Case fatality risk among individuals vaccinated with rVSVΔG-ZEBOV-GP: a retrospective cohort analysis of patients with confirmed Ebola virus disease in the Democratic Republic of the Congo

Rebecca M Coulborn, Mathieu Bastard, Nicolas Peyraud, Etienne Gignoux, Francisco Luquero, Bérengère Guai, Stephane Hans Bateyi Mustafa, Elisabeth Mukamba Musenga, Steve Ahuka-Mundeke

Summary

Background The rVSVΔG-ZEBOV-GP vaccine constitutes a valuable tool to control Ebola virus disease outbreaks. This retrospective cohort study aimed to assess the protective effect of the vaccine against death among patients with confirmed Ebola virus disease.

Methods In this retrospective cohort analysis of patients with confirmed Ebola virus disease admitted to Ebola health facilities in the Democratic Republic of the Congo between July 27, 2018, and April 27, 2020, we performed univariate and multivariate analyses to assess case fatality risk and cycle threshold for nucleoprotein according to vaccination status, Ebola virus disease-specific treatments (eg, mAb114 and REGN-EB3), and other risk factors.

Findings We analysed all 2279 patients with confirmed Ebola virus disease. Of these 2279 patients, 1300 (57%) were female and 979 (43%) were male. Vaccination significantly lowered case fatality risk (vaccinated: 25% [106/423] *vs* not vaccinated: 56% [570/1015]; p<0·0001). In adjusted analyses, vaccination significantly lowered the risk of death compared with no vaccination, with protection increasing as time elapsed from vaccination to symptom onset (vaccinated ≤2 days before onset: 27% [27/99], adjusted relative risk 0·56 [95% CI 0·36–0·82, p=0·0046]; 3–9 days before onset: 20% [28/139], 0·44 [0·29–0·65, p=0·0001]; ≥10 days before onset: 18% [12/68], 0·40 [0·21–0·69; p=0·0022]; vaccination date unknown: 33% [39/117], 0·69 [0·48–0·96; p=0·0341]; and vaccination status unknown: 52% [441/841], 0·80 [0·70–0·91, p=0·0011]). Longer time from symptom onset to admission significantly increased risk of death (49% [1117/2279], 1·03 [1·02–1·05; p<0·0001]). Cycle threshold values for nucleoprotein were significantly higher—indicating lower viraemia—among patients who were vaccinated compared with those who were not vaccinated; the highest difference was observed among those vaccinated 21 days or longer before symptom onset (median 30·0 cycles [IQR 24·6–33·7]) compared with patients who were not vaccinated (21·4 cycles [18·4–25·9], p<0·0001).

Interpretation To our knowledge, this is the first observational study describing the protective effect of rVSVΔG-ZEBOV-GP vaccination against death among patients with confirmed Ebola virus disease admitted to an Ebola health facility. Vaccination was protective against death for all patients, even when adjusted for Ebola virus disease-specific treatment, age group, and time from symptom onset to admission.

Funding Médecins Sans Frontières.

Lancet Infect Dis 2024

Published **Online** February 7, 2024 https://doi.org/10.1016/S1473-3099(23)00819-8

See **Online/Comment** https://doi.org/10.1016/S1473-3099(24)00066-5

For the French translation of the abstract see **Online** for appendix 1

Department of Epidemiology, Intervention, and Training, Epicentre, Paris, France (M Bastard MSc, R M Coulborn MPH, E Gignoux MPH, F Luquero PhD); **Medical Department, Médecins Sans Frontières, Geneva, Switzerland** (N Peyraud PhD); **Department of Medical Biology, Cliniques Universitaires de Kinshasa, University of Kinshasa, Kinshasa, Democratic Republic of the Congo** (Prof S Ahuka-Mundeke PhD); **Department of Virology, Institut National de la Recherche Biomedicale, Kinshasa, Democratic Republic of the Congo** (Prof S Ahuka-Mundeke); **Department of Emergencies, Médecins Sans Frontières, Paris, France** (B Guai RN); **Ministry of Public Health, Hygiene, and Prevention, Expanded Programme on Immunization, Kinshasa, Democratic Republic of the Congo** (E Mukamba Musenga PhD); **Ministry of Public Health, Hygiene, and Prevention, Expanded Programme on Immunization, Goma, Democratic Republic of the Congo** (Prof S H Bateyi Mustafa PhD); **Department of Public Health, Faculty of Medicine, University of Goma, North Kivu, Democratic Republic of the Congo** (Prof S H Bateyi Mustafa);

