Safety, immunogenicity and risk–benefit analysis of rVSV-ΔG-ZEBOV-GP (V920) Ebola vaccine in Phase I–III clinical trials across regions

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To evaluate the risk–benefits balance of the rVSV-ΔG-ZEBOV-GP vaccine. We performed a systematic review to summarize data on safety, immunogenicity and efficacy. About 17,600 adults and 234 children received 11 different doses of the V920 vaccine ranging from 3000 to 100 million and 20 million plaque-forming units, respectively, during Phase I–III clinical trials. Cases of severe but transient arthritis were reported in about 6 and 0.08% of vaccinees in high-income countries (HICs) and low–middle-income countries (LMICs), respectively. The 20 million plaque-forming units dose yielded GP-specific antibody titres which peaked at day 28 with a pooled geometric mean titres of 2557.7 (95% CI: 1665.5–3934.2) versus 1156.9 (95% CI: 832.5–1649.2) but with similar seroconversion rates at 96% (95% CI: 87–100) versus 100% (95% CI: 90–100) for HICs and LMICs, respectively. Data from stringent Phase I–II clinical trials in LMICs and HICs and from the ring efficacy trials yielded a good risk–benefit balance of the V920 vaccine in adults, but also in children and pregnant and lactating women and HIV-infected people.

First draft submitted: 15 August 2019; Accepted for publication: 13 January 2020; Published online: 7 February 2020

Keywords: Ebola vaccine • effectiveness of rVSV-ΔG-ZEBOV-GP • immunogenicity of rVSV-ΔG-ZEBOV-GP • ring vaccination • risk–benefit analysis of rVSV-ΔG-ZEBOV-GP • rVSV-ΔG-ZEBOV-GP in high-income countries • rVSV-ΔG-ZEBOV-GP vaccine • rVSV-ΔG-ZEBOV-GP vaccine in low-and-middle-income countries • safety of rVSV-ΔG-ZEBOV-GP • V920 vaccine Ervebo®

Ebola virus (a negative stranded RNA-enveloped virus) is a genus encompassing five species within the Filoviridae family, affecting humans and nonhuman primates, with case fatality rates ranging from 25 to 90%, and remains a threat to global health security [1,2]. At the time of writing this review, the ongoing Ebola outbreak in the Democratic Republic of Congo in Central Africa registered about 3324 cases and 2206 deaths [3], with concerns that an uncontrolled, smouldering outbreak transforms into long-lasting endemicity with sporadic but continuously emerging cases, due to the conflict situation in the area. Several sporadic and geographically restricted outbreaks, primarily to areas of Central Africa, have been meticulously studied and documented. The largest and most longest-lasting epidemic in history to date occurred between 2014 and 2016 in West Africa, affecting an estimated 28,616 confirmed and unconfirmed cases, and having killed an estimated 11,310 by 10 June 2016 [4]. In humans, the Ebola virus actively induces direct tissue damage through a cascade of harmful inflammatory responses, potentially causing death within 7–16 days after the onset of disease as a result of multiple organ failure and onset of a septic shock-like syndrome [5]. Amidst advancements in diagnostic and therapeutic research, the rapid progression of the viral infection from nonspecific flu-like symptoms (fever, malaise, muscle aches, headaches and chills) to often fatal symptoms of haemorrhage and hypotension, calls for a vaccine as the to date potentially most successful and cost-effective approach in curbing the eventual spread of this highly lethal infection during an outbreak [1].

The West Africa Ebola epidemic spurred an unprecedented global framework to accelerate the licensure of vaccines against Ebola virus disease (EVD). Several Phase I and II clinical trials were initiated simultaneously in Europe, Africa and North America [6–8], with the primary goal to generate safety and immunogenicity data to support the design of Phase III efficacy trials. Over 15 different vaccines went into preclinical development, and eight vaccines entered different stages of clinical trials. These vaccines include DNA, virus-like particles and viral vectors such as live-replicating vesicular stomatitis virus (rVSV), human and chimpanzee adenovirus and vaccinia virus vaccines [9].

The rVSV-ΔG-ZEBOV-GP vaccine candidate

The farthest in clinical development of all Ebola vaccine candidates is the live-replicating recombinant virus based on the backbone of a recombinant vesicular stomatitis virus rVSV-ΔG-ZEBOV-GP (designated as V920) [10].

The live-attenuated rVSV-ΔG-ZEBOV-GP is a replication-competent recombinant Indiana strain vesicular stomatitis virus (rVSV)-based vaccine encoding the gene for the Zaire Ebola virus (ZEBOV-GP) Kikwit 1995 strain. The ZEBOV-GP replaces the gene for the VSV glycoprotein (G), resulting in a highly attenuated nonpathogenic virus with a narrower cell tropism than VSV. The vaccine resembles the VSV bullet structure of a ZEBOV-GP envelope antigen [11]. The VSV, a negative-sense RNA virus of the Rhabdoviridae family suitable as a vaccine vector for ZEBOV exhibits properties such as robust growth in approved and continuous mammalian cell lines; an apparent lack of pathogenic potential in man; and a potential to induce strong cellular and humoral immune responses. Also, the very low VSV prevalence in humans potentiates its use as a viral vector for this vaccine [12,13]. The unique properties of the V920 vaccine, such as its stability of at least 1 week after thawing, and storage in a refrigerator when a vial has been opened, enables its use in remote settings. When undiluted or diluted, the vaccine retains its potency for at least 24 h at 25°C, although its stability will be reduced at temperatures >25°C [14,15].

In preclinical phases, the V920 vaccine, administered in different doses, showed no toxicities in rats, mice [16] and *Cynomolgus* macaques [11,13]. In addition, no teratogenic effects were observed in rats. Transient viremia levels were reported both in rats and nonhuman primates. Significantly, high antibody responses measured using IgE ELISA and neutralization assay coupled with high efficacy were reported in *Cynomolgus* macaques postimmunisation challenge studies [17]. These preclinical data led to the V920 vaccine advancing into clinical trials [13].

Thus far, eleven doses – 3000; 30,000; 100,000; 300,000; 500,000; 3 million; 9 million; 10 million; 20 million; 50 million; and 100 million plaque-forming units (pfu/ml) of this vaccine were or are currently being evaluated across different Phase I–III clinical trials worldwide, and in a variety of settings. These clinical trials form a suitable platform for establishing the safety profile of a vaccine, thereby contributing to its risk–benefit assessment. The risk–benefit assessment of an Ebola vaccine weighs the risk of an individual who suffers from adverse effects (AE) or vaccine failure against the benefits for the individual (prevention of disease pre-exposure, or prevention of sequelae postexposure) and for the community (such as outbreak prevention, reduction of cost associated with treatment, improvement of economic productivity) [18]. This vaccine produced by Merck was given the ‘Breakthrough Therapy Designation’ by the US FDA as well as the Priority Medicines (PRIME) status from the European Medicines Agencies for accelerated regulatory review [18,19].

At this point in clinical development, evaluating the safety, immunogenicity and efficacy of this vaccine across regions and highlighting risk–benefit indicators will strengthen evidence for further policy decisions, especially in Ebola virus endemic countries and inform the design and conduct of further studies enclosed in a potential pharmacovigilance plan. This paper’s primary objective is to assess the safety and immunogenicity of the V920 vaccine across regions (Africa, Europe, North America) using a systematic review of results from available and published Phase I–III clinical trials. As a secondary objective, we reviewed the efficacy data from Guinea and Democratic Republic of the Congo and assessed the risk–benefit indicators of the V920 vaccine.

Materials & methods

Study selection & data extraction

We conducted a review largely based on the PRISMA guidelines for systematic reviews to summarize available data on safety, immunogenicity and efficacy in order to highlight risk–benefit indicators of V920 vaccine in adults, children and other special populations. We conducted a literature search with no language restriction for published articles in EMBASE and Medline/PubMed databases up to 31 January 2019. To track registered on-going or completed reviews and studies in this field, we reviewed the Pan African Clinical Trials Registry (PACTR), the

clinical trials registry (www.clinicaltrials.gov), the systematic review registry database PROSPERO and the Cochrane Library for systematic reviews, using appropriate search terms for Phase I–III clinical trials of this candidate vaccine.

Two authors (BEB, AST) screened titles and abstracts independently for location, study population and general consistency with research objectives. One review author (BEB) extracted information relevant to the review question from all full text articles using standard formats. A second review author (AST) randomly checked 20% of the extracted data for consistency and accuracy.

We used the Brighton Collaboration Template [13,15] to harness evidence from trials to describe the risk–benefit indicators of the V920 vaccine at this current stage of development against the lethal EVD disease, affecting humans in specific regions (Africa, Europe and North America).

Vaccine doses were classified as low ($\leq 500,000$ pfu), intermediate (3 million pfu) and high (≥ 9 million pfu). Clinical trial sites were classified as low–middle-income countries (LMICs) and high-income countries (HICs) according to the world bank data on per capita income [20].

