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Current Opinion in Immunology

Ebola virus disease: current vaccine solutions

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Ebola Virus Disease (EVD) is an emerging zoonotic disease with intermittent outbreaks in Central and West African countries. The unpredictable high case fatality rate has made it a disease of public health concern. Different vaccine platforms have shown prophylactic protection in human and non-human primates, with the progress towards a licensed vaccine greatly accelerated in response to the devastating outbreak of EVD in West Africa from 2013–2016. Currently, two vaccines: Ervebo (rVSV-ZEBOV) and a two-dose combination of Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo) have been licensed and in use. The licensing of an Ebola vaccine for use is challenging for several reasons, including the sporadic and limited nature of EVD outbreaks and the enormous resources needed to bring a vaccine to licensure. While vaccine solutions remain important in reducing the fatality of EVD, other strategic interventions are necessary for the prevention and control of EVD.

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Current Opinion in Immunology 2021, **71**:27–33

This review comes from a themed issue on **Vaccines**

Edited by **Charles S Wiysonge** and **Sara Cooper**

https://doi.org/10.1016/j.coi.2021.03.008

Introduction

Ebola Virus Disease (EVD), an emerging zoonotic disease endemic in some countries of West and Central Africa, with an unpredictable and often high case fatality rate, was identified for the first time in 1976 following two simultaneous outbreaks in South Sudan and Zaire (now, the Democratic Republic of Congo). Since then, over 25 outbreaks of EVD have been reported, mostly in central Africa. Before the 2010s, EVD outbreaks occurred as relatively small number of cases, mostly in remote and rural areas, which were often contained by basic public health and local quarantine/containment measures. Recently, EVD epidemics have affected larger populations, extending to new and urban areas, and changing the perceptions on EVD epidemiology. Between 2014–2016, West Africa suffered the largest and most complex Ebola outbreak [1]. The rapid rate of these recent outbreaks has been attributed to factors such as the increase in international travels, political instability, increasing urban population, and lack of public health infrastructure [2]. The various EVD outbreaks reported since 1976, are presented in Table 1.

The decade of 2010–2019 has been the most devastating, although with the situation in 2020 and now 2021, the current decade may yet turn out to be equally as, or more devastating. This is where the need for safe and efficacious vaccines become highly relevant.

Role of vaccines in protection against Ebola

An ideal vaccine candidate for EVD should provide swift protection after a single-dose immunization, efficacious if given post-exposure and be multivalent or effective across all strains and species of the Ebola virus (including the other Filovirus family, Marburg virus) [3•]. Some vaccine platforms have shown prophylactic protection in non-human primates, and the progress towards a licensed vaccine was greatly accelerated in response to the devastating outbreak of EVD in West Africa from 2013–2016. These are shown in Table 2 and include virus-like-particles (VLPs), Venezuelan equine encephalitis virus replicons (VEEV RP), replication-incompetent adenovirus serotype 5 vectors, replication-competent recombinant human parainfluenza virus 3 (rHPIV3), and recombinant vesicular stomatitis virus (rVSV) [3•].

The two most promising of these EVD vaccine candidates are the Merck's (rVSV-ZEBOV'/Ervebo) and the Johnson and Johnson (Zabdeno) vaccines [4]. The rVSV-ZEBOV'/Ervebo vaccine is a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope GP gene of Zaire Ebola virus (Kikwit 1995 strain, The Zabdeno vaccine on the other hand is a monovalent replication-incompetent adenoviral vector serotype 26 (Ad26) vaccine, which encodes the full-length GP of the EBOV Mayinga variant. MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which encodes the EBOV Mayinga GP, the Sudan virus (SUDV) Gulu GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV, formerly known as Côte d'Ivoire ebolavirus) nucleoprotein (NP).

The rVSV-ZEBOV/Ervebo vaccine has been granted the European Commission a conditional marketing authorization, and WHO prequalification. It has now been

Table 1

Ebola virus disease (evd) outbreaks 1976-date

Decade	Period of outbreaks	Countries affected	Number of		Case fatality rate (%)	
		Location	Cases	Deaths	Average	Range
1970–1979	1976–1979	DRCongo, Sudan, UK#	638	454	71.2	0–100
1980–1989	1989–1990	USA, Philippines, Italy	7[a]	0	0	0
1990–1999	1994–1996	Gabon, DRCongo, South Africa, Philippines, Russia#	467	349	74.7	57–100
2000–2009	2000–2004, 2007	Uganda, Gabon, DRCongo, Sudan, Russia# Philippines[a]	1194	724	60.6	0–100
2010–2019	2011–2019	Uganda, DRCongo, Guinea, Liberia, Sierra Leone, Nigeria, Mali, Senegal, Spain, USA,	32 178	136 489	42.4	36–74
2020-DATE	2020, 2021	DRCongo, Guinea[b]	594	133	22.4	14.5–42

Table adapted from WHO Ebola Disease Factsheet (2021).

