GP_{1,2}) is the only candidate vaccine platform that has been explored for PEP. When tested *in vivo*, rVSIV vaccine protected 100% (n = 4) of rhesus monkeys when administered 20–30 minutes following an otherwise lethal SUDV injection [89]. Later time points of vaccine administration have not yet been reported. As seen with the MARV candidate vaccine, an antigen-specific response may be necessary for an rVSIV-based PEP vaccine to protect from SVD. An rVSIV-LASV candidate vaccine elicited no protection from SUDV when administered under identical conditions in a rhesus monkey [89]. However, until additional experiments with more animals are performed, this result has to be considered with caution.

2.3 Orthohantavirus vaccines

Orthohantaviruses (*Hantaviridae: Orthohantavirus*) are separated into Old World viruses, usually causing hemorrhagic fever with renal syndrome, and New World viruses, which generally cause hantavirus pulmonary syndrome associated with a CFR of 30–50%. These zoonoses are maintained in Europe and Asia by murid and cricetid rodents (Old World orthohantaviruses) or in the Americas by cricetid rodents (New World orthohantaviruses) [90,91]. Of the viruses in this genus, Andes virus (ANDV), a New World orthohantavirus, is of highest concern because ANDV, in contrast to most other orthohantaviruses, has been associated with person-to-person transmission [92–94]. Consequently, orthohantavirus PEP

vaccine research has largely focused on ANDV, again using the rVSIV platform to express the ANDV glycoprotein. *In vivo*, this candidate vaccine protected 90% (9 of 10) of golden hamsters when given 1 day after an otherwise lethal ANDV injection [95]. Interestingly, a rVSIV-vectored EBOV vaccine elicited a similar level of protection (6 of 6) against ANDV in golden hamsters, again questioning whether antigen-specificity is necessary for effective PEP. However, only very few reports are available on the development of an orthohantavirus NHP animal model to date (e.g., [96–98]), and these results of PEP in small animal models have yet to be corroborated in an NHP model.

2.4 Mammarenavirus vaccines

Lassa virus (LASV; *Arenaviridae: Mammarenavirus*), responsible for an estimated 300,000 to 500,000 cases of Lassa fever annually, is predominantly endemic in Guinea, Liberia, Nigeria, and Sierra Leone [99]. Symptoms and clinical signs of Lassa fever include fever, nausea, muscle aches, and in severe cases, hemorrhage, multi-system organ dysfunction, and death. LASV is most commonly transmitted through contact with infected rodents (predominantly Natal mastomys [*Mastomys natalensis* Smith, 1834] or excrement from these rodents, but limited person-to-person transmission has been reported. Vaccine development to prevent Lassa fever has been severely hampered by the high genetic diversity associated with the multitude of LASV isolates [100]. However, with this caveat, a vaccine composed of single-cycle LASV replicating particles (VRPs) resulted in 100% (5 of 5) efficacy when administered 24 hours subsequent to an otherwise lethal LASV Josiah strain exposure in strain 13 guinea pigs [101]. Additionally, a recombinant vaccine, DEF201, has shown PEP efficacy against “arenaviral hemorrhagic fever” in a Pichindé virus golden hamster surrogate model for Lassa fever, but efficacy against other mammarenaviruses, including LASV, is lacking [102]. At this time, no PEP vaccine testing in NHPs infected with LASV has been reported.

2.5 Other RG-4 virus needing PEP vaccines

PEP vaccine research is relatively lacking for most RG-4 agents. However, examples of vaccines that may be good candidates for *in vivo* PEP testing against some important RG-4 agents are described below.

Crimean-Congo hemorrhagic fever virus (CCHFV; *Nairoviridae: Orthonairovirus*) is endemic to countries in Africa, Asia, and Europe [90,103]. Crimean-Congo hemorrhagic fever (CCHF) generally causes headache, fever, joint pain, and other non-specific symptoms and signs, but in severe cases, CCHF can progress to life-threatening hemorrhagic manifestations, multi-organ dysfunction, and death [104–106]. Cases of viral infection correlate with the presence of *Hyalomma* ticks, the predominant CCHFV vector that spreads the virus among CCHFV host reservoirs (hares, hedgehogs, susliks, cattle, goats, ostriches, and sheep) [107]. As with previously described viruses in this section, the knowledge of viral vectors and natural host reservoirs makes a PEP vaccine strategy attractive to counter CCHF. Further research on candidate PEP vaccines, such as an orthopoxvirus-vectored CCHFV vaccine [108], is needed to assess vaccine efficacy post-exposure and establish an effective PEP vaccine treatment following tick exposure.

Nipah virus (NiV; *Paramyxoviridae: Henipavirus*), is responsible for encephalitis outbreaks in Southern and Southeast Asia (in particular, Bangladesh, Malaysia, and India) that have been increasing in regularity and severity. After an incubation period generally ranging from a few days to 2 weeks, human disease most often presents with fever, headache, and other non-specific symptoms. Patients may present with respiratory symptoms and signs, but most prominently will rapidly progress to encephalitis and coma within 5 to 7 days. Disease sequelae have been reported, including relapsing encephalitis developing months or years following recovery [109]. Transmission of NiV to humans has been linked to domestic pigs (*Sus scrofa domesticus* Erxleben, 1777) that have come into contact with NiV natural reservoir hosts (pteropodid bats) [110]. As potential routes of infection are well documented for NiV, PEP vaccination may have the potential to minimize the spread of NiV among humans, especially if implemented following noticeable disease in domestic pigs. Though no currently licensed vaccine for the prevention of NiV infection is available, multiple candidate vaccines have been developed, including rVSIV-vectored and rabies virus-vectored vaccines, which have variable efficacy in animal studies if administered prior to infection [111,112]. These candidate vaccines should be evaluated for PEP efficacy as soon as possible. Likewise, similar candidate PEP vaccines ought to be developed for NiV's closest relative, Hendra virus, which, thus far, has caused a handful of lethal encephalitis cases [113].

Finally, tick-borne encephalitis virus (TBEV; *Flaviviridae: Flavivirus*) is generally transmitted by ixodid ticks in Western (*Ixodes ricinus*) and Eastern (*Ixodes persulcatus*) Europe. The virus is maintained by over 100 species of wild animals, including voles, deer, and domestic animals such as sheep [114–116]. Although patients infected with TBEV normally only present with an initial, non-specific febrile phase, 20–30% of patients progress to a second stage of disease with CNS signs (meningitis, encephalitis, or both). Lethality is generally 1–2% but 30–60% of patients develop chronic neuropsychiatric sequelae [117,118]. Three different vaccines for pre-exposure disease prevention (IPVE, FSME-IMMUN, and Encepur) are generally available in endemic regions [119]. However, fears over the potential of antibody-dependent disease enhancement or increased viral infectivity caused by “sub-optimal” concentrations of virus-specific antibodies, have hampered further vaccine development [120]. For this reason and the potential of other adverse effects [121], none of these vaccines are licensed by the US FDA. Vaccine use is neither recommended by the US Centers for Disease Control and Prevention (CDC) nor the WHO except for high risk individuals, such as laboratory workers or workers with high exposure to potentially infected host ticks [122,123]. Multiple studies into the use of antibody treatments as PEP have produced promising results in laboratory mice with no disease enhancement [124,125].