Regarding data synthesis, the frequency of AEs and titres of GP-specific and neutralization antibodies were aggregated for all vaccine doses across regions at various time points. Pooled estimates of geometric mean concentration (GMC)/geometric mean titres (GMT) and 95% CIs of the GP-specific and neutralizing antibodies per dose level were averaged. Seropositivity is defined by GMC > 50 arbitrary ELISA units (AEU)/ml. Seroconversion is defined by a $\geq$ fourfold rise in GMT. The $p < 0.05$ are given in bold. Pooled estimates and 95% CI of seropositivity and seroconversion rates were performed using Restricted Maximum Likelihood random effects model with Freeman–Tukey double arcsine transformation (suitable for data with proportion close to 1) for each vaccine dose category per region [21]. All analyses were conducted using the R-software version 3.4.2 [22].

Results

Study selection & population

The selection of references reporting results of Phase I–III clinical trials of this vaccine is described in Figure 1. The targeted search yielded 404 references, of which 12 met the inclusion criteria. Studies not reporting safety, immunogenicity or efficacy of any dose of the vaccine were excluded. Two Phase I studies were conducted in Lambaréné, Gabon and Kilifi, Kenya [23], respectively; and two Phase II (II/III) trials were conducted in Liberia [24] and Sierra Leone [25], as well as one Phase III trial in Guinea [26,27]. Three Phase I or Phase I/II trials were conducted in Europe (Geneva, Switzerland [23,28,29] and Hamburg, Germany [23]). Two Phase I [30–32] and one Phase III (lot–lot consistency) trials were conducted in North America (with one site in Canada and multiple sites in the USA [33]).

Approximately, 17,600 adults between 18 and 80 years received 11 doses of the V920 vaccine across Phase I–III trials with diverse objectives to evaluate the safety, tolerability, immunogenicity and efficacy of this vaccine. Also, about 234 children between the 6 and 17 years have received the 20 million pfu dose of this vaccine in two countries in Africa. Table 1 describes the overview and summary results of published clinical trials included in this systematic review.

Safety

Safety of the V920 in adults in Phase I–III trials across various regions

Eleven published studies reported the safety of various doses of this vaccine in adults across Africa, Europe and North America. The minimum follow-up time of participants in these studies was 3 months, and the longest follow-up was 1 year. Assessment of solicited AEs were harmonized across studies. About 12% versus 54% of vaccinees reported mild-to-moderate injection site pain across trials in LMICs and HICs, respectively. However higher proportions (40%) of adults vaccinated with the dose of 2×10^7 pfu reported pain at injection site in LMIC. The others most-frequently reported systemic AE of mild-to-moderate intensity were fever (9%), arthralgia (18%), myalgia (19%), fatigue (30%) and headache (15%) in LMICs compared with fever (16%), arthralgia (16%), myalgia (16%), fatigue (17%) and headache (26%) in HICs. The occurrence of severe AEs was 225/10,319 ($\sim 2\%$) across regions as indicated in Table 2. Generally, unsolicited AE were rare.

A higher proportion of 102/1800 (6%) of vaccinees in HICs reported isolated cases of arthritis compared with about 7/8517 (approximately 8 per 10,000) vaccinees in LMICs. Later, upon data accrual on the V920 vaccine, arthritis was considered a solicited AE, further investigated in other trials. In one trial in the USA, 21 more cases of arthritis were clinically confirmed among vaccinees and resolved without sequelae. In these early-phase trials injection site AEs were dose-dependent regardless of region, but the occurrence of arthritis, arthralgia and other

Table 1. rVSV-Δ G-ZEBOV publications Phase I–III clinical trials objectives, study design and key results.

Study (year)	Trial registration	Included population (mean age [range])	Study recruitment period	Sample size (N)	Dose (pfu/ml)	Main objectives	Study design	Key findings	Ref.
Agnandji (2016)	NCT02283099 NCT02287480 NCT02296983 PACTR201411000919191	Lambaréné, Gabon (29 [20–47]) Kilifi, Kenya (34 [22–52]) Hamburg, Germany (36 [24–51]) Geneva, Switzerland (41 [20–59]) Overall: (36 [20–59])	Lambaréné, Kilifi and Hamburg: 17 November 2014–19 January 2015, and Geneva: 10 November 2014–9 December 2014	Geneva: 59 Kilifi: 40 Lambaréné: 39 Hamburg: 20 Total: 158	300,000, 3 million, 10 million, 20 million and 50 million	Rapid safety and immunogenicity evaluation before deployment of the rVSV-Δ G-ZEBOV-GP vaccine in west Africa	Open-label uncontrolled Phase I trials in Lambaréné, Kilifi and Hamburg evaluating doses (from 300,000 to 20 million pfu). In Geneva, a double-blind, randomized, placebo-controlled Phase I trial of two doses of 10 million and 50 million pfu	V920 vaccine is reactogenic but immunogenic at doses ranging from 300,000–50 million pfu in African and European participants, with higher titers of antibodies recorded at higher doses [23]	
Regules (2017)	NCT02269423, NCT02280408	Baltimore, Washington DC, USA (36 [20–64])	10 October 2014–6 January 2015	Total: 78 adults	3 million, 20 million and 100 million	To evaluate the safety and immunogenicity and to evaluate the boosting effect of this vaccine at day 28 in NIH	Two Phase I placebo controlled, double-blind, dose-escalation trials of the rVSV-Δ G-ZEBOV-GP vaccine	Acceptable safety and immunogenicity profile for upto two doses of the vaccine; robust immune responses and rapid immunity after a single dose, useful in outbreak interventions [31]	
EISherif (2017)	NCT02374385	Halifax, Canada (37 [18–62])	27 November 2014–15 December 2014	Total: 40 adults	100,000, 500,000 and 3 million	Follow-up visits 180 days postvaccination monitoring of safety, immunogenicity, rVSV viremia and any rVSV virus shedding	A Phase I, randomized, dose-ranging, observer-blind, placebo-controlled trial, healthy adults aged 18–65 years	No safety concerns after a single dose of the V920 vaccine. IgG ELISA showed persistent high titres at 180 days. There was a period of reactivity, but in general, the vaccine was well tolerated [30]	
Huttner (2015)	NCT02287480	Geneva, Switzerland: (40 [20–63]) NB: two highest doses for this population initially reported in Agnandji 2015	5 January 2015–26 January 2015	Total: 56 adults received the low dose	300,000	To evaluate safety and immunogenicity low dose vaccinees compared with those receiving high doses before the study hold	Phase I/II, dose-finding, placebo-controlled, double-blind trial Geneva, Switzerland, healthy adults aged 18–65 years	Reducing the dose of rVSV-ZEBOV improved its early tolerability but lowered antibody responses and did not prevent vaccine-induced arthritis, dermatitis or vasculitis [29]	
Halperin (2017)	NCT02503202	Multicentered in Canada, Spain and 40 USA sites† Overall (41 [18–65])	17 August 2015–2 May 2016	Total: 1194 adults	20 million, and 100 million	To evaluate the safety of recombinant vesicular stomatitis virus–Zaire Ebola virus envelope glycoprotein vaccine (rVSV-Δ G-ZEBOV-GP)	A Phase III randomized, double-blind, placebo-controlled study conducted at 40 sites in the USA, one site in Spain, and one site in Canada	The vaccine was well tolerated, with increased rates of injection-site and systemic AEs compared with placebo observed in the lot consistency groups vaccinated with the clinical 20 million pfu dose, as well as the group vaccinated with a higher dose of 100 million pfu. There were no vaccine-related SAEs observed. The study supports the use of the rVSV-Δ G-ZEBOV-GP vaccine in persons at risk for Ebola virus disease [33]	

† Canada (Halifax), Spain (Madrid), USA: (Maryland, Texas, Louisiana, Kentucky, California, Virginia; Utah; Texas; Virginia; South Dakota, New York; Arizona; Ohio; Missouri, Florida; Kentucky; Texas; Rhode Island; North Dakota; Florida; Alabama; California; Illinois; Alabama; South Carolina; Utah, Kansas, North Carolina, Texas; Florida, Texas); California; Texas; Tennessee; Arizona, New York; South Carolina; Missouri; California).

AE: Adverse effect; EVD: Ebola virus disease; PACTR: Pan Africa Clinical Trials Registry; rVSV: Live-replicating vesicular stomatitis virus; SAE: Serious/severe adverse event.

† Canada (Halifax), Spain (Madrid), USA: (Maryland, Texas, Louisiana, Kentucky, California, Virginia, Utah; Texas; Virginia; South Dakota, New York; Arizona; Ohio; Missouri; Florida; Kentucky; Alabama; California; Illinois; Alabama; South Carolina; Utah, Kansas, North Carolina, Texas; Florida; Texas; Tennessee; Arizona, New York; South Carolina; Missouri; California). AE: Adverse effect; EVD: Ebola virus disease; PACTR: Pan Africa Clinical Trials Registry; rVSV: Live-replicating vesicular stomatitis virus; SAE: Serious/severe adverse event.

Table 1. rVSV-ΔG-ZEBOV publications Phase I–III clinical trials objectives, study design and key results (cont.).