[a] Reston Virus infection #, Laboratory infection.
[b] Seven unconfirmed reported cases, with 3 deaths as February 15, 2021.

approved for medical use in the European Union and in the United States [5]. The Zabdeno vaccine has been granted approval by Committee for Medial Products for Human Use -European Medicines Agency (CHMP-EMA) for active immunization of individuals aged 18 years and older at risk of infection with the Ebola virus [6]. Additional information about other candidate vaccines is provided in Table 2.

The journey to approval of Merck's Ervebo vaccine

The performance of rVSV-ZEBOV'/Ervebo vaccine in pre-clinical tests paved the way for the progress to the phase 1–3 clinical trials [7•,8•]. After experiencing signs of disease in mice in the early days of rVSV vaccination, it became necessary to attenuate the vaccine vector. Multiple strategies, including truncating the cytoplasmic tail of the VSV glycoprotein (GP) to reduce virulence, as well as modification of other structural proteins, were developed to achieve attenuation of the VSV vaccine vector [8•,9••,10]. This strategy proved effective for the rVSV-EBOV vaccine, in which the EBOV glycoprotein (GP) was inserted into a VSV vector from which the G-open reading frame was deleted (VSV-ΔG). This produces a replication-competent virus particle that has a rhabdovirus morphology and EBOV-GP expressed on its surface [7•].

Following this success, the efficacy of rVSV-EBOV was demonstrated by several authors in cynomolgus macaques, the gold standard model for Filovirus infection [11–14]. Follow-up studies in various animal species were carried out to demonstrate the post-exposure efficacy [15]. The results of these studies are summarized in Table 3.

In 2015, three phase-3 clinical trials were conducted with the rVSV-EBOV vaccine. The first was in Guinea, using an open-label, cluster-randomized ring vaccination [16••,17]. In this trial, those who had contacts with EVD infected persons, and their subsequent contacts were grouped into clusters and these clusters were randomized to receive a single dose of the VSV-EBOV vaccine (2×10^7 PFU), either immediately or within a 21-day interval. In total, 4539 initial contacts and their subsequent contacts (contacts of contacts) were selected for the immediate vaccination group, while 4557 were in the delayed vaccination group [16••]. In the first group, no one had a case of EVD at 10 or more days after randomization, however, 16 cases of EVD were detected in the group that received the vaccine after 21 days.

The second trial was conducted in Sierra Leone as an open label, individually randomized controlled phase. The vaccination was completed in December 2015, having more than 8000 participants. Only 64 participants presented with symptoms that were investigated as suspected EVD, none of the sixty participants provided specimens for testing, was confirmed as EVD. The trial showed no serious adverse reactions and the data was generally consistent with that of phase 1 trials [18].

The last phase of the clinical trial was a randomized, double-blind, multicenter phase, which was conducted in the USA, Spain, and Canada [19••]. The trial was designed to assess the safety and immunogenicity of 3 consistency lots (2×10^7 PFU) and a high-dose lot (1×10^8 PFU) of the VSV-EBOV vaccine. The vaccine was generally well-tolerated and no vaccine-related severe adverse events or deaths were reported [7•]. Furthermore, it was found that prophylactic vaccination of a small proportion in the general population and health care workers (HCW), could go a long way to minimizing the impact of an Ebola virus disease outbreak [20•].