Introduction

The species *Zaire ebolavirus* causes Ebola virus disease, which is associated with a high case fatality risk in individuals who are infected.[1] Initially confined to remote, isolated settings, Ebola virus disease epidemics have occurred in more densely populated regions since 2014, including urban areas characterised by humanitarian crises related to chronic insecurity, armed conflict, political instability, and high population mobility.[2] Despite—and perhaps even because of—these obstacles, innovative approaches have fostered substantial scientific advances in clinical knowledge of the disease, and its prevention, treatment, and models of care. These advances include new therapeutics and vaccines.[2] The new vaccine rVSVΔG-ZEBOV-GP (Ervebo, Merck & Co, Rahway, NJ, USA), administered as a single dose by the intramuscular route, has been shown to be safe and effective against Ebola virus disease and was prequalified by WHO in November, 2019.[3,4] This vaccine constitutes an additional tool with which to control Ebola virus outbreaks.[3] rVSVΔG-ZEBOV-GP contains the recombinant vesicular stomatitis virus (strain Indiana) with a deletion of the envelope glycoprotein, replaced with the Ebola virus (strain Kikwit 1995) surface glycoprotein.[4] This weakened replication-competent vesicular stomatitis virus—containing ≥72 million plaque-forming

Department of Epidemiology, Faculty of Health and Community Development, Université de Pays de Grand Lacs, Goma, Democratic Republic of the Congo (Prof S H Bateyi Mustafa)

Correspondence to: Ms Rebecca M Coulborn, Department of Epidemiology, Intervention, and Training, Epicentre, 75019 Paris, France rebecca.coulborn@epicentre.msf.org

Research in context

Evidence before this study

The Ebola vaccine rVSVΔG-ZEBOV-GP is the only Ebola vaccine recommended, in combination with other tools, by the Strategic Advisory Group of Experts on Immunization for use during an Ebola outbreak. We searched PubMed for published randomised controlled trials between database inception and Oct 20, 2023 using the terms (filovirus) OR (Ebola) AND (vaccin*) with no language restrictions.

A single phase 3 trial (n=11 841) evaluated the vaccine's clinical efficacy using a cluster-randomised design that identified individuals who were at risk of infection from being around someone newly confirmed (by a laboratory) to have Ebola virus disease. This trial found that administering a single dose of rVSVΔG-ZEBOV-GP was highly protective against laboratory-confirmed Ebola virus disease, with a vaccine efficacy of 100% (95% CI 69·9–100·0; p=0·0045). However, the trial's novel design, wide 95% CIs, and potential sources of bias were all cited as concerns. International and country-level health bodies have since reported breakthrough Ebola virus disease cases among individuals who were vaccinated, calling into question its reported 100% effectiveness (some estimate that vaccine effectiveness for individuals whose symptom onset occurs ≥10 days after vaccination is actually 97·5%, 95% CI 92·4–99·1). Indeed, during the tenth reported Ebola virus disease epidemic in the Democratic Republic of Congo, there were some individuals admitted to an Ebola health facility who received rVSVΔG-ZEBOV-GP vaccination 10 days or more before symptom onset of confirmed Ebola virus disease, although anecdotal observations by clinicians and epidemiologists suggested better outcomes among these patients during their stay in an Ebola health facility.