Study (year)	Trial registration	Included population (mean age [range])	Study recruitment period	Sample size (N)	Dose (pfu/ml)	Main objectives	Study design	Key findings	Ref.
Agnandji (2017)	PACTR201411000919191	Lambaréné, Gabon Adults (26 [18–50]), Adolescents (15 [13–17] yrs) and Children (9 [6–12])	17 November 2014–7 July 2015	Total: 155 115 adults aged 18–50 and 40 children aged 6–17 years	3000; 30,000; 300,000, 3 million, 20 million	Safety and tolerability 28 days postinjection. Immunogenicity, viremia and shedding postvaccination were evaluated	Phase I randomized, open-label, dose-escalation trial at CERMEL in Lambaréné, Gabon	Acceptable safety and immunogenicity profile of the 20 million pfu dose in adults and supports consideration of lower doses for pediatric populations and those who request boosting	[34]
Juan-Giner A (2018)	PACTR201503001057193	Frontline workers in Conakry, Guinea (33 [18–75])	March 2015 to July 2015	Total: 2115 adults	20 million	Additional information on the immunogenicity and safety of 20 million pfu dose	An open-label Phase IIb/III, nonrandomized, immunogenicity evaluation of one dose of vaccine in front-line workers in Conakry, Guinea. Followed for 3 months with a subset followed-up for 6 months after vaccination	Results only on safety confirms that adverse events 3 days after vaccination with the vaccine are common. The occurrence of fever is of concern in the context of ongoing Ebola transmission	[27]
Samai (2018)	NCT02378753, PACTR201502001037220	Frontline/Health care workers in Sierra Leone ([18–80])	April–August 2015	Total: 7998 adults	20 million	Evaluation of the Ebola vaccine safety (occurrence of SAEs) and robust efficacy in Sierra Leone. Safety substudy in 205 vaccinees compared with 231 unvaccinated participants from a total 7998 participants	A randomized, unblinded Phase II/III trial concurrent evaluation of vaccine safety and efficacy. Healthcare and frontline response workers in five districts were randomized to immediate or deferred (18–24 weeks later), followed for 6 months postvaccination	Among almost 8000 high-risk workers vaccinated during the Sierra Leone Ebola epidemic, vaccine was generally well tolerated with no vaccine-related SAEs. Reported joint pain, rash, skin vesicles, and mouth ulcers postvaccination are consistent with conditions associated with transient viral replication described among participants in other trials	[25]
Heppner (2017)	NCT02314923	USA (37 [18–61])	26 December 2014–8 June 2015	Total 512 adults	3000; 30,000; 300,000; 3 million; 20 million; 9 million; 20 million and 100 million	Safety (incidence of adverse events within 14 days) and immunogenicity (IgG antibody titers at day 28)	A Phase Ib double-blind, placebo-controlled, dose-response at eight study sites in the USA to receive a single injection of the vaccine	V920 vaccine was well tolerated and stimulated a rapid onset of binding and neutralizing antibodies, which were maintained through day 360; the immunogenicity results support selection of the 20 million pfu dose	[32]

† Canada (Halifax), Spain (Madrid), USA: (Maryland, Texas, Louisiana, Kentucky, California, Virginia; Utah; Texas; Virginia; South Dakota, New York; Arizona; Ohio; Missouri, Florida; Kentucky; Texas; Rhode Island; North Dakota; Florida; Alabama; California; Illinois; Alabama; South Carolina; Utah, Kansas, North Carolina, Texas; Florida; Texas); California; Texas; Tennessee; Arizona, New York; South Carolina; Missouri; California).
AE: Adverse effect; EVD: Ebola virus disease; PACTR: Pan Africa Clinical Trials Registry; rVSV: Live-replicating vesicular stomatitis virus; SAE: Serious/severe adverse event.

Table 1. rVSV-Δ G-ZEBOV publications Phase I–III clinical trials objectives, study design and key results (cont.).

Study (year)	Trial registration	Included population (mean age [range])	Study recruitment period	Sample size (N)	Dose (pfu/ml)	Main objectives	Study design	Key findings	Ref.
Kennedy (2017)	NCT02344407	Monrovia, Liberia (adults plus 18 years)	2 February 2015–April 2015	Total 1500 adults	20 million	Powered to compare antibody responses to EBOV and the percentage of grade 3 or 4 adverse events 1 month after injection	A Phase II subtrial was embedded to evaluate safety and immunogenicity in a randomized, placebo-controlled, Phase III trial of the chimpanzee adenovirus 3 (ChAd3-EBO-Z) and V920 vaccines	V920 vaccine extended our knowledge of their safety and immunogenicity. The results point to further research to be conducted in order to be better prepared for future outbreaks of EVD	[24]
Henao-Restrepo (2017)	PACTR201503001057193	Guinea, Sierra-Leone Adults (35 [18–50]) Children ((6–18))	23 March 2015–20 January 2016	5643 adults aged 18–50 years and 194 children aged 6–12 years	20 million	The effect of V920 vaccine in preventing EVD in contacts and contacts of contacts of recently confirmed cases in Guinea, West Africa	An open-label, cluster-randomized ring vaccination trial ('Ebola ça Suffit') in the communities of Conakry and eight surrounding prefectures in the Basse, Guinea region of Guinea, and in Tonkolili and Bombali districts in Sierra Leone to assess the efficacy of a single dose	No cases of EVD occurred 10 days or more among randomly assigned contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases (7 clusters affected) among all eligible individuals in delayed clusters. Vaccine efficacy was 100% (95% CI: 68.9–100.0; $p = 0.0045$), and the calculated intraclass correlation coefficient was 0.035. The results add weight to the interim assessment that rVSV-Δ G-ZEBOV offers substantial protection against EVD	[26]
Huttner (2018)	Geneva: NCT02287480 and NCT02933931; Kilifi: NCT02296983 and the Pan-African Clinical Trials Registry (Lambaréné PACTR201411000919191).	Lambaréné, Gabon: (29 [20–47]) Kilifi, Kenya: (34 [22–52]) Geneva, Switzerland: (41 [20–59]) Overall study population: (36 [20–59])	Lambaréné: 17 November 2014–19 January 2015; Kilifi: 17 November 2014–19 January 2015, and Geneva: 10 November 2016–January 2017	Total: 197 adults. Geneva: 95, Lambaréné: 63, Kilifi: 39	300,000, 3 million, 10 million, 20 million and 50 million	A nested extension of the Phase I and II trials across Africa and Europe to assess antibody persistence at 1 and 2 years in volunteers who received single-dose rVSV-Δ G-ZEBOV-GP in three previous trials	A nested observational cohort study, to prospectively followed-up participants from the African and European Phase I V920 trials to assess ZEBOV-glycoprotein (lgG) antibody persistence	Neutralizing antibodies seem to be less durable, with seropositivity dropping from 64–71% at 28 days to 27–31% at 6 months in participants from the Geneva study. Overall, antibody responses to single-dose V920 vaccination are sustained across doses and settings, a key consideration in settings needing booster vaccinations	[28]

† Canada (Halifax), Spain (Madrid), USA: (Maryland, Texas, Louisiana, Kentucky, California, Virginia; Utah; Texas; Virginia; South Dakota, New York; Arizona; Ohio; Missouri; Florida; Kentucky; Texas; Rhode Island; North Dakota; Florida; Alabama; California; Illinois; Alabama; South Carolina; Utah, Kansas, North Carolina, Texas; Florida; Texas; Tennessee; Arizona, New York; South Carolina; Missouri; California).
 AE: Adverse effect; EVD: Ebola virus disease; PACTR: Pan Africa Clinical Trials Registry; rVSV: Live-replicating vesicular stomatitis virus; SAE: Serious/severe adverse event.

Figure 1. Flow chart of study selection.
PACTR: Pan African Clinical Trials Registry.

forms of joint swellings and tissue infiltration remained higher in European and US vaccinees than in participants from LMICs.

Small changes in hematological and biochemistry parameters occurred within 2 weeks postvaccination; such as thrombocytopenia, leukopenia, lymphopenia, monocytosis, increase in ALT and AST in a small proportion of vaccinees, which resolved without sequelae. In ancillary investigations on Phase I participants, monocytes were identified to play an important role in V920 reactogenicity and adverse events [35,36].

Among 11 studies reporting safety data for different doses of the V920 vaccine, about 288 serious/severe adverse events (SAEs) were reported, with two having been judged by investigators to be related to the 20 million pfu vaccine dose in the large Phase III trial in Guinea a LMIC. Table 3 describes the number of SAE across clinical trials regardless of vaccine dose received in adults above 18 years and children between 6 and 17 years.

Safety of the V920 in children in Phase I–III trials in vaccinees

Like in adult vaccinees, children aged 6–17 years vaccinated in two trials in Africa, frequently reported injection pain (12%) postvaccination. Also, the most frequent systemic adverse events solicited within 14–28 days postvaccination were fever (6%), fatigue (12%), arthralgia (5%), myalgia (6%) and headaches (32%) [34,37]. These AEs were mild or moderate and well tolerated by children as indicated in Supplementary Table 1. No case of arthritis was reported in children.

Table 2. Adverse event reported by adults regardless of dose aggregated across studies by region.