Table 2

Status of candidate Ebola vaccines

Company/institution/ country	(Vaccine name)/Ebola component glycoprotein	Vector	Administration	Storage temperature	Target population	Comments
Merck USA/Public Health Agency Canada	(Ervebo)Recombinant VSV-ZEBOV-Ebola Kikwit strain Replication competent vaccine	VSV	Single dose	60°C to −80°C for 36 months and 2 °C–8 °C for 14 says	Active immunization (reactive use) of at risk subjects ≥18 years of age	2016- granted Breakthrough Therapy Designation by the US FDA and PRIME status by the European Medicines Agency (EMA) and in 2019, granted medical use in EU and USA. Used extensively in the Kivu Ebola epidemic under a compassionate use protocol
Johnson & Johnson (USA) and MVA-BN Filo, Bavarian Nordic (Denmark)	(Zabdeno)MVA-BN-Filo encodes Ebola virus, Sudan virus, and Marburg virus glycoproteins, and Tai Forest virus nucleoprotein	Human adenoviral serotype 26 or MVA	Heterologous prime boost regimen	Ad26.ZEBOV: 20°C or 60°C for up to 60 months and +2 to +8°C for up to 12 months MVA-BN-Filo: 20°C or 60°C for up to 60 months and +2 to +8°C for up to 6 months	Adults and children ≥ 1 year of age	Granted approval by Committee for Medial Products for Human Use -European Medicines Agency (CHMP-EMA) in 2020 as a two-dose regimen for the prevention of Ebola virus disease. Seeking licensure under the Animal Rule and/or to European Medicines Agency. Collaborative.
GlaxoSmithKline (UK) and, for MVA-BN-Filo, Bavarian Nordic (Denmark)- NIAID/GSK	(ChAd3-EBO-Z) with or without MVA-BN-Filo Ebola virus, Mayinga strain (1976)	Chimpanzee adenoviral serotype 3 or MVA	Single dose or heterologous prime-boost regimen			**Ongoing clinical evaluationl**
Academy of Military Medical Sciences and CanSino Biologics (China)	(Ad5-ZEBOV) Ebola virus, Makona strain (2014)	Human Adenoviral serotype 5	Single dose or homologous prime-boost regimen	Freeze-dried powder, stable for more than 2 weeks even if kept at a temperature of 37°C;		Licensed in China
Gamalei Scientific Research Institute of Epidemiology and Microbiology (Russia)	(GamEvac-Combi and GamEvac-Lyo) Monovalent Zaire (Makona)	VSV and Ad5-vectored vaccine	Heterologous prime boost regimen	16°C to −20°C for 12 months 4°C for lyophilized formulation	18–55 years	Licensed in Russia
Novavax, USA	(NVX-CoV2373). Nanoparticle recombinant Ebola GP Vaccine) Monovalent Zaire (Makona)	Contains the full-length SARS-CoV-2 spike protein and Novavax' patented Matrix-M1 adjuvant	2 doses 21 days apart,	2° to 8°C for six months, and 24 hours at room temperature	18–65 years	Efficacy 89.3 %.
Inovio Pharmaceuticals, USA	(INO-4201 DNA vaccine) Plasmid of Ebola outbreak strains from 1976–2006		2 doses four weeks apart	+2°C to +8°C for 3 years and 25°C for 1 year 37°C for 1 month 60°C for several days	≥ 18 years	In 95% (170/179) of evaluable subjects generated an Ebola-specific antibody immune response,
FBRI SRC VB VECTOR, Rospotrebnadzor, Russia	(EpivacEbola) Monovalent Zaire (Makona)		2 doses (prime + boost on 28 days)	2–8°C for 1 year Can extend shelf life to 2 years	18–55 years	Licensed in Russia since 2016

VSV-vesicular stomatitis Indiana virus. MVA = modified vaccinia Ankara virus. Ad5=human adenoviral serotype 5. *The year the strain (from which the glycoprotein was derived) was isolated is given in brackets.

Update of https://www.who.int/immunization/sage/meetings/2019/october/6_Ebola_Candidate_Vaccines_19-09-19.pdf.

Table 3

rVSV-EBOV protection efficacy on Pre- and Post-infection exposure

Animal subjects	Pre-Infection Vaccination outcome	Post-Infection Vaccination outcome	
		Vaccinated <24 hours post infection	24 hours – 48 hours post infection
Mice	Fully protected at 24 hours before infection	Exhibited only mild disease when treated within 24 hours	–
Guinea Pigs	Partial protection (66%) at 24 hours pre-infection	Partial protection (67%) if treated within 24 hours	>95% fatality if treated after 48 hours
Hamsters	Full protection (100%) at 72 hours before infection	100% survival if treated within 24 hours of infection.	100% fatality if treated at 48 hours after infection.
Rhesus Macaques	100% survival when vaccinated 7 days pre-infection	50% survival when treated within 20–30 minutes after infection	–

Current vaccine solutions and availability among local populace

Before the outbreak of EVD in West Africa, cases of EVD in previous epidemics were managed by supportive care due to the lack of an effective or approved vaccine or drugs to treat Filovirus infections. For the first time, vaccine candidates and specific antiviral components were used for experimental tests or compassionate use, during the West Africa Ebola outbreak [21].

