REVIEW

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# Current recombinant vaccine strategy as a novel approach to prevent Ebola virus diseases: a literature review

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## ABSTRACT

Ebola virus has resulted in a devastating hemorrhagic fever epidemic spanning several African countries and leading to thousands of deaths. There have been no vaccines approved or medication strategies toward successful prophylaxis and therapeutics critical until the rVSV-ZEBOV vaccine approved by the US Food and Drug Administration (FDA) in December 2019 as a preventative measure for people aged 18 years old and/or older. Several experimental vaccines are showing some promise. The most advanced vaccine is the clinically tested recombinant vesicular-stomatitis virus (rVSV) which encodes EBOV glycoprotein, widely known as the V920 vaccine candidate. This vaccine induces antibody-producing responses in non-human primate models, and current clinical trials suggest protective efficacy in humans. Although generally well-tolerated, the administration of this vaccine was complicated by occurrences of side effects. The development of vaccine platforms is also challenging, given that Ebola virus diseases have now reached epidemic proportions in some localities. Outcomes in terms of viral persistence after recovery are unknown, and a study explaining the role of adaptive immunity in recovery may be essential to inform effective vaccine design. This review aims to give a basic understanding on the general immunity mechanism elicited by recombinant vector vaccines and the current implementation of this relatively new technology to tackle a major infectious disease outbreak.

**Keywords:** Ebola virus, epidemic, hemorrhagic fever, recombinant vaccine.
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## INTRODUCTION

Ebola hemorrhagic fever (EHF), a fatal disease due to the Ebola virus, is accidentally transmitted by direct contact involving bodily fluids, both with infected animals and other humans. It has an incubation period of fewer than 21 days. Ebola virus diseases (EVD) were discovered in Zaire (Democratic Republic of Congo) in 1976. EVD has been a persistent global concern over the past few decades because they are easily transmitted and have a high mortality rate, ranging from 50-90% of actively symptomatic patients. Ebola virus infections cause a robust systemic inflammatory response leading to endothelial damage, disseminated intravascular coagulation, multi-organ failure, bleeding, shock and, finally, death. Ebola virus diseases due to lipid-coated negative-sense single-stranded RNA virus particles from five genetically different organisms that all belong to the Filoviridae family. These include Bundibugyo ebolavirus (BDBV), Tai Forest ebolavirus (TAFV), Zaire ebolavirus (ZEBOV), Sudan ebolavirus (SEBOV), and an organism that only causes diseases in non-human primates (NHP), called Reston ebolavirus (REBOV). The natural reservoir of EVD has not been determined by current knowledge despite the advancement of discoveries and molecular techniques to decipher these complex organisms. Thus, it has been difficult to contain transmission.[1]

The current epidemic of EVD began in February 2014 in West Africa, in which by March 2016, the World Health Organization (WHO) had reported 28,616 suspected cases, including 11,310 deaths (Figure 1). Although staggeringly high, these numbers are deemed to be an underestimate, and it is believed to be the most devastating Ebola outbreak throughout humankind's history. They include about 450 frontline health-care professionals, who suffered a higher mortality rate than in the overall EVD infected population, with over 50% or 244 deaths reported.[2] Fundamental approaches to managing EVD are providing supportive therapy to resuscitate infected patients, educating anxious communities, and minimizing infection transmission.

The viral transmission chain can be interrupted by implementing strict public health policies in a timely manner. These include patient isolation, use of personal protective devices, and comprehensive contact tracing. There are no currently approved post-exposure treatments or prevention to fight the Ebola virus until rVSV-ZEBOV vaccine was approved by FDA in December 2019 as effective agent to prevent and overcome this deadly ailment.[3]

The main goals of this review are to describe the devastating consequences of EVD outbreak in West Africa and to highlight the importance of implementing a novel molecular technique to create a recombinant vaccine, which triggers excellent protective immune responses, causes acceptable side effects, is cost-effective, reachable and fits with the infrastructure available in the most affected community, as one of the approaches to curb the epidemic.