Adverse events	Low-middle income countries [†] N = 8519		High-income countries [‡] N = 1800	
	Mild/moderate	Severe	Mild/moderate	Severe
Local injection site n (%)				
– Pain	1035 (12)	17 (0.1)	981 (54.5)	–
– Swelling	1 (0)	–	8 (0.4)	–
– Redness	3 (0)	–	6 (0.3)	–
– Tenderness/other	693 (8)	–	148 (8)	–
Systemic adverse events n (%)				
– Fever	765 (9)	4 (0)	287 (16)	22 (1)
– Subjective fever	133 (2)	–	137 (8)	10 (0.5)
– Fatigue	2518 (30)	21 (0.2)	298 (17)	11 (0.6)
– Chills	50 (0.5)	1 (0)	222 (12)	18 (1)
– Myalgia	1636 (19)	10 (0.1)	280 (16)	14 (0.7)
– Headaches	1279 (15)	8 (0)	463 (26)	37 (2)
– Sweating	16 (0.2)	–	67 (4)	2 (0)
– Arthralgia	1571 (18)	7 (0)	296 (16)	15 (0.8)
– Joint swelling	–	–	34 (2)	–
– Arthritis	7 (0)	–	102 (6)	8 (0.4)
– Nausea	99 (1)	–	115 (6)	9 (0.5)
– Abdominal pain	106 (1.2)	1 (0)	54 (3)	–
– Diarrhoea	133 (2)	3 (0)	54 (3)	–
– Vomiting	66 (0.7)	3 (0)	32 (2)	4 (0.2)
– Rash	–	–	34 (2)	–

[†]Low-middle income countries mainly in African sites (Gabon, Kenya, Liberia, Sierra Leone and Guinea), where participants received doses 3000 pfu; 30,000 pfu; 300,000; 3 million pfu; and 20 million pfu.
[‡]High-income countries mainly in European and North American (USA and Canada) sites, doses administered ranged from 3000 pfu to 100 million pfu.
N: Number of participants receiving vaccine with safety evaluation reported; n (%): Number of events and proportion in percentages.

Among children vaccinated with the 20 million pfu/ml in Gabon and Guinea, 5/24 participants reported serious adverse events, of which one was judged related to the vaccine [26].

Safety of the V920 in pregnant women & immune-compromised people in Phase I–III trials across various regions

In one Phase II trial in Liberia with HIV positive (immune-compromised) participants being vaccinated with the 20 million pfu/ml doses, no serious AEs were reported 1 month postvaccination. These participants tolerated the vaccine well [24].

No trial has enrolled pregnant and lactating women; however, EVD in pregnancy always yields poorer outcomes and in cases of survival, acute EVD during pregnancy is always associated with fetal loss as a result of spontaneous abortion, elective abortion, still birth or death of the neonate [38–40]. Table 4 highlights the studies reporting pregnancies counts during trial follow-up and outcome of these pregnancies regardless of the V920 dose received. About 60% of pregnancies resolved to live births and the 32% of pregnancies with unfavorable outcomes were judged by investigators to be unrelated to V920 vaccination. Therefore, specific evaluation of the V920 vaccine in this subgroup is relevant as a potentially vulnerable population to EVD during outbreaks.

Viremia & viral shedding

In seven studies that monitored rVSV viremia, shedding in saliva and urine in adults, high viremia was reported in vaccinees on Day 2 postvaccination but diminished by Day 7. Viral shedding in urine and saliva was reported only in about 5/692 adult vaccinees across the seven clinical trials monitoring this outcome [23,29–32,34]. Viremia in adults did not exceed 3000 copies/ml in clinical Phase I trials at different doses. However, one US participant who shed viral RNA in urine and saliva exhibited highest levels of viremia by Day 2 of 23,936 copies per ml postvaccination with the 3000 pfu dose as represented in Supplementary Table 3 [32].

Study (year)	e-track number	Trial registration	Total sample (n)	Doses/ml (pfu)	Follow-up (days)	SAE	SAE related to vaccine	Ref.
Agnandji (2016)	DOI:10.1056/NEJMoa1502924	NCT02283099 NCT02287480 NCT02296983 PACTR201411000919191	158	300,000; 3 million, 10 million, 20 million and 50 million	180	NA	None	[23]
Regules (2017)	DOI:10.1056/NEJMoa1414216	NCT02269423, NCT02280408	78	3 million, 20 million and 100 million	180	NA	None	[31]
ElSherif (2017)	DOI:10.1503/cmaj.170074	NCT02374385	30	500,000	180	2	None	[30]
Huttner (2015)	DOI:10.1016/S1473-3099(15)00154-1	NCT02287480	51	300,000	180	NA	None	[29]
Halperin (2017)	DOI:10.1093/infdis/jix189	NCT02503202	1050	20 million and 100 million	180	23	None	[33]
Agnandji (2017)	DOI:10.1371/journal.pmed.1002402	PACTR201411000919191	115 (adults)	3000; 30,000; 300,000; 3 million; and 20 million	180	11	None	[34]
Juan-Giner (2018)	DOI:10.1016/j.vaccine.2018.09.009	PACTR201503001057193	40 (children)	20 million	180	1	None	[34]
Samai (2018)	DOI:10.1093/infdis/jiy020	NCT02378753, PACTR201502001037220	2016/106 7541	20 million	84/180 180	8 110	None	[27] [25]
Heppner (2017)	DOI:10.1016/S1473-3099(17)30313-4	NCT02314923	418	3000; 30,000; 300,000; 3 million, 20 million, 9 million 20 million and 100 million	360	3	None	[32]
Kennedy (2017)	DOI:10.1056/NEJMoa1614067	NCT02344407	500	20 million	360	51	None	[24]
Henao-Restrepo (2017)	DOI:10.1016/S0140-6736(16)32621-6	PACTR201503001057193	5643 (adults)	20 million	84	76	2	[26]
			194 (children)	20 million	84	4	None	[26]
Total	NA	NA	17,600 (234)	NA	NA	269	2	All
NA: Not applicable; SAE: Serious/severe adverse event.								

Table 4. Number of pregnancies and outcome across published clinical Phase I–III trials.

Study	Phase	Location	Number of pregnancies [†]	Number of live births	Unfavorable pregnancy outcome	Unknown outcome	Ref.
Juan-Giner (2018)	Phase IIb/III	Conakry, Guinea	12	10	2	0	[27]
Halperin (2017)	Phase III	Canada, Spain and USA	5	2	1	2	[33]
Agnandji (2017)	Phase I	Lambaréné, Gabon	3	3	0	0	[34]
Samai (2018)	Phase II/III	Sierra Leone	43	23	17	3	[25]
Total			63	38 (60%)	20 (32%)	5 (8%)	

[†] Pregnancy counts across published studies regardless of V920 dose received.

In the Lambaréné, Gabon Phase I trial which vaccinated both adults 18–50 years with the same dose as used in children, children exhibited higher median viremia than adults at day 2 postvaccination. At day 7, in the pediatric cohort in this setting, 2/40 and 21/40 children shed the viral RNA in urine and saliva, respectively. However, viral shedding in saliva and urine was not correlated with occurrence of oral symptoms. Higher proportion of children and adolescents shed the viral RNA in urine and saliva, mean viremia levels of 1109 (range: 663–1963 copies/ml) and 1592 (1019–2704 copies/ml) by day 2 postvaccination with 20 million pfu dose as shown on Supplementary Table 2. Although these high viremia levels in a younger population were not associated with arthritis and oral lesions, this warrants close monitoring in large effectiveness trials [34]. Further investigations are needed to elucidate the clinical significance of the higher viremia observed in this cohort with reference to reactogenicity and immunogenicity in younger children. Also, the proportion of shedding the viral RNA in saliva was greater when the vaccine was administered to children, this is a unique site finding and thus warrants further investigations.

Immunogenicity

Immune monitoring for responses to V920 vaccine was assessed either by measuring GP-specific antibodies or neutralizing antibodies. Across eight references reporting immunogenicity findings, GP-specific antibodies were quantified using the homologous Zaire-Kikwit strain glycoprotein, following USAMRIID's standard operating procedure (SOP AP-03–35; USAMRIID ELISA) later approved as the Filovirus Animal Non-Clinical Group (FANG) assay [23,24,28–32,34]. Direct whole virion capture ELISA assay was used only in four VEBCON trials to detect ZEBOV-specific antibodies based on inactivated Ebola Zaire Makona virus particles [23,29,34]. One Phase I/II trial also assessed the EBOV-gp-specific antibodies using the commercially available (Alpha Diagnostic, TX, USA; ADI ELISA) ELISA assay [29]. In addition, two types of neutralization assays were used in these trials, eight trials used Pseudovirion Neutralization Assay (PsVNA, USAMRIID) [23,29–32,34], three Phase I trials used the Neutralization Assay (Ebola Virus, Marburg) [23] and one trial used the 60% plaque-reduction neutralization test (PRNT60) [32] to measure neutralizing antibodies induced by various doses of V920 vaccine. Despite assay heterogeneity, higher GMT of gp-specific and neutralizing antibodies were observed at 28 days postvaccination with varying proportions of seroconversion rates with respect to dose received. These antibodies remained significantly higher than prevaccination levels in most participants up to 365 days [28,32] and 720 days in the Geneva vaccinees [28] as indicated in Tables 5 & 6.