3. Conclusion

RG-4 pathogens remain a significant public health concern as these viruses re-emerge around the world. Endemic and emerging viruses that continue to cause large-scale outbreaks and consequential death and disability can be mitigated once an effective treatment or preventative measure is developed. In addition to the use of vaccines to prevent

disease and disease therapeutics to assist recovery, PEP vaccines can have effective epidemiologic and therapeutic roles in virus-exposed individuals.

Multiple candidate vaccines have elicited PEP protection for a few important RG-4 pathogens. The most thoroughly researched PEP vaccines are those based on the rVSIV platform, which are efficacious against ANDV, EBOV, MARV, and SUDV in animal models. However, other vaccine vectors, such as Ad5 or VLPs also have promise. However, data on PEP vaccine use in humans during an outbreak setting is lacking.

Conflicting observations raise important questions about the mechanistic correlates of protection of rVSIV vaccines, among others. Most reported experiments included an rVSIV encoding a seemingly irrelevant viral protein as a negative control next to the rVSIV encoding the target virus glycoprotein. Two of the six studies reviewed here that included such a negative vaccine control reported these controls provided similar levels of protection against the target virus as the target-specific vectors. Others reported a lack of efficacy using negative vaccine controls. However, control groups receiving these negative control vaccines were generally small [87]. Repeat vaccine studies may be necessary to confirm efficacy of these negative control vaccines and to determine whether animal model choice influences outcomes. The absolute requirement for antigen-specificity for effective PEP remains unconfirmed.

Whereas a number of studies have been completed on PEP vaccines against RG-4 pathogens, post-exposure vaccine research is lacking for many important viruses. Some of these viruses, including CCHFV and TBEV, are endemic in specific regions of the world in the absence of licensed MCMs. Development of a safe PEP vaccine could provide much needed protection from the potential life-threatening conditions these viruses cause.

4. Expert opinion

Based on the reported research on PEP vaccine treatments against RG-4 pathogens, a major drawback for the further development of the vaccine candidates listed in this review is the lack of understanding of their mechanisms of action. As knowledge of vaccine mechanisms emerges, researchers could identify focused paths forward in vaccine development and licensure. Furthermore, investigations into other types of vaccines for PEP could broaden the search for an effective treatment. This review shows that most of the vaccines tested for PEP efficacy have been infectious, recombinant, viral-vectored vaccines, such as the thoroughly studied rVSIV platform. Testing of additional vaccine platforms could lead to a better understanding of what is required for PEP vaccine efficacy.

Further testing into alternative treatment regimens could also provide more effective PEP vaccine treatments. Of the studies reviewed, only one had a treatment group in which two vaccine administrations were included in the post-exposure vaccination schedule [81]. Multiple administrations given post-exposure have the potential to boost the protective nature of PEP vaccines after an individual has been exposed to a particular RG-4 pathogen. However, the potential for PEP vaccine strategies and virus-specific therapeutics to positively or negatively interact is typically poorly defined. On one hand, the PEP treatment

recommendation for humans potentially exposed to rabies virus is to co-treat with both a PEP vaccine and a human anti-rabies virus immunoglobulin. This treatment regimen is only recommended if exposed individuals have not previously received a pre-exposure vaccine, otherwise only a PEP vaccine will be administered. This combination of either human immunoglobulin or pre-exposure vaccination with PEP vaccination increases the efficacy of post-exposure treatments against rabies [13].

However, the effectiveness of combination PEP with other therapy may not be true of other infections. The potential to increase the duration and degree of PEP vaccine efficacy with combination approaches that do not compromise either treatment should be investigated for RG-4 pathogens. In addition to expanding research into other vaccine types and treatment regimens, research into whether PEP protection can be elicited by non-specific vaccines is needed. Non-specific vaccines used as negative controls in various studies were sometimes found to elicit robust protection from virus infection. This observation suggests that innate immune activation may play a role in protection, and hence that broad-spectrum PEP vaccines could be developed.

Before further PEP vaccine studies are performed, however, RG-4 PEP research could benefit from a few study design improvements. Firstly, the inclusion of baseline and subsequent blood draws in ring vaccination studies are important to demonstrate PEP efficacy in humans, though collections of these samples can be difficult in outbreak settings. Although statistical assumptions can provide good evidence of overall vaccine efficacy, serological and viral quantification testing of serum samples could provide more evidence as to when any vaccinated individuals had been exposed to the target virus. These tests would also confirm viral exposures did occur and further add evidence to the assertion that these vaccines were protective. Providing a rough temporal relationship between vaccination and exposure can further decipher whether the vaccine was effective pre-exposure, post-exposure, or both.

Further animal model development and methods of characterization are needed to more strictly mimic disease and infection progression in humans. While animal testing can be suitable for demonstrating vaccine or treatment efficacy, the observed treatment time at which efficacy is lost comes with a few caveats. If a vaccine protects from an otherwise lethal viral dose up to 48-hours post-exposure, that 48-hour time frame is in reference to the disease progression of the animal model being used. If the animal model generally progresses to disease faster than humans, as is the case with EBOV exposure in rhesus monkeys for example [64,65], then vaccine PEP treatment efficacy in humans may extend to later time points following viral exposure. A modified animal model that more strictly follows viral disease progression in humans will further refine candidate PEP vaccines.

Additionally, for all RG-4 pathogens, PEP vaccine efficacy data supporting use in humans in an outbreak setting are lacking. This lack can be explained by the limited understanding of the mechanism of action involved in PEP vaccine treatment and the hesitancy to use experimental vaccines as PEP over experimental therapeutics. Administration of vaccines during an outbreak is hampered by resistance to receiving experimental vaccines by local populations and uneven data collection. Implementors of ring-vaccination strategies, such as

the rVSV G-ZEBOV-GP trial in Guinea and the ongoing ring vaccination in the Democratic Republic of the Congo, should pay special attention to contacts who may have been vaccinated post-exposure and further assess whether these vaccines have PEP efficacy [70]. From streamlined data collection in the field, researchers could compare human and animal efficacy of these PEP vaccines and better assess whether PEP vaccination is worthwhile to add to the clinician's toolbox.