Added value of this study

It is important to describe rVSVΔG-ZEBOV-GP's effectiveness not only against infection, but also against severe disease and death. Our study fills notable gaps in knowledge left open by the only other published evidence collected during an outbreak available on this vaccine. We describe the case fatality risk (CFR) among patients with confirmed Ebola virus disease admitted to Ebola health facilities during the 10th Ebola virus disease epidemic in the Democratic Republic of the Congo from Aug 1, 2018, to June 25, 2020, comparing patients who were vaccinated with those who were not vaccinated and comparing the effect of vaccination timing on outcomes. It is crucial that this evidence reach Ebola-treating clinicians and policy makers to inform strategies for vaccination and treatment during future Ebola outbreaks. To our knowledge, our research is the first observational study to describe the protective effect of vaccination against death among patients with confirmed Ebola virus disease admitted to an Ebola health facility.

Implications of all the available evidence

In our analysis, CFR among patients who were vaccinated was 25% (106/423). This CFR differs from the CFR observed in patients who were not vaccinated (56% [570/1015]) in this cohort and in all previous literature and outbreaks, where high CFR was reported for patients with confirmed Ebola virus disease. Vaccination with rVSVΔG-ZEBOV-GP greatly reduced the risk of death, even when adjusted for Ebola virus disease-specific treatment, age group, and time from symptom onset to admission. An additional observation explains the possible effect of rVSVΔG-ZEBOV-GP on the reduction of the CFR: patients with Ebola virus disease who were vaccinated showed higher cycle threshold values at admission—signifying lower viraemia—compared with patients who were not vaccinated; this difference increased as the time between vaccination and symptom onset increased. Our evidence reinforces the importance of vaccinating populations who are at risk of exposure to Ebola virus as early as possible during outbreaks to reduce the risk of infection and severe complications of Ebola virus disease, including death. Our findings also support the importance of early access to care to improve access to Ebola virus disease-specific treatment. Furthermore, our results suggest no antagonistic effect between the vaccine and monoclonal antibody treatment, even when administered within a short interval, highlighting the possibility of using the vaccine in post-exposure prophylaxis. Incorporating these elements into policy and clinical practice is essential to protect people at risk of death from Ebola virus disease.

units—has little to no effect on humans.[3,4] Because the vaccine only contains one protein from Ebola virus, it cannot cause Ebola virus disease.[3]

Before its marketing authorisation, which became valid throughout the EU in November, 2019, the Strategic Advisory Group of Experts on Immunization (SAGE) recommended that rVSVΔG-ZEBOV-GP be promptly deployed under the expanded access framework in Ebola virus disease outbreaks with informed consent obtained from recipients and in compliance with Good Clinical Practice.[3,5] Since the declaration of the ninth Ebola virus disease epidemic in the Democratic Republic of the Congo in May, 2018, the Democratic Republic of the Congo has experienced six additional Ebola virus disease epidemics, or seven total epidemics in less than 5 years (all linked to Ebola virus disease).[1,6] Following the SAGE recommendation, rVSVΔG-ZEBOV-GP was deployed during the West African epidemic from 2014 to 2016, then during the ninth and subsequent Ebola virus disease outbreaks in the Democratic Republic of the Congo provinces of North Kivu, South Kivu, Ituri, and Equateur.[1,3,7,8] The WHO-recommended vaccine delivery strategy is primarily based on the concept of ring vaccination and targets individuals who are at risk of exposure to Ebola virus including: contacts of individuals with confirmed

Ebola virus disease; contacts-of-contacts of individuals with confirmed Ebola virus disease; health-care workers and front-line workers in the affected areas; and heath workers in areas into which the outbreak could expand.[7] Between Aug 1, 2018, and Feb 18, 2019, infants aged 6–11 months and pregnant or lactating women were not eligible to receive rVSVΔG-ZEBOV-GP in the Democratic Republic of the Congo. However, new 2019 SAGE recommendations advised that these groups are eligible for rVSVΔG-ZEBOV-GP vaccination.[9]