In this review, gp-specific antibody responses were reported for 1262/10,319 (12%) by day 28 with seroconversion rates above 80% for doses equal to and above 3 million pfu (intermediate dose – by day 28 97%; 95% CI: 92–100; and 97%; 95% CI: 89–100, respectively, for HICs and LMICs) regardless of region as indicated in Supplementary Table 3. Generally, higher antibody titers were observed for high doses for both LMICs and HICs with point estimates of seroconversion rates above 80%. The selected dose – 20 million pfu currently used in efficacy trials for both adults and children, yielded peak day 28 gp-specific antibody titers like other high doses with pooled GMT 2557.7 (95% CI: 1665.5–3934.2) versus 1156.9 (95% CI: 832.5–1649.2), with seroconversion rates at 96% (95% CI: 87–100) versus 100% (95% CI: 90–100) for HICs and LMICs, respectively as indicated in Table 5 & Supplementary Tables 4 & 5. Only five different doses (3000; 30,000; 300,000; 3 million; and 20 million pfu/ml) of the V920 vaccine were evaluated in two Phase I trials in LMICs [23,28,34]. These doses yielded detectable IgG antibodies, but the highest titres were detected at high doses. European [28,29] and North American [31,32] clinical trials evaluating doses higher than the 20 million dose (50 million and 100 million pfu/ml) showed that there were no significant differences in the GMT of antibodies [41]. More variations between LMICs and HICs

Table 5. ZEBOV-GP specific antibodies measured by ANTI-GP ELISA Assay (USAMRIID).

Study (year)	Population	Dose / pfu	Dose category	Day 0 N[GMT(95%CI)]	Day 14 N[GMT(95%CI)]	Day 28 N[GMT(95% CI)]	Day 180 N[GMT(95% CI)]	Day 365 N[GMT(95% CI)]	Day 720 N[GMT(95% CI)]	Ref.
High income countries/adult										
Heppner (2017)	Eight USA sites	3000	Low	–	61 (70.9–131.8)	64 (629.4–1347.5)	61 (959.5–1354.0)	51 (941.7–1411.1)	–	[32]
Heppner (2017)	Eight USA sites	30,000	Low	–	59 (109.5–207.8)	61 (866.2–1217.1)	58 (709.9–1157.9)	52 (789.4–1157.9)	–	[32]
EISherif (2017)	Halifax, Canada	100,000	Low	10	96.8 (36.9–253.7)	10 (636.2–1565.2)	9 (586.4–2333.2)	–	–	[30]
Heppner (2017)	Eight USA sites	300,000	Low	–	61 (104.5–189.3)	64 (847.1–1511.1)	61 (927.4–1282.6)	56 (975.2–1441.1)	–	[32]
Huttner (2018)	Geneva	300,000	Low	51	30.0 (28.9–31.1)	51 (175.3–407.9)	51 (583.9–1273.5)	49 (618.2–1789.4)	41 (440.8–297.8–652.5)	[28]
EISherif (2017)	Halifax, Canada	500,000	Low	10	27.7 (–)	10 (110.5–340.359.1)	10 (603.5–1273.5)	–	–	[30]
Pooled estimates 95% CI				71	28 (28.9–31.1)	201 (99.8–71.2–228.3)	260 (885.1–468.8–1220.3)	208 (831–559.7–1234.4)	41 (440.8–297.8–652.5)	
EISherif (2017)	Halifax, Canada	3 million	Intermediate	10	27.7 (–)	10 (187.3–126.0–278.4)	10 (1321.3–830.2–2102.9)	–	–	[30]
Heppner (2017)	Eight USA sites	3 million	Intermediate	83	–	82 (249.2–197.1–315.0)	79 (1376.7–1063.7–1781.7)	75 (1201.4–908.0–1589.7)	–	[32]
Agnandji (2016)	Hamburg	3 million	Intermediate	10	25 (–)	–	9 (1392.9–893.7–2170.8)	–	–	[23]
Rejules (2017)	USA	3 million	Intermediate	20	–	20 (283–150–534)	10 (2786–1248–6218)	–	–	[31]
Pooled estimates 95% CI				123	26.3 (–)	112 (240–157.7–375.8)	123 (1347.7–904.7–2022.4)	75 (1201.4–908.0–1589.7)	–	
Heppner (2017)	Eight USA sites	9 million	High	–	–	44 (241.6–160.4–364.1)	41 (786.6–555.6–1113.6)	38 (942.7–644.8–1378.4)	–	[32]
Agnandji (2016)	Geneva	10 million	High	–	–	–	–	–	–	[23]

GP-ELISA following USAMRIID SOP AP-03-35-00 later licensed as the FANG assay-lower limit of detection of antibody titres were ranges from 25 to 50 arbitrary ELISA units/ml. Seroconversion end point titres were at least fourfold higher than prevaccination concentration or titres.
 Bold font indicates pooled data from several samples or a single sample.
 GMT: Geometric mean titer; N: Number of vaccines at the dose level; pfu: Plaque-forming unit.

Table 5. ZEBOV-GP specific antibodies measured by ANTI-GP ELISA Assay (USAMRIID) (cont.).

Study (year)	Population	Dose/ pfu	Dose category	Day 0 N[GMT(95%CI)]	Day 14 N[GMT(95%CI)]	Day 28 N[GMT(95% CI)]	Day 180 N[GMT(95% CI)]	Day 365 N[GMT(95% CI)]	Day 720 N[GMT(95% CI)]	Ref.
Huttner (2018)	Geneva	10 million	High	36 (28.2–37.7)	–	34 (579.7–1163.5)	34 (747.6–1036.9)	32 (1005.7–1450.4)	31 (761.3–1122.8)	[28]
Rejules (2017)	USA	20 million	High	–	20 (502–1465)	20 (2601–6396)	10 (1196–5396)	–	–	[31]
Agnandji (2016)	Hamburg	20 million	High	10 (23–41.1)	–	10 (1249.6–3105.2)	10 (974.3–1612.2)	–	–	[23]
Heppner (2017)	Eight USA sites	20 million	High	–	44 (286.8–632.8)	46 (1146.4–2301.5)	41 (1520.9–1151.3–2009.1)	39 (1387.9–1050.6–1833.6)	–	[32]
Agnandji (2016)	Geneva	50 million	High	–	–	–	–	–	–	[23]
Huttner (2018)	Geneva	50 million	High	16 (31.9–28.4–36.0)	–	14 (1383.0–996.0–1920.4)	15 (865.7–630.6–1188.6)	14 (1037.9–804.2–1339.6)	14 (707.8–546.6–916.4)	[28]
Heppner (2017)	Eight USA sites	100 million	High	–	44 (475.7–344.8–656.2)	45 (1837.9–1366.3–2472.3)	41 (1927–1419.6–2615.8)	44 (1786.5–1345.4–2372.4)	–	[32]
Rejules (2017)	USA	100 million	High	–	20 (888–448–1760)	20 (4079–2740–6070)	10 (2786–1169–6638)	–	–	[31]
Pooled estimates 95% CI				62 31.8 (26.5–38.3)	174 577.7 (348.4–975.6)	234 2089.15 (1417.4–3088.6)	202 1596.7 (954.4–2701.2)	167 1232.1 (908.5–1674.9)	45 734.5 (531.4–1019.6)	
Low–middle income countries/adult										
Agnandji (2017)	Lambaréné, Gabon	3000	Low	20 (24–9–60)	–	19 (81–35–184)	–	–	–	[34]
Agnandji (2017)	Lambaréné, Gabon	30,000	Low	20 (23–9–63)	–	19 (489–264–908)	–	–	–	[34]
Agnandji (2017)	Lambaréné, Gabon	300,000	Low	19 (10–4–22)	–	20 (556–280–1101)	16 (365–187–713)	–	–	[34]
Huttner (2018)	Lambaréné, Gabon	300,000	Low	–	–	–	15 (602.3–357.9–1013.7)	–	–	[28]
Pooled estimates 95% CI				59 19 (7.3–48)	–	59 375 (193–731)	16 365 (187–713)	15 602.3 (357.9–1013.7)	–	

GP-ELISA Following USAMRIID SOP AP-03-35-00 later licensed as the FANG assay-lower limit of detection of antibody titres were ranges from 25 to 50 arbitrary ELISA units/ml. Seroconversion end point titres were at least fourfold higher than prevaccination concentration or titres.

Bold font indicates pooled data from several samples or a single sample.

GMT: Geometric mean titer; N: Number of vaccines at the dose level; pfu: Plaque-forming unit.

Table 5. ZEBOV-GP specific antibodies measured by ANTI-GP ELISA Assay (USAMRIID) (cont.).