Over the next 5 years, more animal data will become available to assess the therapeutic window of vaccines currently under development for infection prevention. Combination treatments and alternative treatment regimens that increase the efficacy of PEP vaccines will begin to be tested in a laboratory setting. The use of these and other vaccines that have already been established for PEP use may be submitted to the FDA for licensure and aid in emerging disease prevention. The ongoing EVD outbreak in the Democratic Republic of the Congo occurs in a challenging setting for patient follow-up and evaluation of the utility of PEP vaccination in exposed, already infected individuals. Hopefully, the results from the efficacy of PEP vaccination will further inform a growing evidence base.

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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* of interest

** of considerable interest

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Article highlights

- PEP vaccines have the potential to be effective tools against diseases caused by RG-4 pathogens. However, research on RG-4 pathogen PEP vaccines is relatively lacking compared to research on other treatments and preventative measures.
- PEP candidate vaccines against ANDV, EBOV, MARV, and SUDV have been tested successfully in some animal models.
- The rVSIV vaccine vector is the best-studied PEP vaccine platform in RG-4 pathogen research and has been developed for multiple viruses. However, a few alternatives, including a DNA vaccine and a VLP vaccine, are efficacious in certain animal models.
- Innate immune activation may play a role in the PEP elicited by available candidate vaccines.
- Further animal model development is needed to more strictly model disease progression in humans to further define the therapeutic window of PEP vaccines.
- Research into different types of vaccines and vaccination regimens may broaden the search for an effective PEP vaccine treatment.
- Only one ring vaccination trial using a rVSIV-vectored vaccine against EBOV has been published in a peer reviewed, scientific journal. Future trials may benefit from inclusion of baseline and subsequent blood draws for serological and viral quantification testing to raise confidence in trial results.
- No research into PEP vaccines has been reported for many important RG-4 pathogens, including Crimean-Congo hemorrhagic fever and Nipah viruses.

Table 1.

Risk Group 4 (RG-4) pathogens (US)

Family Virus (Abbreviation)	Biosafety classification [2]	Biosafety Category: 1) CDC Bioterrorism Agent [126] 2) US NIAID Priority Pathogen [127] 3) US DHHS Select Agent [128] 4) Australia Group Human Pathogen for Export Control [129]	Human Disease [130]	Post-exposure prophylactic vaccine candidate reported (candidates listed in Tables 2–4)
<i>Arenaviridae</i>				
Chapare virus (CHAPV)	N ¹ / _I ¹	1) Yes, Category A ² 2) Yes, Category A 3) Yes 4) Yes	Other specified arenavirus disease	No
Guanarito virus (GTOV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A 3) Yes 4) Yes	Venezuelan hemorrhagic fever	No
Junin virus (JUNV)	(A)BSL-4 ³	1) Yes, Category A ² 2) Yes, Category A 3) Yes 4) Yes	Argentinian hemorrhagic fever	Yes
Lassa virus (LASV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A 3) Yes 4) Yes	Lassa fever	Yes
Lujo virus (LUJV)	N ¹ / _I ¹	1) Yes, Category A ² 2) Yes, Category A 3) Yes 4) Yes	Other specified arenavirus disease	No
Machupo virus (MACV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A 3) Yes 4) Yes	Bolivian hemorrhagic fever	No
Sabiá virus (SBV)	(A)BSL-4	1) Yes, Category A ² 2) No 3) Yes 4) Yes	Other specified arenavirus disease	No
<i>Filoviridae</i>				
Bundibugyo virus (BDBV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A ⁴	Bundibugyo virus disease	No

Family Virus (Abbreviation)	Biosafety classification [2]	Biosafety Category: 1) CDC Bioterrorism Agent [126] 2) US NIAID Priority Pathogen [127] 3) US DHHS Select Agent [128] 4) Australia Group Human Pathogen for Export Control [129]	Human Disease [130]	Post-exposure prophylactic vaccine candidate reported (candidates listed in Tables 2–4)
		3) Yes (Tier 1) ⁵ 4) Yes		
Ebola virus (EBOV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A ⁴ 3) Yes (Tier 1) 4) Yes	Ebola virus disease	Yes
Marburg virus (MARV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A ⁶ 3) Yes (Tier 1) 4) Yes	Marburg virus disease	Yes
Ravn virus (RAVV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A ⁶ 3) Yes (Tier 1) ⁷ 4) Yes	Marburg virus disease	No
Reston virus (RESTV)	(A)BSL-4	1) No 2) Yes, Category A ⁴ 3) Yes (Tier 1) ⁵ 4) Yes	N/A ⁸	No
Sudan virus (SUDV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A ⁴ 3) Yes (Tier 1) ⁵ 4) Yes	Sudan virus disease	Yes
Tai Forest virus (TAFV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A ⁴ 3) Yes (Tier 1) ⁵ 4) Yes	Other specified Ebola disease	No
Flaviviridae				
Alkhurma hemorrhagic fever virus (AHFV)	(A)BSL-4 ³	1) Yes, Category A ² 2) Yes, Category C 3) No 4) No	Alkhurma hemorrhagic fever	No
Kyasanur Forest virus (KFDV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category C	Kyasanur Forest disease	No

Family Virus (Abbreviation)	Biosafety classification [2]	Biosafety Category: 1) CDC Bioterrorism Agent [126] 2) US NIAID Priority Pathogen [127] 3) US DHHS Select Agent [128] 4) Australia Group Human Pathogen for Export Control [129]	Human Disease [130]	Post-exposure prophylactic vaccine candidate reported (candidates listed in Tables 2–4)
		3) Yes 4) Yes		
Omsk hemorrhagic fever virus (OHFV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category C 3) Yes 4) Yes	Omsk hemorrhagic fever	No
Tick-borne encephalitis virus (TBEV)	(A)BSL-4 (Far Eastern subtype only)	1) No 2) Yes, Category C 3) Yes (Far Eastern and Siberian subtypes only) 4) Yes (Far Eastern subtype only)	Tick-borne encephalitis	No
Hantaviridae				
Amur/Soochong virus (ASV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hemorrhagic fever with renal syndrome	No
Dobrava–Belgrade virus (DOBV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hemorrhagic fever with renal syndrome	No
g u virus (GOUV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hemorrhagic fever with renal syndrome	No
Hantaan virus (HTNV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hemorrhagic fever with renal syndrome	No
Puumala virus (PUUV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hemorrhagic fever with renal syndrome, hantavirus (cardio)pulmonary syndrome	No
Seoul virus (SEOV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hemorrhagic fever with renal syndrome	No