To date, the only phase 3 trial showing rVSVΔG-ZEBOV-GP's clinical protection used a cluster-randomised design that identified individuals who were at risk of exposure from being around someone newly confirmed (by a laboratory) to have Ebola virus disease. In this trial, involving 11 841 people in Guinea in 2015, administering a single dose of rVSVΔG-ZEBOV-GP was highly protective against laboratory-confirmed Ebola virus disease: no new Ebola cases were recorded 10 days or more after vaccinating all contacts and contacts-of-contacts of individuals with confirmed Ebola virus disease, producing a vaccine efficacy of 100% (95% CI 69·9–100·0, p=0·0045).[10–12] Despite the high efficacy described in this trial that used a novel design to generate evidence on individual and cluster-level effects of the vaccine,[10,12] the 95% CIs remained wide, and several experts raised concerns about potential sources of bias from differences in exposures among health-care workers in the immediate versus delayed rings.[10,12–14]

SAGE thus strongly encourages generation of additional evidence on rVSVΔG-ZEBOV-GP.[7] It is important to describe the effectiveness of rVSVΔG-ZEBOV-GP not only against infection, but also against severe disease and death. Moreover, the Institut National pour la Recherche Biomedicale in the Democratic Republic of the Congo and WHO have both reported breakthrough Ebola virus disease cases in previously vaccinated people, rendering the vaccine's effectiveness less than 100%. These organisations estimate that the vaccine effectiveness for individuals whose symptom onset occurs 10 days or more after vaccination is 97·5% (95% CI 92·4–99·1).[15] During the tenth Ebola virus disease epidemic in the Democratic Republic of the Congo (from August, 2018 to June, 2020), there were some individuals admitted to an Ebola health facility who reported receiving rVSVΔG-ZEBOV-GP 10 days or more before symptom onset of confirmed Ebola virus disease, although anecdotal observations by clinicians and epidemiologists suggested better outcomes in these patients during their stay in an Ebola health facility. Here, we describe the case fatality risk (CFR) among patients with confirmed Ebola virus disease admitted to Ebola health facilities during the 10th Ebola virus disease epidemic in the Democratic Republic of the Congo. We compare outcomes in both vaccinated and unvaccinated patients and the effect of vaccine timing on efficacy.

Methods

Study design and participants

This is a retrospective cohort analysis of patients with confirmed Ebola virus disease admitted from July 27, 2018 to April 27, 2020 to any of the Ebola health facilities in North Kivu, South Kivu, and Ituri provinces during the 10th Ebola virus disease epidemic in the Democratic Republic of the Congo (appendix 2 p 2). There were no exclusion criteria.

See Online for appendix 2

This study is a retrospective analysis of data collected for clinical purposes during the emergency response to an Ebola epidemic, not in the context of research. This study was conducted with the approval and collaboration of the Ministry of Health of the Democratic Republic of the Congo. As data were de-identified, the risk to patients was minimal.

Procedures

The compiled line list—which was obtained via routine data collection over the course of the epidemic—of patients with suspected and confirmed Ebola virus disease admitted to Ebola health facilities, from which we extracted all confirmed case data on July 15, 2022, constituted the data source. The line list recorded data gathered from viral haemorrhagic fever notification forms, Ebola health facility registers, patient medical files, and laboratory results. Patients self-reported their vaccination status, vaccine administration date, and symptom onset. Baseline characteristics were obtained via routine data collection over the course of the epidemic. Sex data came from the Ministry of Health-standardised viral haemorrhagic fever notification form, with male or female as the only options.

Vaccination status was first categorised into three primary groups: (1) individuals who were not vaccinated; (2) those vaccinated less than 10 days before symptom onset (hereafter referred to as post-Ebola virus disease-exposure); and (3) those vaccinated 10 days or more before symptom onset (hereafter referred to as pre-Ebola virus disease-exposure; appendix 2 p 6). Selection of the 10-day cutoff was based on the published phase 3 trial of rVSVΔG-ZEBOV-GP.[10,12] Considering the Ebola virus disease incubation period of 2–21 days, the two groups who were vaccinated were each subdivided to differentiate patients who were clearly vaccinated before or after exposure to Ebola virus disease from those for whom it was less clear if they were exposed to Ebola virus disease before or after vaccination. This resulted in five total vaccination status categories for analysis: (1) individuals who were not vaccinated; (2) those vaccinated post-Ebola virus disease-exposure (≤2 days before symptom onset); (3) those probably vaccinated post-Ebola virus disease-exposure (3–9 days before symptom onset); (4) those probably vaccinated pre-Ebola virus disease-exposure (≥10 days before symptom onset); and (5) those vaccinated pre-Ebola virus disease-exposure (≥21 days before symptom onset). Patients