Study (year)	Population	Dose /pfu	Dose category	Day 0 N[GMT(95%CI)]	Day 14 N[GMT(95%CI)]	Day 28 N[GMT(95%CI)]	Day 180 N[GMT(95%CI)]	Day 365 N[GMT(95%CI)]	Day 720 N[GMT(95%CI)]	Ref.
Agnandji (2016)	Kilifi	3 million	Intermediate	20 (23–47.3)	–	20 (995.5–2238.6)	20 (1,392.6–2003.4)	–	–	[23]
Agnandji (2017)	Lambaréné, Gabon	3 million	Intermediate	39 (9–27)	–	39 (899–1724)	37 (546–858)	–	–	[34]
Huttner (2018)	Kilifi	3 million	Intermediate	–	–	–	–	20 (667.9–484.7–920.2)	–	[28]
Huttner (2018)	Lambaréné, Gabon	3 million	Intermediate	–	–	–	–	36 (616.1–441.3–860.1)	–	[28]
Pooled estimates 95% CI				59 (24.5–16–37.2)	–	59 (1,369–947.3–1981.3)	57 (1,038.8–757.2–1430.7)	56 (642–463–890)	–	
Agnandji (2016)	Kilifi	20 million	High	–	–	–	–	–	–	[23]
Agnandji (2017)	Lambaréné, Gabon	20 million	High	–	–	–	–	–	–	[34]
Huttner (2018)	Lambaréné, Gabon	20 million	High	16 (69.1–39.7–120.2)	–	16 (1503.0–943.6–2394.0)	15 (1514.4–972.1–2359.3)	12 (1433.3–571.8–3592.7)	–	[28]
Huttner (2018)	Kilifi	20 million	High	20 (29.4–29.4)	–	20 (944.6–625.8–1425.7)	20 (877.9–625.7–1231.9)	19 (1083.1–766.8–1529.8)	–	[28]
Kennedy (2017)	Monrovia, Liberia	20 million	High	–	–	491 (928–1128)	485 (746–881)	828 (762–899)	–	[24]
Pooled estimates 95% CI				36 (49.3–34.6–74.8)	–	527 (1156.9–832.5–1649.2)	520 (1067.8–781.3–1490.7)	517 (1114.8–700–2007.2)	–	
Adolescents (13–17 years)										
Agnandji (2017)	Lambaréné, Gabon	20 million	High	15 (5–12)	–	15 (1024–1989)	17 (1317–4906)	–	–	[34]
Children (6–12 years)										
Agnandji (2017)	Lambaréné, Gabon	20 million	High	20 (7–35)	–	20 (806–3259)	20 (2069–1005–4258)	–	–	[34]

GP-ELISA following USAMRIID SOP AP-03-35-00 later licensed as the FANG assay-lower limit of detection of antibody titres were ranges from 25 to 50 arbitrary ELISA units/ml. Seroconversion end point titres were at least fourfold higher than prevaccination concentration or titres.
 Bold font indicates pooled data from several samples or a single sample.
 GMT: Geometric mean titer; N: Number of vaccines at the dose level; pfu: Plaque-forming unit.

Table 6. Neutralizing antibodies measured by functional pseudovirion neutralization assay.

Study (year)	Population	Dose	Dose category	Day 0	Day 14	Day 28	Day 180	Day 365	Ref.	
High income countries										
Heppner (2017)	Eight USA sites	3000	Low	–	63 (10.8–15.3)	63 (72.4–146.3)	63 (111.1–227.7)	53 (143.8–221.4)	[32]	
Heppner (2017)	Eight USA sites	30,000	Low	–	59 (13.3–19.8)	61 (63.9–133.6)	58 (89.9–198.0)	52 (136.0–213.0)	[32]	
EISherif (2017)	Halifax, Canada	100,000	Low	–	–	10 (28.2–177.8)	–	–	[30]	
Huttner (2015)	Geneva, Switzerland	300,000	Low	51 10 (–)	–	35.4 (24.7–50.7)	–	–	[29]	
Heppner (2017)	Eight USA sites	300,000	Low	–	63 (21.5–40.9)	64 (112.0–209.0)	61 (125.4–250.5)	56 (159.0–239.9)	[32]	
EISherif (2017)	Halifax, Canada	500,000	Low	–	–	10 (25.12–141.25)	–	–	[30]	
Pooled estimates										
95% CI				51	10 (–)	185 19.6 (15.2–25.3)	208 85.1 (54.4–143.1)	182 156.6 (108.8–225.4)	161 146.3 (95.3–224.7)	
Agnandji (2016)	Hamburg, Germany	3 million	Intermediate	10	10 (–)	–	10 (62.9–147.3)	9 16.5 (8.3–32.8)	–	[23]
Heppner (2017)	Eight USA sites	3 million	Intermediate	–	83 (28.7–45.2)	83 (147.5–227.9)	80 (185.8–314.3)	76 229.2 (175.1–300.1)	[32]	
EISherif (2017)	Halifax, Canada	3 million	Intermediate	–	–	10 (35.48–177.82)	–	–	[30]	
Rejules (2017)	USA	3 million	Intermediate	20	39 (24–62)	20 (145–342)	10 (74–256)	–	[31]	
Pooled estimates										
95% CI				10	10 (–)	103 37.5 (26.4–53.6)	123 145.5 (97.7–223.8)	90 132 (89.3–201)	76 229.2 (175.1–300.1)	
Heppner (2017)	Eight USA sites	9 million	High	–	45 (33.0–59.4)	45 (120.8–227.1)	42 (147.5–250.4)	42 152.9 (102.6–227.8)	[32]	
Agnandji (2016)	Geneva, Switzerland	10 million	High	43 10 (–)	–	34 (61.9–158.8)	33 (12.8–26.4)	–	[23]	
Agnandji (2016)	Hamburg, Germany	20 million	High	10 10 (–)	–	10 (120.6–233.1)	10 (11.0–31.4)	–	[23]	
Heppner (2017)	Eight USA sites	20 million	High	–	45 (58.0–122.0)	46 (175.9–355.1)	42 (243.2–464.1)	42 335.9 (243.2–464.1)	[32]	
Rejules (2017)	USA	20 million	High	10 (20–107)	47 (20–107)	20 (236–825)	10 (106–275)	–	[31]	
Pseudovirion Neutralization Assay (PsyNA, USAMRIID)-Ebola GP used in pseudo-typing was provided by a plasmid expressing the EBOV Zaire 95 Kikwit GP, pWRG7/077 EBOVco and one study used plaque neutralization reduction test (PRNT60) measured neutralizing antibody response against ZEBOV-GP. Cut-off was <20 is considered 10 for statistical analyses. Sero-conversion is defined as at least fourfold (i.e., 4×) increase in titer compared with prevaccination titer.										
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Pseudovirion Neutralization Assay (PsyNA, USAMRIID)-Ebola GP used in pseudo-typing was provided by a plasmid expressing the EBOV Zaire 95 Kikwit GP pWRG7077 EBOVco and one study used plaque neutralization reduction test (PRNT60) measured neutralizing antibody response against ZEBOV-GP. Cut-off was <20 is considered 10 for statistical analyses. Sero-conversion is defined as at least fourfold (i.e., 4x) increase in titer compared with prevaccination titer.

Bold font indicates pooled estimate.

Table 6. Neutralizing antibodies measured by functional pseudovirion neutralization assay (cont.).

Study (year)	Population	Dose	Dose category	Day 0	Day 14	Day 28	Day 180	Day 365	Ref.			
Agnandji (2016)	Geneva, Switzerland	50 million	High	13	10 (–)	13	272.7 (156.6–475.0)	15	17.9 (10.6–30.1)	[23]		
Rejules (2017)	USA	100 million	High	–	–	20	461 (312–681)	10	219 (98–486)	[31]		
Heppner (2017)	USA sites	100 million	High	–	–	44	356.2 (269.6–470.6)	41	437.9 (339.5–564.8)	44	453.1 (353.6–580.7)	[32]
Pooled estimates 95% CI				66	10 (–)	164	276.7 (181.7–428.2)	203	176.2 (121.1–266)	128	314 (233–424.2)	
Low—middle income countries												
Agnandji (2017)	Lambaréné, Gabon	3000	Low	19	19 (–)	–	24 (19–32)	–	–	–	–	[34]
Agnandji (2017)	Lambaréné, Gabon	30,000	Low	19	19 (–)	–	70 (36–135)	–	–	–	–	[34]
Agnandji (2017)	Lambaréné, Gabon	300,000	Low	19	19 (–)	–	66 (34–128)	16	21 (17–27)	–	–	
Pooled estimates 95% CI				57	19 (–)	58	53 (29.7–98.3)	16	21 (17–27)			
Agnandji (2016)	Kilifi, Kenya	3 million	Intermediate	20	10 (–)	–	67.3 (38.9–116.7)	20	18.0 (12.1–26.7)			[23]
Agnandji (2017)	Lambaréné, Gabon	3 million	Intermediate	39	19 (–)	–	81 (56–119)	37	20 (19–22)	–	–	[34]
Pooled estimates 95% CI				59	14.5 (–)	59	74.2 (47.5–117.9)	57	19 (15.6–24.4)			
Agnandji (2017)	Lambaréné, Gabon	20 million	High	16	19 (–)	–	126 (56–285)	15	26 (21–34)	–	–	[34]
Adolescents 13–17 years												
Agnandji (2017)	Lambaréné, Gabon	20 million	High	15	19 (–)	–	76.5 (36.9–158.5)	–	–	–	–	[34]
Children 6–12 years												
Agnandji (2017)	Lambaréné, Gabon	20 million	High	20	19 (–)	–	118.2 (56.2–248.6)	–	–	–	–	[34]
Pseudovirion Neutralization Assay (PsyNA, USAMRIID)-Ebola GP used in pseudo-typing was provided by a plasmid expressing the EBOV Zaire 95 Kikwit GP, pWRG7/077 EBOVco and one study used plaque neutralization reduction test (PRNT60) measured neutralizing antibody response against ZEBOV-GP. Cut-off was <20 is considered 10 for statistical analyses. Sero-conversion is defined as at least fourfold (i.e., 4×) increase in titer compared with prevaccination titer.												
Bold font indicates pooled estimate.												