Family Virus (Abbreviation)	Biosafety classification [2]	Biosafety Category: 1) CDC Bioterrorism Agent [126] 2) US NIAID Priority Pathogen [127] 3) US DHHS Select Agent [128] 4) Australia Group Human Pathogen for Export Control [129]	Human Disease [130]	Post-exposure prophylactic vaccine candidate reported (candidates listed in Tables 2–4)
Tula virus (TULV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hemorrhagic fever with renal syndrome	No
Anajátuba virus (ANJV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Andes virus (ANDV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No
Araraquara virus (ARAV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Araucária virus (ARAVV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hantavirus (cardio)pulmonary syndrome	No
Bayou virus (BAYV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No
Bermejo virus (BMIV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Black Creek Canal virus (BCCV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hantavirus (cardio)pulmonary syndrome	No

Family Virus (Abbreviation)	Biosafety classification [2]	Biosafety Category: 1) CDC Bioterrorism Agent [126] 2) US NIAID Priority Pathogen [127] 3) US DHHS Select Agent [128] 4) Australia Group Human Pathogen for Export Control [129]	Human Disease [130]	Post-exposure prophylactic vaccine candidate reported (candidates listed in Tables 2–4)
Blue River virus (BRV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No
Castelo dos Sonhos virus (CASV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Chocho virus (CHOV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hantavirus (cardio)pulmonary syndrome	No
El Moro Canyon virus (ELMCV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No
Juquitiba virus (JUQV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Laguna Negra virus (LANV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hantavirus (cardio)pulmonary syndrome	No
Lechiguana virus (LECV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No
Maciel virus (MCLV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No

Family Virus (Abbreviation)	Biosafety classification [2]	Biosafety Category: 1) CDC Bioterrorism Agent [126] 2) US NIAID Priority Pathogen [127] 3) US DHHS Select Agent [128] 4) Australia Group Human Pathogen for Export Control [129]	Human Disease [130]	Post-exposure prophylactic vaccine candidate reported (candidates listed in Tables 2–4)
Maripa virus	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hantavirus (cardio)pulmonary syndrome	No
Monongahela virus (MGLV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No
Muleshoe virus (MULV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
New York virus (NYV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hantavirus (cardio)pulmonary syndrome	No
Orán virus (ORNV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No
Paranoá virus	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Pergamino virus (PRGV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) Yes	Hantavirus (cardio)pulmonary syndrome	No
Río Mamoré virus (RIOMV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category C ^{1/3} 3) No 4) No	Hantavirus (cardio)pulmonary syndrome	No

Family Virus (Abbreviation)	Biosafety classification [2]	Biosafety Category: 1) CDC Bioterrorism Agent [126] 2) US NIAID Priority Pathogen [127] 3) US DHHS Select Agent [128] 4) Australia Group Human Pathogen for Export Control [129]	Human Disease [130]	Post-exposure prophylactic vaccine candidate reported (candidates listed in Tables 2–4)
Sin Nombre virus (SNV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Tunari virus (TUNV)	(A)BSL3/4 ^{1/1}	1) Yes, Category A/C ^{1/2} 2) Yes, Category A/C ^{1/2} 3) Yes, Category C ^{1/3} 4) No	Hantavirus (cardio)pulmonary syndrome	No
Herpesviridae				
Herpes B virus	(A)BSL-4	1) No 2) No 3) No 4) No	Viral encephalitis not elsewhere classified	No
Nairoviridae				
Crimean-Congo hemorrhagic fever virus (CCHFV)	(A)BSL-4	1) Yes, Category A ² 2) Yes, Category A 3) Yes 4) Yes	Crimean-Congo hemorrhagic fever	No
Paramyxoviridae				
Hendra virus (HeV)	(A)BSL-4	1) Yes, Category C 2) Yes, Category C 3) Yes 4) Yes	Henipavirus encephalitis	No
Nipah virus (NiV)	(A)BSL-4	1) Yes, Category C 2) Yes, Category C 3) Yes 4) Yes	Henipavirus encephalitis	No
Poxviridae				
Variola virus (VARV)	(A)BSL-4	1) Yes, Category A 2) Yes, Category A 3) Yes 4) Yes	Smallpox	Yes

(A)BSL, (animal) biosafety level; N/i, not included.

^{1/}Due to the virus's close relationship to other human VHF-causing mammarenaviruses, this virus is typically handled at (A)BSL-4

² CDC lists “Viral hemorrhagic fevers, including...” as Category A. Hence all human VHF-causing agents are listed here as Category A

³ Work with virus vaccine strains may be conducted at (A)BSL-2

⁴ Interpreted here to be included in the list phrase “Ebola”

⁵ Interpreted to be included in the list phrase “Ebola virus;”

⁶ Interpreted to be included in the list phrase “Marburg;”

⁷ Interpreted to be included in the list phrase “Marburg virus;”

⁸ Not known to cause disease in humans.

¹¹ Depending on the experiment performed

¹² Covered by CDC’s “Viral hemorrhagic fevers, including...” as Category A Bioterrorism Agents, but included also in Category C as “Emerging infectious diseases such as ... hantavirus [sic];”

¹³ Covered by the phrase “Additional hantaviruses”.