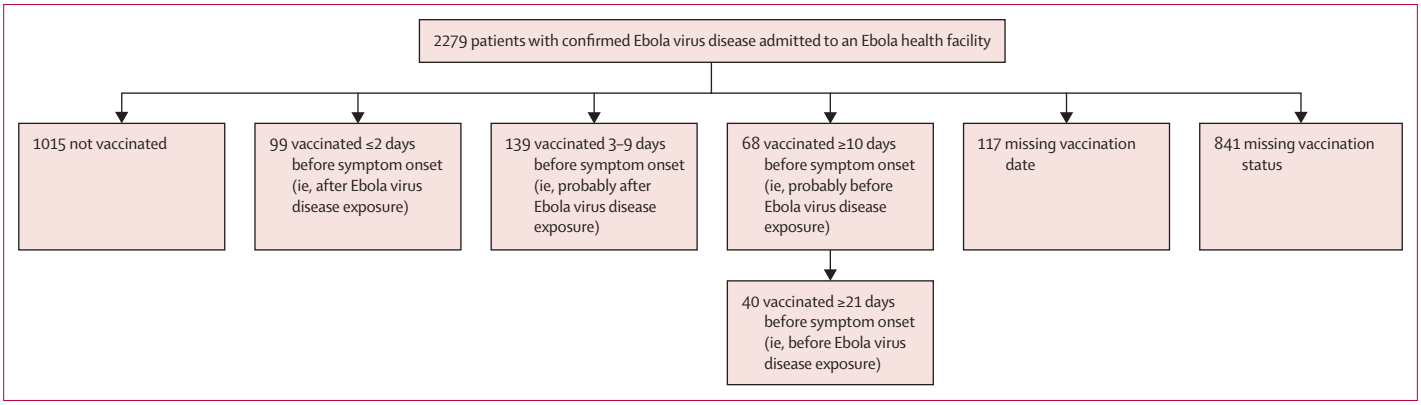

Figure: **Flowchart of patients included in the analysis**

	Not vaccinated (N=1015)	Post-Ebola virus disease-exposure		Pre-Ebola virus disease-exposure		Incomplete data	
		Vaccinated ≤2 days before symptom onset (N=99)	Vaccinated 3–9 days before symptom onset (N=139)	Vaccinated ≥10 days before symptom onset (N=68)	Vaccinated ≥21 days before symptom onset (N=40)	Vaccination date unknown (N=117)	Vaccination status unknown (N=841)
Age group							
<5 years	138 (14%)	10 (10%)	5 (4%)	2 (3%)	2 (5%)	9 (8%)	83 (10%)
5–14 years	109 (11%)	6 (6%)	6 (4%)	0	0	9 (8%)	83 (10%)
15–29 years	339 (33%)	35 (36%)	45 (32%)	28 (41%)	18 (45%)	52 (44%)	249 (30%)
30–59 years	373 (37%)	41 (42%)	71 (51%)	37 (54%)	20 (50%)	40 (34%)	363 (43%)
≥60 years	56 (6%)	6 (6%)	12 (9%)	1 (1%)	0	7 (6%)	62 (7%)
Median age, years	26·0 (15·0–39·0)	28·5 (20·0–45·0)	32·0 (22·0–42·0)	31·5 (24·0–40·0)	29·5 (23·0–40·0)	26·0 (20·0–37·0)	30·0 (18·0–42·0)
Sex							
Female	575 (57%)	58 (59%)	73 (53%)	32 (47%)	16 (40%)	76 (65%)	486 (58%)
Male	440 (43%)	41 (41%)	66 (47%)	36 (53%)	24 (60%)	41 (35%)	355 (42%)
Ebola virus disease-specific treatment							
None	255 (25%)	9 (9%)	6 (4%)	4 (6%)	3 (8%)	16 (14%)	403 (48%)
mAb114	93 (9%)	11 (11%)	15 (11%)	10 (15%)	6 (15%)	5 (4%)	84 (10%)
REGN-EB3	112 (11%)	10 (10%)	15 (11%)	8 (12%)	5 (12%)	18 (15%)	74 (9%)
Remdesivir	82 (8%)	13 (13%)	14 (10%)	12 (18%)	7 (18%)	5 (4%)	57 (7%)
ZMapp	7 (1%)	4 (4%)	1 (1%)	1 (1%)	1 (2%)	0	25 (3%)
RCT*	466 (46%)	52 (53%)	88 (63%)	33 (49%)	18 (45%)	73 (62%)	198 (24%)
Time from symptom onset to admission							
Median time, days	4·0 (3·0–7·0)	3·0 (2·0–6·0)	2·0 (1·0–4·0)	2·0 (1·0–4·0)	2·0 (1·0–4·0)	3·0 (2·0–4·0)	4·0 (2·0–7·0)
Cycle threshold for glycoprotein at admission							
Median	25·6 (23·3–29·8)	29·2 (25·2–32·4)	28·5 (26·1–32·0)	29·5 (26·6–34·0)	29·7 (25·0–34·6)	28·1 (25·5–32·1)	26·7 (24·1–31·1)
Missing	101 (10%)	6 (6%)	14 (10%)	3 (4%)	2 (5%)	16 (14%)	245 (29%)
Cycle threshold for nucleoprotein at admission							