Pseudovirion Neutralization Assay (pSVNA, USAMRIID)-Ebola GP used in pseudo-typing was provided by a plasmid expressing the EBOV Zaire 95 Kikwit GP, pWRG7077 EBOVco and one study used plaque neutralization reduction test (PRNT60) measured neutralizing antibody response against ZEBOV-GP. Cut-off was <20 is considered 10 for statistical analyses. Sero-conversion is defined as at least fourfold (i.e., 4×) increase in titer compared with prevaccination titer.

Bold font indicates pooled estimate.

were noted for gp-specific antibodies GMT and seroconversion rates for low doses given in these regions. Higher titres of gp-specific antibodies were reported in the HICs vaccinees receiving doses equal to or less than 500,000 pfu as shown in Table 2. By day 365, there was an overall decline in gp-specific antibodies GMTs coupled with lower seroconversion rates across doses although higher than baseline values whereas there was no clear pattern for neutralizing antibodies-GMT seem to decrease or increase at this time point compared with their day 28 titres as indicated in Tables 5 & 6 & Supplementary Table 2.

Immunogenicity in children & special populations

One Phase I and one Phase III trial assessed the immunogenicity and efficacy, respectively, of the 20 million pfu/ml dose of the V920 vaccine in African children [26,34]. Like in adults who received this dose across trials worldwide, healthy children (6–12 years) and adolescents (13–17 years) in the Lambaréné extended Phase I trial elicited ZEBOV-GP specific antibodies and neutralizing antibodies as early as on day 28 postvaccination. Peak ZEBOV-GP GMT of 2069 (95% CI: 1005–4258) and 2541 (95% CI: 1317–4906) were reported 180 days postvaccination, respectively. Also, this cohort of vaccinees reported higher day 28 neutralizing antibody titres assessed by ZEBOV pseudovirus neutralization-50 ELISA assay, with approximately 60% seroconversion rates [34]. By the time of writing this review, this is the only trial, which reported immunogenicity in 40 vaccinees between the age of 6 and 17 years and findings from this study was pivotal to the enrolment of a similar cohort of children in the efficacy trial in Guinea [26]. However, the Guinea efficacy trial did not compare immunogenicity in this subgroup. Thus, further studies in this cohort and lower age groups shall be pivotal for establishment of the risk–benefit profile of this vaccine in a representative population vulnerable to EVD in outbreaks.

The V920 vaccine was immunogenic when administered to females who later became pregnant [25,27,33,34], or to HIV-positive individuals [24]. Lower proportions of HIV positive participants seroconverted 1 month postvaccination compared with negative participants in the same setting [24]. However, further studies enrolling pregnant women and HIV positive individuals are ongoing in Democratic Republic of Congo and Uganda to generate more safety and immunogenicity data in these subgroups (NCT03161366 and NCT03031912).

Duration of immunogenicity

Three Phase I and one Phase I/II trials reported the persistence of ZEBOV-GP specific and neutralizing antibodies up to 365 days postvaccination amidst lower sero-conversion rates, when assessed using the FANG ZEBOV-GP ELISA and the PsNVA or PRNT neutralization, respectively [28,32]. Two Phase I and one Phase I/II trials extended the follow-up of vaccinees to a duration of 5 years. In the first publication of these studies, ZEBOV-GP-specific antibodies persisted up to 720 days postvaccination in the Geneva participants [28]. Thus far, this is the most comprehensive assessment of the duration of the immune responses induced by the V920 in humans [42]. The ZEBOV-GP specific antibody persisted up to 2 years and the magnitude of the antibodies is not dose-dependent. The clinical relevance of the persistence of postvaccination antibodies remains an area of research, as the V920 vaccine correlates or surrogates of protection are still under investigation. Studies evaluating the durability of the antibody responses in special population such as children, pregnant women and people with impaired immune response status are warranted.

Clinical efficacy

A Phase III open label, cluster randomized ring vaccination (clusters of contacts of confirmed case and contacts of the contacts were vaccinated) trial evaluated the clinical efficacy of the 20 million pfu dose against EVD in Guinea. A clinical efficacy of 100% (95% CI: 68.9–100.0; $p = 0.0045$), implying that the V920 vaccine was able to prevent EVD within 10 days in adults who received immediate vaccination (4123 adults) compared with those (3528 adults) whose vaccination was delayed for 21 days [26].

The favorable efficacy observed in Guinea is being confirmed; preliminary results on the efficacy of V920 following of 93,965 people from 679 rings at risk and 28,888 health care workers/front line workers considered at high risk were vaccinated as part of the effort to control the ongoing Ebola outbreak in the Democratic Republic of the Congo showed a vaccine efficacy of 97.5%, 95% CI (95.8–98.5%).

Together the two trials: PACTR201503001057193 and NCT03161366 demonstrated that ring vaccination is an effective public health strategy to control Ebola outbreaks. The interval time of about 2 weeks needed for transmission of Ebola virus between humans facilitates the identification and capture of contacts and contacts of contacts for vaccination.

Author's risk–benefit discussion

SAEs both local and systemic were less than 2% for all doses administered across diverse epidemiological settings and ages ranging from 6 years and above. This is favorable compared with devastating health outcomes inflicted when people are infected with Ebola virus and is consistent with WHO classification of the frequency of occurrence of rare severe vaccine reactions [43]. The cases of arthritis, dermatitis and vasculitis that occurred mainly in participants aged 40 years and above from HICs, were self-limiting, transient and with no sequelae and thus should not prevent vaccination in western individuals above 40 years of age, including health professionals and possibly selected types of travellers with a nonchangeable itinerary to a high-risk/outbreak area.

In children, the administration of the V920 vaccine was associated with a high level of rVSV' RNA in plasma, as well as persistence of the viraemia (viremia) beyond day 7 after vaccination. This was coupled with high proportion of children and adolescents shedding the vaccine in saliva and urine. Persistence of the rVSV' RNA in plasma of children and vaccine shedding in their saliva were not associated with clinical symptoms suggestive of inflammation.

Children aged 6–18 years who had been vaccinated in Phase I trial as well as in the ring trial in Guinea showed comparable safety profiles to those of adults. In Phase I–II trials, V920 did not induce SAEs of special interest in immunocompromised vaccinees [24], and no related adverse outcomes were observed in pregnant women [25,27,33,34].

Although safety and immunogenicity data are still being gathered from children and HIV-infected individuals, and still need to be accrued in pregnant and lactating women, the V920 vaccine has so far shown a favorable risk–benefit balance in these special populations compared with the devastating effect of EVD.

Higher GMT for both gp-specific and neutralizing antibodies was observed at higher vaccine doses with seroconversion rates above 80%. Based on the immunogenicity profile, the vaccine dose of 20 million pfu remains acceptable as the primary vaccine dose. When V920 vaccine was administered to people with natural anti-gp antibodies against EV prior to vaccination [23,24,28,34] or when a second dose was given at day 28, a boosting effect was observed [31].

Recently, a WHO Expert Meeting recommended the 20 million pfu dose for people at higher risk of Ebola including contacts, contacts of contacts, health care workers and frontline workers. People at lower risk and the broader population may receive up to a fifth of the reduced dose. Further research into dose optimization was encouraged [44]. Since then, each of the 11 different doses tested in clinical trials showed to be immunogenic and to induce seroconversion at least in a proportion of vaccinees. For the time being, a wide range of doses might turn out to offer optimal protection in different epidemiological settings.

Research, assessing potential correlates or surrogates of V920 vaccine protection that will provide insights into the direct interpretation of vaccine-induced immune responses and assessment of the long-term effect of this vaccine beyond outbreaks [36,45], is ongoing.

Our study has limitations, as potential pitfalls arise from attempting to pool results from different studies that utilize different adverse event reporting systems, different PCR methods to detect viremia and shedding, as well as different immunological assays.

Postmarketing & regulatory affairs

The European Medicine Agency has positively evaluated the V920 vaccine, which has been immediately followed by WHO prequalification for its use in adults. Now, as the vaccine has entered the list of WHO prequalified vaccines, national regulatory authorities in at-risk countries will have to deliberate and review the vaccine uptake in their respective countries. Several stakeholders in Europe and America and at WHO are working in collaboration with regulatory agencies in Africa to move forward with the licensure at national or regional levels.

Conclusion

We have reviewed safety, immunogenicity and efficacy data from V920 clinical trials conducted in Africa, Europe and North America. We found acceptable safety and tolerability as well as satisfactory vaccine-induced immunogenicity which lasts at least 1 year across trials and regions. In the course of the present work, the V920 vaccine has received a positive evaluation by EMA and prequalified by WHO. Our findings suggest that the V920 vaccine in children, pregnant women and immune-compromised individuals also show an acceptable risk–benefit balance including good safety and immunogenicity. However, additional safety and immunogenicity data in the above populations are being gathered and will be essential to inform decision-making.