Table 2

Small Animal Model Testing of Post-exposure Prophylactic Vaccines

Virus Vaccine	Animal [131]	Virus-Strain Dose Exposure Route	Vaccine Regimen Post-exposure (PE)	Survival %
Andes virus				
VSV G/ANDVGPC [95]	Golden hamster	ANDV-Chile 154 FFU IP	1 x 10 ⁵ IP 24 h PE 1 x 10 ⁵ IP 72 h PE 1 x 10 ⁵ IP 120 h PE	90 (9 of 10) 0 (0 of 10) 0 (0 of 10)
Ebola virus				
VSV G/ZEBOV-GP [61]	Laboratory BALB/c mice	maBOV-Mayinga 1000 x LD ₅₀ ⁵ IP	2 x 10 ⁵ PFU IP 30 min PE	100 (5 of 5)
VSV G/ZEBOV-GP [61]	Hartley guinea pig	gpBOV-Mayinga 1000 x LD ₅₀ ⁶ IP	2 x 10 ⁵ PFU IP 1 h PE 2 x 10 ⁵ PFU IP 24 h PE	100 (5 of 5) 80 (4 of 5) 60 (3 of 5)
EBOV-like-particles ⁴ [82]	Laboratory C57BL/6 mice	maBOV-Mayinga 1 x 10 ⁵ PFU IP	10 µg IP 24 h PE	60 (6 of 10)
			25 µg IP 24 h PE	100 (10 of 10)
			50 µg IP 24 h PE	90 (9 of 10)
			10 µg IM 24 h PE	0 (0 of 10)
			25 µg IM 24 h PE	30 (3 of 10)
VSV G/ZEBOV [62]	Golden hamster	maBOV-Mayinga 100 x LD ₅₀ ⁵ IP	50 µg IM 24 h PE 1 x 10 ⁵ PFU IP 0 h PE 1 x 10 ⁵ PFU IP 24 h PE 1 x 10 ⁵ PFU IP 48 h PE	70 (7 of 10) 100 (5 of 5) 100 (5 of 5) 100 (5 of 5) 0 (0 of 5)
VSV G/Dual (EBOV and ANDV GP) [62]	Golden hamster	maBOV-Mayinga 100 x LD ₅₀ ⁵ IP	1 x 10 ⁵ PFU IP 0 h PE 1 x 10 ⁵ PFU IP 24 h PE 1 x 10 ⁵ PFU IP 48 h PE	80 (4 of 5) 40 (2 of 5) 0 (0 of 5)
pATX VSV G-HA-ZGP [66]	Laboratory BALB/c mice	maBOV-Mayinga 22 PFU IP	1 x 10 ⁷ PFU IM 30 min PE	90 (9 of 10)
Lassa virus				
Single-cycle LASSV replicon particles (VRPs) [101]	Laboratory Strain 13 Hamster	LASSV-Josiah 1 x 10 ⁴ FFU SubC	1 x 10 ⁷ FFU SubC 24 h PE	100 (5 of 5)
Variola virus				
Modified VACV-Ankara [46]	Laboratory BALB/c mice	VACV-Western Reserve 5 x 10 ⁴ PFU	1 x 10 ⁸ IU IM 3 h PE 1 x 10 ⁸ IU IM 24 h PE	100 (5 of 5) 100 (5 of 5) 0 (0 of 5)

Virus Vaccine	Animal [131]	Virus-Strain Dose Exposure Route	Vaccine Regimen Post-exposure (PE)	Survival %
		IN	1 x 10 ⁸ IU IM 48 h PE	
VACV-E[stree] [46]	Laboratory BALB/c mice	VACV-Western Reserve 1 x 10 ⁶ PFU IN	1 x 10 ⁶ PFU SC 3 h PE 1 x 10 ⁶ PFU SC 24 h PE	0 (0 of 5) 0 (0 of 5)
VACV-E[stree] (Lister) [47]	Laboratory BALB/c mice	ECTV-Moscow 3 PFU IN	1 x 10 ⁶ PFU SC 0 h PE 1 x 10 ⁶ PFU SC 24 h PE 1 x 10 ⁶ PFU SC 48 h PE	100 (6 of 6) 83 (5 of 6) 16 (1 of 6)
			1 x 10 ⁶ PFU IM 0 h PE 1 x 10 ⁶ PFU IM 24 h PE 1 x 10 ⁶ PFU IM 48 h PE 1 x 10 ⁶ PFU IM 72 h PE 1 x 10 ⁶ PFU IM 96 h PE	100 (10 of 10) ¹ 90 (9 of 10) ¹ 40 (4 of 10) ¹ 30 (3 of 10) ¹ 20 (1 of 5)
			1 x 10 ⁸ PFU IM 0 h PE 1 x 10 ⁸ PFU IM 24 h PE 1 x 10 ⁸ PFU IM 48 h PE 1 x 10 ⁸ PFU IM 72 h PE	100 (5 of 5) 100 (5 of 5) 80 (4 of 5) 80 (4 of 5)
			1 x 10 ⁸ PFU (inactivated) IM 0 h PE 1 x 10 ⁸ PFU (inactivated) IM 24 h PE 1 x 10 ⁸ PFU (inactivated) IM 48 h PE 1 x 10 ⁸ PFU (inactivated) IM 72 h PE	100 (5 of 5) 100 (5 of 5) 100 (5 of 5) 80 (4 of 5)
			1 x 10 ⁶ PFU IM 0 h PE 1 x 10 ⁶ PFU IM 24 h PE 1 x 10 ⁶ PFU IM 48 h PE 1 x 10 ⁶ PFU IM 72 h PE	100 (5 of 5) 100 (5 of 5) 80 (4 of 5) 60 (3 of 5)
Modified VACV-Ankara [47]	Laboratory BALB/c mice	ECTV-Moscow 3 PFU IN	1 x 10 ⁸ PFU IM 0 h PE 1 x 10 ⁸ PFU IM 24 h PE 1 x 10 ⁸ PFU IM 48 h PE 1 x 10 ⁸ PFU IM 72 h PE	100 (10 of 10) ¹ 100 (10 of 10) ¹ 100 (10 of 10) ¹ 70 (7 of 10) ¹ 20 (1 of 5)
			1 x 10 ⁸ PFU IM 0 h PE 1 x 10 ⁸ PFU IM 24 h PE 1 x 10 ⁸ PFU IM 48 h PE 1 x 10 ⁸ PFU IM 72 h PE	100 (10 of 10) ¹ 100 (10 of 10) ¹ 100 (10 of 10) ¹ 70 (7 of 10) ¹ 20 (1 of 5)
			1 x 10 ⁸ PFU IM 0 h PE 1 x 10 ⁸ PFU IM 24 h PE 1 x 10 ⁸ PFU IM 48 h PE 1 x 10 ⁸ PFU IM 72 h PE	100 (10 of 10) ¹ 100 (10 of 10) ¹ 100 (10 of 10) ¹ 70 (7 of 10) ¹ 20 (1 of 5)
			1 x 10 ⁸ PFU IM 0 h PE 1 x 10 ⁸ PFU IM 24 h PE 1 x 10 ⁸ PFU IM 48 h PE 1 x 10 ⁸ PFU IM 72 h PE	100 (10 of 10) ¹ 100 (10 of 10) ¹ 100 (10 of 10) ¹ 70 (7 of 10) ¹ 20 (1 of 5)
			1 x 10 ⁸ PFU IM 0 h PE 1 x 10 ⁸ PFU IM 24 h PE 1 x 10 ⁸ PFU IM 48 h PE 1 x 10 ⁸ PFU IM 72 h PE	100 (10 of 10) ¹ 100 (10 of 10) ¹ 100 (10 of 10) ¹ 70 (7 of 10) ¹ 20 (1 of 5)
Modified VACV-Ankara [47]	Laboratory C57BL/6 mice	ECTV-Moscow 240 PFU IN	1 x 10 ⁸ PFU IM 0 h PE 1 x 10 ⁸ PFU IM 24 h PE 1 x 10 ⁸ PFU IM 48 h PE	100 (6 of 6) 100 (6 of 6) 50 (3 of 6)
Modified VACV-Ankara [49]	Laboratory C57BL/6 mice	ECTV-Moscow 3 x 10 ⁴ TCID ₅₀ IN	5 x 10 ⁷ TCID ₅₀ IV 48 h PE 5 x 10 ⁷ TCID ₅₀ IV 72 h PE 5 x 10 ⁷ TCID ₅₀ IV 120 h PE	100 (undefined) 100 (5 of 5) 20 (undefined)
			5 x 10 ⁷ TCID ₅₀ IN 48 h PE 5 x 10 ⁷ TCID ₅₀ IN 72 h PE	33 (1 of 3) 0 (0 of 5)
			1 x 10 ⁸ TCID ₅₀ SC 24 h PE 1 x 10 ⁸ TCID ₅₀ SC 48 h PE 1 x 10 ⁸ TCID ₅₀ SC 72 h PE	100 (10 of 10) 100 (10 of 10) 33 (3 of 9)
			1 x 10 ⁸ TCID ₅₀ SC 24 h PE 1 x 10 ⁸ TCID ₅₀ SC 48 h PE 1 x 10 ⁸ TCID ₅₀ SC 72 h PE	100 (10 of 10) 100 (10 of 10) 33 (3 of 9)
			1 x 10 ⁸ TCID ₅₀ SC 24 h PE 1 x 10 ⁸ TCID ₅₀ SC 48 h PE 1 x 10 ⁸ TCID ₅₀ SC 72 h PE	100 (10 of 10) 100 (10 of 10) 33 (3 of 9)