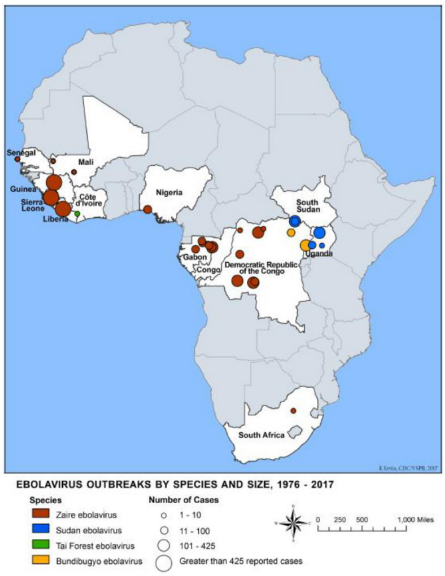


**Figure 1.** Ebola virus disease distribution map, 1976-2017.[4]

## EBOLA VIRUS STRUCTURE, GENOME, REPLICATION AND PATHOGENESIS

Ebola virus is a member of the family Filoviridae, an enveloped bacilliform or filamentous branched particles sized 800-900 x 80 nm with a helical nucleocapsid diameter of 50 nm. Its genetic material comprises one molecule of negative-sense single-stranded ribonucleic acid (ssRNA) containing around 19,000 nucleotides, which is fully transcribed into proteins.[5]

The Ebola virus genome consists of seven essential proteins (Figure 2). These proteins are important for Ebola virus replication in host cells, and they also have an immunogenic reactivity in EVD pathogenesis, causing a septic shock condition and multiorgan failure (Figure 3). The nucleocapsid protein (NP) serves as the main structure to encapsulate and protect viral genetic material. The VP35 and VP24 proteins are major virulence factors that reduce interferon production by host immune cells to create an evasive antiviral response. These proteins also work synergistically with VP30 and the terminal L protein, playing an essential role in viral RNA synthesis. The VP40 protein mainly mediates the assembly and budding of new viral particles. The glycoprotein (GP) is highly immunogenic and is composed of two major components, namely GP1 as a viral entry mediator and GP2, which promotes viral fusion with the host cell. The extracellular viral particles use these two essential surface proteins to attach to a specific receptor on the host cell membrane. Shortly following the attachment, viral particles are then engulfed by a process defined as micropinocytosis characterized by the rearrangement of actin and other cytoskeletal structures on the host cell membrane forming early endosomes containing the viruses. These endosomes are then fused with cellular lysosomes, which digest and release the viral particles into the cytosol. The life cycle of the Ebola virus occurs mainly without the nucleus involvement, which entails cytosolic viral genome replication and translation using the cellular machinery accompanied by the assistance of encoded viral non-structural proteins. The replicated viral genomes are finally packed into new viral particles released into the extracellular environment by budding from the host cell membrane. It is essential to advocate for cutting edge study of these proteins to understand better their molecular functions, which potentially is leading to the fundamental of vaccine discovery.[6–8]