Future perspective

The first-ever clinical trial with the V920 vaccine started concomitantly in Geneva, Switzerland; Lambaréné, Gabon; Kilifi, Kenya and Hamburg, Germany in November 2014. Five years later, on 11 November 2019, the V920 vaccine was licensed for and marketable as Ervebo® in the European Union. The vaccine has been also been prequalified by WHO; paving the way for its licensure in Sub-Saharan African countries where EVD outbreaks occur, and for financial support of major funding agencies like GAVI and BMGF for access to the vaccines in case of outbreaks.

The V920 is so far licensed to be used in adults aged 18 years and older. Several ongoing studies to address the ‘unfinished business’ with regard to the V920 and other Ebola vaccines are ongoing. The Innovative Medicine Initiative (IMI); the world’s biggest public–private partnership that includes the European Union Commission and pharmaceutical companies has funded the main studies on V920 vaccine as well as other Ebola vaccine candidates.

The project ‘Systems analysis of adult and pediatric responses to VSV-ZEBOV vaccine’ funded by IMI is identifying immune and molecular signatures of adult and pediatric immune responses induced by the rVSV-ΔG-ZEBOV-GP vaccine. This project will provide information on which markers correlate best with safety, immunogenicity as well as with long-lasting immune responses in adults and children. Because the project involves also samples from efficacy testing in nonhuman-primates, signatures found in humans will be assessed as correlates of protection using the animal rule approach.

IMI has concomitantly funded several clinical trials in adults and children with the goal to evaluate in European and African volunteers the heterologous prime-boost approach. Practically, the volunteers receive a first vaccine to prime the immune response and a different vaccine to boost the immune system. A large Phase II trial enrolling around 1500 children aged 1–17 across three African countries (Guinea, Sierra Leone and RDC) is testing the following vaccine strategies: Ad26.ZEBOV (rHAd26) vaccine + MVA-BN-Filo (MVA) boost; rVSV-ΔG-ZEBOV-GP vaccine + rVSV-ΔG-ZEBOV-GP boost, and rVSV-ΔG-ZEBOV-GP vaccine + placebo boost.

The consortia leading the systems analysis project and the clinical trials are liaised and share data with the purpose to accelerate the safety and immunogenicity data collection in pediatric populations for the V920 but also the Ad26.ZEBOV (rHAd26) vaccine + MVA-BN-Filo (MVA) vaccines as well as the identification of key markers of safety, immunogenicity and ideally also correlates of protection of Ebola vaccines. We hypothesize that the findings from these studies will lead to the licensure of the V920 in children within the next 5 years; and that of the Ad26.ZEBOV (rHAd26) and MVA-BN-Filo (MVA) vaccines in adults and children within a time period which will most likely not exceed 10 years.

A trial is ongoing in Burkina Faso, Canada and Senegal to assess the safety and immunogenicity of the V920 vaccine in HIV infected people. The anticipated end date of the trial is 31 December 2019. If the results of this trial are similar to the findings gathered through the trials we reviewed, the V920 vaccine may be also licensed for HIV infected people in the next 5–10 years.

The licensure of the first ever Ebola vaccine within 5 years is a major game changer not only for the field of emerging and re-emerging diseases but, in our view, in general for the field of vaccine development against neglected tropical diseases. The availability of Ervebo® on the market is the success of international commitment, multilateral initiatives, accelerated reviews from Ethical boards and Regulatory authorities while maintaining the standard of good clinical practices and a very unprecedented bridging of research and public health agendas. Ring vaccination of individuals at risk and following-up on them has in parallel been used as a frame to assess the efficacy/effectiveness of vaccine.

We understand that the experience from the Ebola vaccine field will be essential in revisiting and reshaping current paradigms with the goal to accelerate vaccine development against several tropical viral and nonviral diseases.

Executive summary

The rVSV-ΔG-ZEBOV-GP vaccine candidate

- A live attenuated rVSV-ΔG-ZEBOV-GP is a replication-competent recombinant Indiana strain vesicular stomatitis virus-based vaccine encoding the gene for the Zaire ebolavirus (ZEBOV-GP) Kikwit 1995 strain.
- A highly attenuated nonpathogenic vaccine.
- Vesicular stomatitis virus, a negative sense RNA virus of the Rhabdoviridae family is suitable as a ZEBOV vaccine vectors due to its robust growth in approved and continuous mammalian cell lines, its apparent lack of pathogenic potential in man and its potential to induce strong cellular and humoral immune responses.

Safety of the V920 in adults in Phase I–III trials across various regions

- Local adverse events (AEs) were mostly of a mild to moderate severity which resolved without sequelae.
- Higher proportion of participants in high-income countries (HICs) reported mild to moderate injection site pain compared with vaccinees in low–middle-income countries (LMICs).
- Most frequently reported systemic AEs were fever, arthralgia, myalgia, fatigue and headache of mild to moderate intensity in both LMICs and HICs.
- So far in adults as few as two of 288 serious adverse events (SAEs) reported were judged by investigators to be directly related to the 20 million pfu in the Guinea Phase III trial.
- Higher proportion of vaccinees in HICs reported isolated cases of arthritis compared with vaccinees in LMICs.

Safety of the V920 in children in Phase I–III trials in vaccinees

- Children/adolescents aged 6–17 years vaccinated in two trials in Africa with 20 million pfu dose.
- Most frequently reported local AEs were injection pain and swelling postvaccination.
- No arthritis was reported in children/adolescents, most frequent systemic AEs solicited within 14–28 days postvaccination were fever, fatigue, arthralgia and myalgia relatively of mild to moderate.
- Only one SAE in children was judged related to the vaccine by the investigator in the Guinea trial.

Safety of the V920 in pregnant women & immune-compromised people in Phase I–III trials across various regions

- Among these trials few actively recruited pregnant/lactating women or people living with HIV/AIDS.
- Participants who received V920 vaccine and were later tested positive for HIV tolerated the vaccine very well.
- About 60% of pregnancies during the V920 trials resolved to live births and 32% of pregnancies with unfavorable outcomes were judged by investigators to be unrelated to V920 vaccination.
- The direct effect of the vaccine given to women at different stages of gestation and outcome of the foetus and neonates needs to be investigated.

Viremia & viral shedding

- Viremia in adults did not exceed 3000 copies/ml in clinical Phase I trials at different doses.
- Very few adults shedding the viral RNA in saliva and urine.
- In Gabon a LMIC, children exhibited higher median viremia values than adults vaccinated with same 20 million pfu dose at day 2 postinjection.
- Higher proportion of children and adolescents also observed viral RNA shedding in urine and saliva.
- Higher viremia, shedding in urine and saliva in children/adolescents was not correlated with occurrence of oral symptoms, and other inflammatory skin and joint conditions.

Immunogenicity

- All administered doses were immunogenic across the different epidemiological settings.
- Despite assay heterogeneity, higher geometric mean titres (GMT) of gp-specific and neutralizing antibodies were observed at 28 days postvaccination with varying proportions of sero-conversion rates.
- Although only five doses of the vaccine were evaluated in LMICs, higher GMTs and sero-conversion rates were observed at high doses.
- At high doses there were no significant differences between antibody responses between LMIC and HICs.
- For low doses, vaccines in HICs reported higher GMTs and sero-conversion rates.

Immunogenicity in children & special populations

- Thus far, immunogenicity in children/adolescents is reported only for the 20 million pfu/ml dose of the V920 vaccine in Lambaréné, Gabon, a LMIC.
- Like in adults, these children elicited ZEBOV-GP-specific antibodies and neutralizing antibodies as early as on day 28 postvaccination.
- Further studies in children/adolescents and lower age groups will be pivotal for establishment of the risk–benefit profile of this vaccine.
- V920 vaccine was immunogenic at different doses when administered to females who later became pregnant or to people who were later diagnosed to be HIV positive.
- More studies enrolling pregnant women and HIV positive individuals on-going in Congo and Uganda will generate more safety and immunogenicity data in these subgroups.

Durability of immunogenicity

- ZEBOV-GP-specific and neutralizing antibodies persisted up to 365 days postvaccination but lower seroconversion rates compared with day 28.
- The longest duration of the persistence of ZEBOV-GP-specific antibodies is reported up to 720 days postvaccination in vaccinees in Geneva, an HIC, the clinical significance of this persistence and potential waning effect is under investigation.
- So far no immune correlates or surrogates of V920 vaccine protection.

Clinical efficacy

- The V920 vaccine prevented Ebola virus disease in clusters of contacts of confirmed case and contacts of the contacts (ring vaccination) when vaccinated within 10 days.
- Two Phase III trials in context of outbreaks have demonstrated high vaccine protection using the ring vaccination approach.

- Ring vaccination is an effective public health strategy to control Ebola outbreaks using the V920 vaccine.

Risk–benefit discussion

- The established favorable safety profile of the V920 vaccine observed in preclinical stages of development is widely confirmed in clinical trials.
- More than 250,000 people have received one of the 11 doses of the V920.
- The V920 vaccine is currently applied to control the at this time (December 2019) ongoing Ebola outbreak in the Democratic Republic of Congo in Central Africa.
- The V920 vaccine has been licensed and prequalified.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fmb-2019-0237

Financial & competing interests disclosure

This work has been partly supported by the European developing countries clinical trial partnership (EDCTP) and the innovative médecine initiative (IMI) with the two respective grants EDCTP-CSA-Ebola363 and number 116068 VSV-Eboplus. The two funders had no decision the content of the work. The authors have no other 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 apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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