Virus Vaccine	Animal [131]	Virus-Strain Dose Exposure Route	Vaccine Regimen Post-exposure (PE)	Survival %
Modified VACV-Ankara (Dryvax) [50]	Laboratory A/J mice	ECTV-Moscow 40 PFU IN	2.5 x 10 ⁵ PFU SC 0 h PE 2.5 x 10 ⁵ PFU SC 48 h PE 2.5 x 10 ⁵ PFU SC 96 h PE	0 (0 of 10) 0 (0 of 10) 0 (0 of 10)
v50 B13RMγ [52]	Laboratory C57BL/6 mice	VACV-Western Reserve 1 x 10 ⁶ PFU IN	1 x 10 ⁷ PFU IN 24 h PE	100 (undefined)
			1 x 10 ⁷ PFU IN 48 h PE	40 (undefined)
			1 x 10 ⁷ PFU IN 72 h PE	20 (undefined)
			1 x 10 ⁷ PFU IN 24 h PE ³	80 (undefined)
			1 x 10 ⁷ PFU INON 24 h PE	40 (undefined)
VACVE3L 7C [52]	Laboratory C57BL/6 mice	VACV-Western Reserve 1 x 10 ⁶ PFU IN	1 x 10 ⁷ PFU IM 24 h PE	20 (undefined)
			1 x 10 ⁷ PFU SC 24 h PE	15 (undefined)
			1 x 10 ⁷ PFU IN 24 h PE	30 (undefined)
VACVE3L 26C [52]	Laboratory C57BL/6 mice	VACV-Western Reserve 1 x 10 ⁶ PFU IN	1 x 10 ⁷ PFU IN 24 h PE	20 (undefined)
VACVE3L [52]	Laboratory C57BL/6 mice	VACV-Western Reserve 1 x 10 ⁶ PFU IN	1 x 10 ⁷ PFU IN 24 h PE	30 (undefined)
VACVE3L::ATVeiF2α [52]	Laboratory C57BL/6 mice	VACV-Western Reserve 1 x 10 ⁶ PFU IN	1 x 10 ⁷ PFU IN 24 h PE	30 (undefined)
v50 B13RMIL-18 [52]	Laboratory C57BL/6 mice	VACV-Western Reserve 1 x 10 ⁶ PFU IN	1 x 10 ⁷ PFU IN 24 h PE	60 (undefined)
v50 B13R [52]	Laboratory C57BL/6 mice	ECTV-Moscow 5 x 10 ³ PFU IN	3 x 10 ⁷ PFU FP 24 h PE	50 (15 of 30)
v50 B13RMγ [52]	Laboratory C57BL/6 mice	ECTV-Moscow 5 x 10 ³ PFU IN	3 x 10 ⁷ PFU FP 24 h PE	83 (25 of 30)

¹Numbers combined between two experiments²Data from “simultaneous vaccination” not included³Tested with a 1 x 10⁷ PFU exposure dose⁴Data from knock-out mice experiments not included⁵LD50 for maEBOV-Mayinga injected IP into laboratory BALB/c mice is reported as 0.025–0.04 PFU; LD50 not listed for golden hamsters [132]

LD50 for gpEBOV-Mayinga not listed in referenced journal article [133]; Abbreviations – ATV: Ambystoma tigrinum virus; ECTV: ectromelia virus; eIF2α: Eukaryotic initiation factor 2 alpha; VSV G/ANDVGP: recombinant vesicular stomatitis Indiana virus expressing the Andes virus surface glycoprotein precursor; VSV G/ZEBOV-GP: recombinant vesicular stomatitis Indiana virus expressing the transmembrane glycoproteins of Ebola virus; VSV G/ZEBOV: recombinant vesicular stomatitis Indiana virus expressing the Ebola virus and Andes virus glycoproteins; pATX VSV G-HA-ZGP: recombinant vesicular stomatitis Indiana virus expressing both H5N1 influenza A virus hemagglutinin and Ebola virus glycoprotein; v50 B13RMγ: recombinant vaccinia virus without B13R expressing IFNG; VACVE3L 7C: recombinant vaccinia virus containing an E3L gene with the 7 C-terminal amino acids deleted; VACVE3L 26C: recombinant vaccinia virus containing an E3L gene with the 26 C-terminal amino acids deleted; VACVE3L: recombinant vaccinia virus without the E3L gene; VACVE3L::ATVef2α: recombinant vaccinia virus with the eukaryotic initiation factor 2 alpha (eIF2α) homologue gene from Ambystoma tigrinum virus replacing the E3L gene; v50 B13RMIL-18: recombinant vaccinia virus without B13R expressing IL-18; v50 B13R: recombinant vaccinia virus without B13R; FP: foot pad inoculation; IM: intramuscular; IN: intranasal; INON: opposite naris; IP: intraperitoneal; SubC: subcutaneous; FFU: focus-forming units; LD50: median lethal dose; maEBOV: mouse-adapted Ebola virus; PFU: plaque forming units; VACV: vaccinia virus; SC: scarification; TCID50: median tissue culture infectious dose.

Table 3.