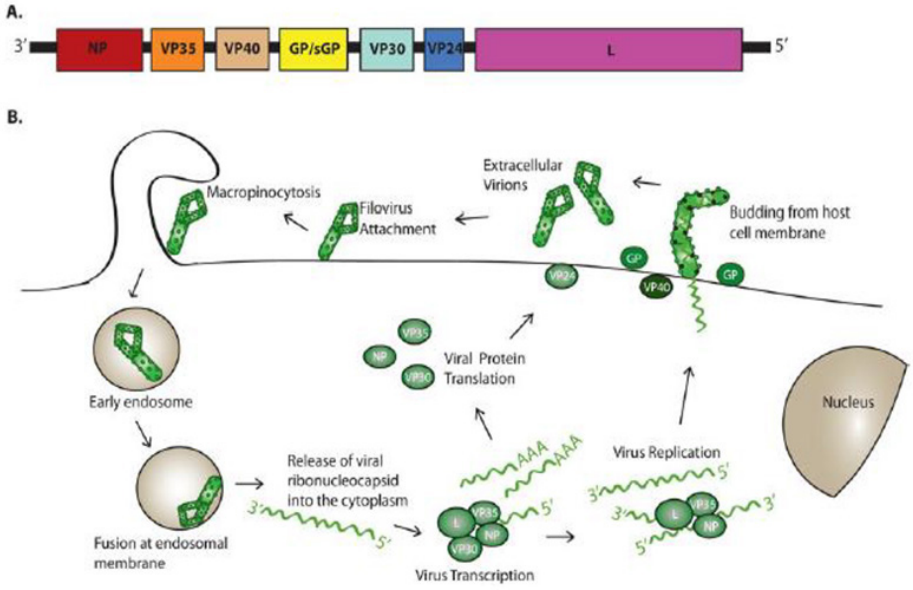


**Figure 2.** A. Ebola virus genomic structure, B. Ebola virus life cycle.[8]

## RECOMBINANT VESICULAR-STOMATITIS VIRUS (RVSV) AS A POTENTIAL VACCINE AGAINST EVD

In recent years, animal models have been studied that evaluate the efficacy of live-attenuated Ebola virus vaccines. Hong et al. and Ye et al., study with guinea pigs and non-human primates has not produced a satisfactory result. However, gene-based approaches utilizing DNA recombinant vaccines have generated promising results

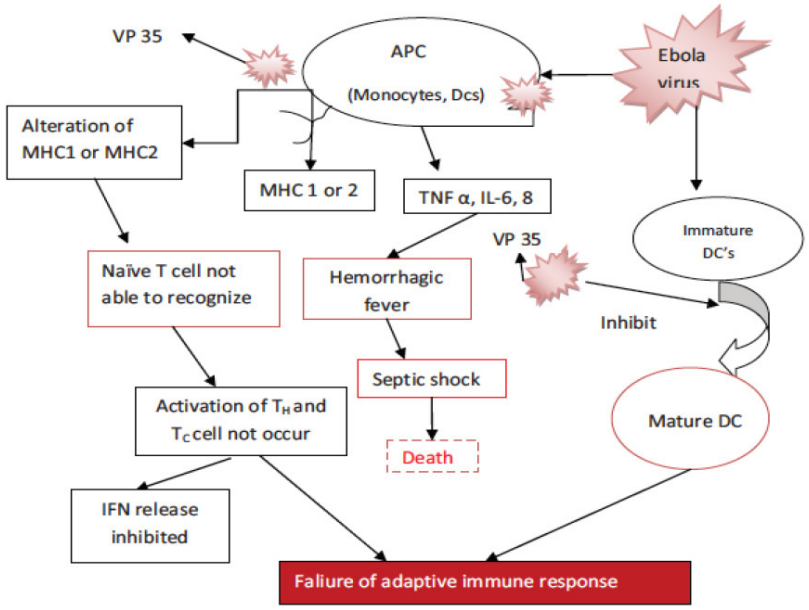


**Figure 3.** Pathogenesis of Ebola virus diseases.[8]

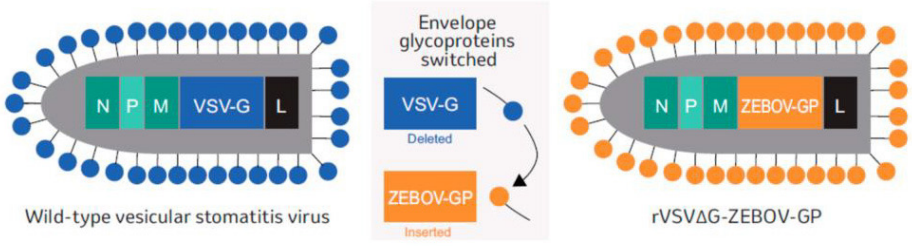


**Figure 4.** rVSV-ZEBOV schematic representation (V920 vaccine candidate).[12]

**Table 1. Experimental vaccine development using the recombinant VSV vectors.**[15]

| Vaccine type | Experiment subjects | Authors and year of publication | Contents |
|---|---|---|---|
| VSV vector | Human | Gunther et al., 2011[16] | There was a lab staff unveiled Ebola vaccine unexpectedly treated by rRSV vaccine |
| | NHP | Geisbert et al., 2011[17] | Marburg and Ebola virus were defeated by rRSV vaccine |
| | | Mire et al., 2012[18] | VSV vaccine safety |
| | | Falzarano et al., 2011[19] | NHPs cross-protection |
| | | Marzi et al., 2013[20] | rRSV mechanism of action entails antibodies |
| | | Geisbert et al., 2008[21] | Immunocompromised macaques were protected by rVSV vaccine |
| | | Feldmann et al., 2007[22] | Treatment for NHPs experiencing EVD post-exposure |
| | | Mire et al., 2013[23] | NHPs were protected by a heterologous vaccine |
| | Rodents | Wong et al., 2014[24] | rVSV vaccine protects guinea pigs and accomplishes cross-protection possibility |
| | | Marzi et al., 2011[25] | Enhanced cross-protection efficacy in guinea pig |

in chimpanzees and mice. These findings provide a positive prospect towards discovering a successful Ebola vaccine as a preventative measure in highly endemic areas.[9,10]