Median	21·4 (18·4–25·9)	25·0 (20·2–28·0)	24·9 (21·8–28·1)	28·1 (24·0–32·8)	30·0 (24·6–33·7)	22·8 (20·7–27·2)	22·5 (19·5–27·6)
Missing	97 (10%)	7 (7%)	13 (9%)	0	0	16 (14%)	236 (28%)
Health-care worker							
Yes	36 (4%)	11 (11%)	7 (5%)	22 (32%)	17 (42%)	12 (10%)	42 (5%)
No	941 (93%)	84 (85%)	129 (93%)	45 (66%)	23 (58%)	99 (85%)	710 (84%)
Missing	38 (4%)	4 (4%)	3 (2%)	1 (1%)	0	6 (5%)	89 (11%)

Data are n (%) or median (IQR). *RCT refers to participation in a randomised controlled trial (ie, patient received either mAb114, REGN-EB3, remdesivir, or ZMapp).

Table 1: **Characteristics at admission of patients with confirmed Ebola virus disease by vaccination status**

with unknown vaccination status or date were also included to assess potential bias associated with missing data.

Cycle threshold is defined as the number of cycles required to cross the PCR detection threshold. Cycle threshold and viraemia are inversely related: the higher

the cycle threshold, the lower the viraemia. Cycle threshold for nucleoprotein was assessed given its presence in Ebola virus but not in rVSVΔG-ZEBOV-GP.

Ebola virus disease-specific treatment is defined as the patient having received mAb114 (ie, ansuvimab-zyk; Ebanga, Ridgeback Biotherapeutics, Miami, FL, USA), REGN-EB3 (ie, atoltivimab, maftivimab, and odesivimab; Inmazeb, Regeneron Pharmaceuticals, Tarrytown, NY, USA), remdesivir, ZMapp, or randomised controlled trial (RCT).[16] RCT refers to any patient participating in an RCT who received an EVD-specific treatment without specification of treatment name.

Outcomes

The primary outcome of interest was CFR among patients with confirmed Ebola virus disease, calculated as the number of patients with confirmed Ebola virus disease who died divided by the number of patients with confirmed Ebola virus disease in each vaccination category, excluding patients lost to follow-up and those who were transferred to another centre. The secondary outcome of interest was the cycle threshold for nucleoprotein among patients with confirmed Ebola virus disease.