Nonhuman Primate Testing of Post-exposure Prophylactic Vaccines

Virus Vaccine	Animal Common Name [131]	Virus-Strain Dose Exposure Route	Vaccine Regimen Post-exposure (PE)	Survival %
Variola virus				
VACV-Elstree [51]	Crab-eating macaque	MPXV (VARV surrogate) 1 x 10 ⁷ PFU IT	“Human dose” IC 24 h PE	17 (1 of 6)
Ebola virus				
rVSV G-ZEBOV-GP [61]	Rhesus monkeys	EBOV/Kikwit; 1000 PFU IM	2 x 10 ⁷ PFU IM 20–30 min PE	50 (4 of 8)
rVSV G-ZEBOV-GP [63]	Rhesus monkeys	EBOV/Makona 1000 PFU IM	2 x 10 ⁷ PFU IM 1 h PE 2 x 10 ⁷ PFU IM 24 h PE 1 x 10 ⁷ PFU IM 1 h and 24 h PE	33 (1 of 3) 7 (2 of 3) 33 (1 of 3)
Ad5-Zaire EBOVGP (ZGP) adjuvanted with Ad5-IFN- α then type 1 IFN [81]	Crab-eating macaques	EBOV/Kikwit 1000 PFU Route not provided	Initial: 2 x 10 ¹⁰ IFU Ad5-ZGP/kg, then 2 x 10 ⁹ PFU/kg Ad5-IFN- α IM at 30 min PE. Delayed: 0.44 μ g/kg of type 1 IFN IM daily for 5–21 d PE	67 (2 of 3)
Ad5-Zaire EBOVGP (ZGP) adjuvanted with Ad5-IFN- α then type 1 IFN and rNAPc2 [81]	Crab-eating macaques	EBOV/Kikwit 1000 PFU Route not provided	Initial: 2 x 10 ¹⁰ IFU Ad5-ZGP/kg, then 3 x 10 ⁹ PFU/kg Ad5-IFN- α IM at 30 min PE. Delayed: 0.44 μ g/kg of type 1 IFN IM daily and rNAPc2 30 μ g/kg at d 5–21 PE	67 (2 of 3)
Ad5-Zaire EBOVGP (ZGP) adjuvanted with Ad5-IFN- α then type 1 IFN and rNAPc2 [81]	Crab-eating macaques	EBOV/Kikwit 1000 PFU Route not provided	Initial: 2 x 10 ¹⁰ IFU Ad5-ZGP/kg, then 3 x 10 ⁹ PFU/kg Ad5-IFN- α IM at 30 min PE. Delayed: 0.44 μ g/kg of type 1 IFN IM daily and rNAPc2 30 μ g/kg at d 5–21 PE	67 (2 of 3)
Ad5-Zaire EBOVGP (ZGP) adjuvanted with Ad5-IFN- α then type 1 IFN [81]	Crab-eating macaques	EBOV/Kikwit 1000 PFU Route not provided	Initial: 4 x 10 ⁹ IFU Ad5-ZGP/kg, then 3 x 10 ⁹ PFU/kg Ad5-IFN- α IM at 30 min PE. Delayed: 0.44 μ g/kg of type 1 IFN IM daily at d 5–21 PE	67 (2 of 3)
Ad5-Zaire EBOVGP (ZGP) adjuvanted with Ad5-IFN- α then type 1 IFN [81]	Crab-eating macaques	EBOV/Kikwit 1000 PFU Route not provided	Initial: 4 x 10 ⁹ IFU Ad5-ZGP/kg, then 2 x 10 ⁹ PFU/kg Ad5-IFN- α IM at 30 min PE. Delayed: 0.44 μ g/kg of type 1 IFN IM daily at d 5–21 PE	67 (2 of 3)
Ad5-Zaire EBOVGP (ZGP) adjuvanted with Ad5-IFN- α then type 1 IFN [81]	Crab-eating macaques	EBOV/Kikwit 1000 PFU Route not provided	Initial: 4 x 10 ⁹ IFU Ad5-ZGP/kg, then 2 x 10 ⁹ PFU/kg Ad5-IFN- α IM at 24 h PE. Delayed: 0.44 μ g/kg of type 1 IFN IM daily at d 5–21 PE	25 (1 of 4)
Ad5-Zaire EBOVGP (ZGP) adjuvanted with Ad5-IFN- α then type 1 IFN [81]	Rhesus monkeys	EBOV/Kikwit 1000 PFU Route not provided	Initial: 4 x 10 ⁹ IFU Ad5-ZGP/kg, then 2 x 10 ⁹ PFU/kg Ad5-IFN- α IM at 24 h PE. Delayed: 0.44 μ g/kg of type 1 IFN IM daily at d 5–21 PE	33 (1 of 3)
rVSV G-MARV GP [63]	Rhesus monkeys	EBOV/Makona 1000 PFU IM	1 x 10 ⁷ PFU IM 1 h and 24 h PE	67 (2 of 3)
Marburg virus				

Virus Vaccine	Animal Common Name [131]	Virus-Strain Dose Exposure Route	Vaccine Regimen Post-exposure (PE)	Survival %
rVSV G-ZEBOV-GP [86]	Rhesus monkeys	MARV/Musoke 1000 PFU IM	1 x 10 ⁷ PFU IM 20–30 min PE	0 (0 of 3)
rVSV G-MARV-GP [86]	Rhesus monkeys	MARV/Musoke 1000 PFU IM	1 x 10 ⁷ PFU IM 20–30 min PE	100 (5 of 5)
rVSV G-MARV-GP [87]	Rhesus monkeys	MARV/Musoke 1000 PFU IM	≈2 x 10 ⁷ PFU IM 24 h PE	83 (5 of 6)
rVSV G-LassaGPC [87]	Rhesus monkeys	MARV/Musoke 1000 PFU IM	≈2 x 10 ⁷ PFU IM 48 h PE	33 (2 of 6)
rVSV G-LassaGPC [87]	Rhesus monkeys	MARV/Musoke 1000 PFU IM	≈2 x 10 ⁷ PFU IM 24 h PE	0 (0 of 1)
rVSV G-MARV-GP [88]	Rhesus monkeys	MARV/Angola 1000 PFU IM	≈2 x 10 ⁷ PFU IM 48 h PE	0 (0 of 1)
rVSV G-MARV-GP [88]	Rhesus monkeys	MARV/Angola 50 PFU IM	1 x 10 ⁷ PFU IM 30 min PE	25 (1 of 4)
rVSVN4CT1/MARV-Angola-GP [88]	Rhesus monkeys	MARV/Angola 50 PFU IM	1 x 10 ⁷ PFU IM 30 min PE	75 (3 of 4)
Sudan virus			1 x 10 ⁷ PFU IM 30 min PE	60 (3 of 5)
rVSV G-SUDV-GP [89]	Rhesus monkeys	SUDV ¹ 1000 PFU IM	≈2 x 10 ⁷ PFU IM 20–30 min PE	100 (4 of 4)
rVSV G-LassaGPC [89]	Rhesus monkeys	SUDV ¹ 1000 PFU IM	≈2 x 10 ⁷ PFU IM 20–30 min PE	0 (0 of 1)