Shortly after the West Africa outbreak began, a World Health Organization (WHO) panel of experts met to discuss potential forms of treatment. The panel accepted the use of some unregistered interventions for treatment if they had yielded positive results during laboratory and animal testing [22]. Licensing an Ebola vaccine had been previously challenging due to the sporadic and limited nature of previous Ebola outbreaks; the enormous effort and resources needed to bring a vaccine to licensure; the political willingness of unaffected countries to pay for the licensed vaccines; and the overall lack of efficient data on EBOV vaccine candidates in humans. Thus, the chances of getting the US Food and Drug Administration (FDA) to license an EBOV vaccine previously slim. However, the nature of the 2013–2016 EBOV epidemic accelerated phase 1–3 human clinical trials of several EBOV vaccine candidates that had previously been effective against the Ebola virus in Non-Human Primate models [23•].

The rVSV-EBOV Ebola vaccine (Ervebo) was first to be approved, by the US Food and Drug Administration (FDA), in December 2019 for the prevention of Ebola virus disease (EVD) among persons ≥18 years. The vaccine is given as a single dose and is safe and protective against Zaire ebolavirus, which has caused the largest and most deadly Ebola outbreaks to date [24]. It is made up of a rice-derived recombinant human serum albumin and contains live attenuated recombinant Vesicular Stomatitis Virus (rVSV) [22].

In 2017, the World Health Organization's Strategic Advisory Group of Experts (SAGE) on Immunization, acknowledged the rVSV-EBOV vaccine candidate as a Priority Medicine (PRIME) designation through the European Medicine Agency (EMA), and as a 'Breakthrough Therapy' designation by the FDA due of its human efficacy data. Other vaccines, such as the Zabdeno (rAd26-EBOV) prime and Mvabea (MVA-BN-Filo) boost vaccine, were also submitted for WHO Emergency Use Assessment and Listing (EUAL) approval.

In August 2018, the Democratic Republic of the Congo (DRC) experienced a severe outbreak, which is currently ongoing and has been the largest on record in the country. The rVSV-EBOV is currently being used to help interrupt the ongoing human transmission in the eastern region of Kivu, where over 28 000 people have received the vaccine [23•]. This prompted the WHO's SAGE to review the use of vaccines in the ongoing outbreak, issuing a set of new recommendations which included adjusting the dose of the rVSV-EBOV vaccine, evaluating a second vaccine under appropriate protocols, changing strategies in areas of conflict, and increasing vaccination rates in communities with active transmission, sometimes enrolling the entire villages.

The increasing cases and rapid spread of the Ebola outbreak in the Democratic Republic of the Congo has prompted the approval of the new Zabdeno/Mvabea vaccine to complement the current use of the rVSV-EBOV vaccine. This vaccine is approved for administration in persons ≥1 year of age. Clinical results have indicated that the prime dose induces an immune response which is further enhanced by the boost dose, inducing a durable immunity to *Zaire* Ebola (ZEBOV). Both the prime and boost doses are well tolerated with a good safety profile. Recently, EBOV-GP-specific antibody titers, lasting up to one year after vaccination, have been reported from five trials while one other trial has reported high levels of antibody two-year post vaccinations [25•]. These trials have identified a peak in early immune responses at about two to three months post-injection and with mild decline between three months to six months. However, the durability of immune responses remains strong after both one year and two years post-administration. It is noteworthy that the persistence of

seropositivity is a factor of the vaccine dose, but two years after vaccination, the magnitude of EBOV-GP-specific IgG titers is no longer dose-dependent [25•,26••].

Following the approval of the Ebola vaccine (rVSV-EBOV) by US-FDA and the European Medicines Agency (EMA), the manufacturers of the vaccine (Merck), has given permission to stockpile and, potentially, distribute to areas of need, particularly in Africa [27,28]. After examining the Zabdeno/Mvabea vaccine in 5 different clinical studies among a total of 3367 adults, adolescents, and children in Europe, Africa, and the United States of America, the vaccine regimen was approved as capable of inducing an immune response against EBOV. However, the exact level of protection provided by the vaccine regimen is not yet fully known [28].

Currently, the WHO–SAGE is reviewing available evidence on both Ervebo and Zabdeno/Mvabea vaccines and is expected to issue policy recommendations for preventive use in 2021. The Ervebo vaccine was initially indicated for use in adults of 18 years and above, excluding pregnant and lactating women. However, it was used, as recommended by the WHO–SAGE, in children above 6 months old and in pregnant and lactating women during the 2018–2020 DRC outbreak [29]. The WHO–SAGE will continue to review its safety among these populations and further recommendations are expected in 2021.