Numerous vaccine candidates had been investigated clinically for humans. Most breakthrough development is recombinant Vesicular Stomatitis Virus (rVSV) vector-based Ebola vaccine. Compared with other recombinant or other vaccine development technologies, this vector-based strategy shows good immunogenicity after one injection dose, excellent protective efficacy, acceptable safety profiles, and requires less stringent conditions for storage. It uses a single attenuated rVSV wild-type isolate vector in which glycoprotein on the VSV coat was exchanged with the fully expressed ZEBOV GP (Figure 4). This technique produced a bullet-shaped rVSVDG-ZEBOV-GP (rVSV-ZEBOV or the V920 candidate vaccine) which retained the ability to replicate in host cells without producing neurovirulence associated with the wild-type VSV. Protection towards EVD was first investigated in non-human primates (NHP) following a single dose intramuscular injection of the V920 with a potency of 1-2 x $10^7$ plaque-forming units (pfu). Study by Jones et al., and Coller et al., demonstrated no evidence of Ebola virus reproduction and replication observed after intravenous examination with ZEBOV in high lethal doses. It conferred 100% vaccine protection by eliciting humoral and cellular immune responses in every vaccinated test subjects.[11,12]

Rapid partial and complete protection accomplished by a single injection before the inoculation, demonstrating V920 can be used as pre-exposure prophylaxis during outbreaks. Moreover, the V920 also exhibited a 33-67% efficacy after a 24-hour post-injection of Rhesus macaques infected by the Ebola virus, which can be translated into an efficient post-exposure prophylaxis measure in clinical settings. Based on studies performed by Kanapathipillai et al. and Medaglini et al., in these animal subjects, this vaccine has also shown a good safety profile in hosts with immunocompromised conditions, a principal consideration in target

populations where HIV co-infection is common. A single administration with the V920 provided essential cross-protection, with 75% survival, encouraging monovalent rVSV-based vaccines that could effectively emerge Ebola virus species. **Table 1** shows the results of experimental trials in human and animal subjects using rVSV as vectors. Because of all of these properties, in 2014, V920 was approved by the WHO is one of only two candidates of the Ebola vaccine to proceed to a clinical testing phase involving humans.[13,14]

Phase I of the clinical trial was administered and showed high immunogenicity, favorable safety profiles and statistically significant

**Table 2. Phase I of clinical trials with the V920 vaccine candidate.**[12]

| Place | Number of Participants | Description of trial | Level of dose (pfu) |
|---|---|---|---|
| Halifax (Canada) | 40 | Randomized, single-center, double blind controlled, dose-ranging study | Placebo (n = 10), 3 x $10^6$, 5 x $10^5$, 1 x $10^5$ (each of n = 10) |
| WRAIR (US) | 39 | Randomized, single-center, double-blind, placebo-controlled, dose-escalation study of 3 sequential cohorts | Placebo (n = 9), 3 x $10^6$, 2 x $10^7$, 1 x $10^8$ (each, n = 10) |
| NIAID (US) | 39 | Randomized, placebo-controlled, dose-escalation study of a two-dose prime (day 0)-boost (day 28) regimen | Placebo (n = 9), 1 x $10^8$, 2 x $10^7$, 3 x $10^6$ (each of n = 10) |
| NewLink-Ib (US) | 512 | A randomized multi-center, double-blind, placebo-controlled study | Placebo (n = 90), 3 x $10^5$, 3 x $10^4$, 3 x $10^3$ (each of n = 64), 1 x $10^8$, 2 x $10^7$, 9 x $10^6$ (each of n = 50), 3 x $10^6$ (n = 80) |
| WHO (Geneva) | 115 | Dose-finding, randomized, single-center, double-blind, placebo-controlled study | Placebo (n = 15), 5 x $10^7$ (n = 15), 3 x $10^5$ (n = 50), 1 x $10^7$ (n = 35), |
| WHO (Hamburg) | 30 | Open-label, single-centre, dose-escalation study | 2 x $10^7$, 3 x $10^5$, 3 x $10^6$ (each of n = 10) |
| WHO (Kenya) | 40 | Open-label, dose escalation study | 3 x $10^6$, 1 x $10^7$ (each of n = 20) |
| WHO (Gabon) | 115 | Randomized, open-label, dose-escalation study | 2 x $10^7$ (n = 16), 3 x $10^6$ (n = 39), 3 x $10^5$ (n = 20), 3 x $10^4$ (n = 20), 3 x $10^3$ (n = 20), |