¹ Strain of exposure stock not provided. Abbreviations – Ad5-ZGP: adenovirus 5 expressing Ebola virus glycoprotein; EBOV: Ebola virus; GP: glycoprotein gene; IC: Intracutaneous; IFN: interferon; IFU: infectious units; MPXV: monkeypox virus; PFU: plaque forming units; PE: post-exposure; IM: intramuscular; IFN-α: interferon-alpha; IT: intratracheal; MARV: Marburg virus; rNAPc2: recombinant nematode anticoagulant protein c2; rVSV G-MARV GP: recombinant vesicular stomatitis Indiana virus expressing MARV glycoprotein instead of VSIV G protein; rVSV G-ZEBOV-GP: recombinant vesicular stomatitis Indiana virus expressing EBOV glycoprotein instead of VSIV G protein; Ad5-Zaire EBOV/GP: adenovirus serotype 5 expressing Ebola virus glycoprotein; rVSV G-LassaGPC: recombinant vesicular stomatitis Indiana virus expressing Lassa virus glycoprotein instead of VSIV G protein; rVSVN4CT1/MARV-Angola-GP: recombinant vesicular stomatitis Indiana virus expressing MARV glycoprotein and translocating the VSIV nucleoprotein (N) gene from the first to the fourth (N4) genomic position and truncating the VSIV G cytoplasmic tail; rVSV G-SUDV-GP: recombinant vesicular stomatitis Indiana virus expressing Sudan virus glycoprotein instead of VSIV G protein; SC: Scarification; SUDV: Sudan virus; VACV: vaccinia virus; VARV: variola virus.

Table 4

Post-exposure Prophylactic Vaccine Use in Humans

Virus Vaccine	Location (Time-frame)	Vaccine Regimen Post-exposure (PE)	Data interpretation (for previously unvaccinated individuals)
Ebola virus			
rVSV G-ZEBOV-GP	Germany (2009) [16]	Following a needlestick injury, vaccine was administered 48 h post-exposure.	The individual survived exposure, however evidence of EBOV infection could not be established to assess PEP vaccine efficacy.
rVSV G-ZEBOV-GP	Sierra Leone (2014) [67]	Following a needlestick injury at an Ebola treatment unit (ETU), vaccine was given 43 h post-exposure.	The individual survived exposure, however evidence of EBOV infection could not be established to assess PEP vaccine efficacy.
rVSV G-ZEBOV-GP	Liberia (2014) [69]	Following a needlestick injury, physician was evacuated and administered the vaccine 2 d post-exposure.	The individual survived exposure, however evidence of EBOV infection could not be established to assess PEP vaccine efficacy.
rVSV G-ZEBOV-GP	Western Africa (2014–2015) [68]	Five healthcare workers at high risk of EBOV exposure were vaccinated from 1 to 3 d post-exposure.	All individuals survived exposure, however evidence of EBOV infection could not be established to assess PEP vaccine efficacy.
rVSV G-ZEBOV-GP	Sierra Leone (2015–2016) [70]	Trial participants, including case contacts, were randomized into immediate vaccination and delayed vaccination groups.	Strong evidence of EBOV infection for vaccinated individuals not established. Post-exposure efficacy hard to elucidate.
Variola virus			
VACV Infection	Scotland (1942) [34]	Some patients vaccinated following presumed infection. No statistics on PEP provided.	Those vaccinated 9+ days prior to rash showed “significant improvement in fatality and reduction in severity.”
VACV Infection	Libya (1946) [35]	Contacts vaccinated following occurrence of smallpox cases	1–5 days PEP: 100% Survival (21 of 21) 6–10 days PEP: 81% Survival (25 of 31) 10+ days PEP: 75% Survival (3 of 4) Unvaccinated: 74% Survival (98 of 132)
VACV Infection	England (1947) [36]	Contacts vaccinated following occurrence of smallpox cases. No statistics on PEP provided.	“Modified cases” were described for individuals vaccinated 12 d prior to rash.
VACV Infection	Europe: Imported Cases (1950–1971) [37]	Contacts vaccinated following exposure. No information provided on exact timing of PE vaccination.	PEP: 71% Survival (50 of 70) Unvaccinated: 48% Survival (38 of 79)
VACV Infection	India (1961–1972) [45]	Vaccination given following presumed exposure. No information provided on exact timing of PE vaccination.	PEP: 79% Survival (n=426) Unvaccinated: 63% Survival (n=1296)
VACV Infection	England (1962) [38]	Two individuals vaccinated within 24 h of exposure. No statistics on PEP provided.	Individuals vaccinated PE were described as developing a “very mild form” of the disease.
VACV Infection	India (1965–1968) [39]	Familial contacts of smallpox cases were vaccinated. No participant numbers or survival information provided.	Vaccinated (including PEP): 29.5% developed disease Unvaccinated: 47.6% developed disease
VACV Infection	West Pakistan (1967) [40]	Contacts were offered vaccination, including following suspected exposure.	0–10 days PE: 75% (12 of 16) developed disease Unvaccinated 0–10 days PE: 96% (26 of 27) developed disease
VACV Infection	West Pakistan (1968–1970) [41]	Contacts vaccinated following presumed exposure. Contacts vaccinated longer than 7 days PE were considered “unvaccinated.”	0–7 days PEP: 0% (0 of 2) developed disease Unvaccinated: 79% (73 of 93) developed disease
VACV Infection	Bangladesh (1972) [42]	Vaccination given following presumed exposure. No information provided on exact timing of PEP.	PEP: 2% (10 of 414) developed disease Unvaccinated: 9% (5 of 54) developed disease

Virus Vaccine	Location (Time-frame)	Vaccine Regimen Post-exposure (PE)	Data Interpretation (for previously unvaccinated individuals)
VACV Infection	Bangladesh Evacuees in India (1972) [43]	Vaccination given following presumed exposure. No participant numbers provided.	0–1 day PEP: 63% Survival 2 days PEP: 58% Survival Unvaccinated: 53% Survival
VACV Infection	India (1973) [44]	Vaccination given following presumed exposure.	1–7 days PEP: 60% (15 of 25) Survival 8–14 days PEP: 56% (5 of 9) Survival Unvaccinated: 47% (419 of 901) Survival

EBOV: Ebola virus; PEP: post-exposure prophylaxis; rVSV G-ZEBOV-GP: recombinant vesicular stomatitis Indiana virus expressing EBOV glycoprotein instead of VSIV G protein; VACV: vaccinia virus.