Conclusion

Of the nine Ebola candidate vaccines, three have been licensed, another three have completed or are in trials up to Phase 1 phase, while two vaccines up to or in Phase 2 stage. The last one has completed Phase 3 stage [30,31]. In view of continuing reports of EVD outbreaks in Africa, the search for safe and efficacious vaccines must continue. However, as outlined by WHO, the administration of a vaccine is only one out of several other strategies aimed at controlling the Ebola outbreak. The other important strategic components include; early detection of new cases of infections by close monitoring of contacts; availability and use of functional laboratory services for confirmation of infections; effective isolation and quarantine system, enforcing the safe and non-contagious burial of deceased patients to prevent transmission and community mobilization and engagement in disease response.

Conflict of interest statement

Nothing declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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UUsing data from different clinical trials and laboratory experiments, these authors identified the advantage of rVSV-EBOV over other vaccine candidates and highlighted its inter-specific and multivariate potential against other strains and species of Ebola. Also, it was highlighted that the rVSV vaccine is amenable to adaptation to other emerging and re-emerging pathogens of concern. This was a solid ground for selecting rVSV-EBOV as a vaccine of choice for Ebola.

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This study was aimed at testing the effect of rVSV-ZEBOV in preventing Ebola virus disease in contacts and contacts of contacts of recently confirmed cases in Guinea, West Africa. The results from the study shows vaccine efficacy of 100%, with a calculated intraclass correlation coefficient of 0·035. These results add weight to the assertion that rVSV-ZEBOV offers substantial protection against Ebola virus disease, as vaccinated individuals presented no case of disease at 10+ days after vaccination.

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In a Phase-3 Clinical trial experiment on potential Ebola vaccine candidate, the authors evaluated the safety of recombinant Vesicular Stomatitis Virus–Zaire Ebola virus envelope glycoprotein vaccine (rVSVΔG-ZEBOV-GP) using different doses by lots of rVSVΔG-ZEBOV-GP. Results show that rVSVΔG-ZEBOV-GP was well-tolerated, and no vaccine-related Serious Adverse Effects or deaths. These findings support the use of rVSVΔG-ZEBOV-GP vaccine in persons at risk for Ebola virus disease.

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This study made use of a mean-field compartmental stochastic model in assessing the potential impact of Ebola vaccine candidates on morbidity and mortality of Ebola. The model was validated by simulating the 2014 Sierra Leone Ebola epidemic, accessing the impacts of prophylactic vaccination of healthcare workers (HCW) both alone and in combination with the vaccination of the general population (entire susceptible population other than HCW). Results of this study reveals that the prophylactic vaccination of even small proportions of HCW significantly reduces the incidence of Ebola and associated mortality. This is even greatly enhanced by additional vaccination of small percentages of the general population. These findings could be used to inform the planning of prevention strategies.

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This study investigates and highlights the strategies, interventions, and procedure of Ebola vaccine administration in a conflict zone with Ebola disease outbreak. It was the first outbreak in a conflict zone. Authors highlighted the use of swift case detection and rapid isolation of cases; contact tracing; population mapping and identification of high-risk areas to inform coordinated effort, as the strategies used in this location. The coordinated was aimed at screening, ring vaccination and laboratory diagnoses using GeneXpert (Cepheid) polymerase chain reaction. To prevent the spread and further outbreak of the disease, rVSV-ZEBOV-GP vaccine was administered first to populations at high risk, followed by a Ad26.ZEBOV/MVA-BN-Filo, to reinforce the prevention. This study clarifies the best and effective strategies for administration of Ebola vaccines under various conditions, for positive results.

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Following the approval and use of the rVSV-ZEBOV vaccine, the authors carried out a survey on the durability of human responses to rVSV-ZEBOV, examining the determinants of initial responses and of their persistence. The authors identified that the persistence of EBOV-GP-specific antibody responses is strong at 2 years after a single injection. The authors also opined that vaccine dose predicts persistence of seropositivity, though the magnitude of antibody responses at later time becomes less dose dependent. Findings also revealed that vaccine-related arthritis is a significant predictor of both persistence and magnitude of the antibody response. This study is relevant in understanding the length of period and the immunological response of humans in resistance to Ebola virus disease.

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