**Table 3. Phase II and III major clinical trials using the V920 vaccine candidate.**[12]

| Supporting agents | Location of study | Vaccine | Time of study | Objectives of study |
|---|---|---|---|---|
| NIH (NIAID) (PREVAIL) | Liberia | -V920<br>-ChAd3 (GSK)<br>-Placebo | February 2015 | • Comparison of every vaccine regarding to their safety and efficacy (3 arms; n = 9000 per arm)<br>• Phase II study of immunogenicity and safety (n = 1500, 500 subjects receiving V920 |
| MSF/NIPH/ WHO | Guinea | -V920 | March -April 2015 | • Efficacy and safety of rapid versus detained ring vaccination (n = 10,000)<br>• Collateral immunogenicity and safety of forefront workers (n = 1800) |
| CDC (STRIVE) | Sierra Leone | -V920 | April 2015 | • Efficacy and safety in rapid versus detained vaccination class group<br>• Investigation focuses on workers with high risk together with health care worker (n = 8000)<br>• Substudy of safety (n = 400)<br>• Substudy of immunogenicity (n = 500) |
| MSD V920-012 | Canada, US, Spain | -V920<br>-Placebo | August 2015 | • D42 PD safety study covering skin and joint disorder symptoms (n = 1200)<br>• Examination of D28 and D180 immunogenicity with much consistency examination of D28<br>• Subject subclass expanded follow-up absent for 2 years |

protective efficacy across all dose levels in healthy humans. Based on current clinical trials, this vaccine was generally well-tolerated. However, a few vaccine-related side effects, including headaches, fever, fatigue, myalgia, injection site reactions, arthralgia, and more debilitating arthritis, were reported. Any kind of major side effects leading to debilitating consequences or even death has not been reported yet. There have also been promising preliminary results in current phase II and III clinical trials done in both epidemic and non-endemic areas. However, the results of these major trials still need to be finalized and validated using statistical solid analysis.[12] Many questions left are still open for discussion. They mostly correlate to immunogenicity and safety of the V920 in vulnerable people e.g., immunocompromised hosts, pregnant women, young children; long-term duration of protection. Advocacy is required for more work on these specific areas of research. Tables 2 and 3 show completed and current major clinical trials using the V920.[14]

## CONCLUSION

The current devastating epidemic of EVD in several African countries has resulted in an urgent need to accelerate the development of a vaccine competent of shield protection for high-risk populations situated in endemic areas. V920 is currently an Ebola vaccine with proven efficacy, excellent immunogenicity, and acceptable safety profiles in several clinical trials involving humans and primates. The results from these clinical trials are likely to provide a solid foundation for the vaccine licensure process to be completed as quickly as possible. The vaccine will need to be made readily available to at-risk populations through close collaboration between relevant governments and key international organizations. Nations with risk of upcoming Ebola outbreaks have to contemplate Ebola vaccine program implementation as a successful approach for prevention and control of the disease and be employed by traditional epidemic containment strategy to reduce transmission and high mortality rates associated with EVD.

## DISCLOSURES

### Conflicts of interest

No conflicts of interest regarding the manuscript.


### Funding

No funding was received in this study.


### Ethical Statement

Not applicable

### Author contribution

Author 1 conceptualizes the manuscript. Author 1 and 2 are the guarantors. All of the authors contribute for content definition, definition, literature exploration, design, as well as manuscript preparation, editing, and review.

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