Statistical analysis

We describe patient characteristics by vaccination status using proportions for categorical variables and appropriate measures of central value and dispersion for continuous variables. We calculated the CFR and its 95% binomial CI among patients with confirmed Ebola virus disease by vaccination status, comparing CFR using two-sided Fisher's exact testing. Cycle threshold values for nucleoprotein at admission according to vaccination status were compared using Wilcoxon rank-sum testing. Stratified explanatory analyses were performed to calculate the CFR according to the Ebola virus disease-specific treatment received (ie, no Ebola virus disease-specific treatment, mAb114, REGN-EB3, remdesivir, ZMapp, or RCT[16]) and the time from symptom onset to admission at an Ebola health facility. To explore the effect of vaccination on Ebola virus disease-related mortality, we used Poisson regression models with robust error variance.[17] In adjusted analyses, we included risk factors for death from Ebola virus disease that had been identified in previous studies or by an expert in the field, including age group, sex, health-care worker status, time from symptom onset to admission, vaccination group, and Ebola virus disease-specific treatment.[18–21] Routine data cleaning and data analyses were performed using R (version 4.2) and Stata (version 17.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Deaths (number of deaths/ total number of patients)	Case fatality risk	Fisher's two-sided p-value
Vaccination status			
Not vaccinated	570/1015	56·2%	Ref
Vaccinated ≤2 days before symptom onset	27/99	27·3%	<0·0001
Vaccinated 3–9 days before symptom onset	28/139	20·1%	<0·0001
Vaccinated ≥10 days before symptom onset	12/68	17·6%	<0·0001
Vaccinated ≥21 days before symptom onset	7/40	17·5%	<0·0001
Unknown vaccination date	39/117	33·3%	<0·0001
Unknown vaccination status	441/841	52·4%	0·16
Ebola virus disease-specific treatment received			
None	530/693	76·5%	Ref
mAb114	65/218	29·8%	<0·0001
REGN-EB3	71/237	30·0%	<0·0001
Remdesivir	89/183	48·6%	<0·0001
ZMapp	15/38	39·5%	0·0044
RCT*	347/910	38·1%	0·0037

*RCT refers to participation in a randomised controlled trial (ie, patient received either mAb114, REGN-EB3, remdesivir, or ZMapp).

Table 2: **Case fatality risk and crude risk difference by vaccination status and Ebola virus disease-specific treatment**

Results

A total of 2279 patients with confirmed Ebola virus disease were recorded in the compiled line list from July 27, 2018, to April 27, 2020 and analysed (figure). Of these 2279 patients, 1015 (45%) were not vaccinated; 99 (4%) were vaccinated 2 days or less before symptom onset; 139 (6%) were vaccinated 3–9 days before symptom onset; and 68 (3%) were vaccinated 10 days or more before symptom onset, among whom 40 (2%) were vaccinated 21 days or more before symptom onset, 117 (5%) were vaccinated but no date of vaccination was reported, and 841 (37%) had unknown vaccination status. Characteristics of these patients are shown in table 1, stratified by timing of vaccination. Most vaccinated patients were aged 15–59 years and received an Ebola virus disease-specific treatment. The time between symptom onset and admission was shorter for vaccinated patients (table 1).

Crude CFRs for the different vaccination categories are presented in table 2. Among the 1015 patients who were not vaccinated, the CFR was 56·2% (ie, 570 patients died), whereas among the 423 patients who were vaccinated, CFR decreased to 25·1% (ie, 106 patients died; p<0·0001). CFR was 27·3% (27/99; p<0·0001) for those vaccinated ≤2 days before symptom onset and 20·1% (28/139; p<0·0001) for those vaccinated 3–9 days before symptom onset. Among those who were probably vaccinated before their Ebola virus exposure, the CFR was 17·6% (12/68; p<0·0001) for patients vaccinated 10 days or more before symptom onset and 17·5% (7/40; p<0·0001) for those vaccinated 21 days or more before symptom onset. CFR was even lower when selecting patients with even longer time from vaccination to symptom onset (ie, ≥30, ≥60,

	Univariate analysis				Adjusted analysis			
	Deaths (number of deaths/total number of patients)	Univariate RR	95% CI	p value	Deaths (number of deaths/total number of patients)	Adjusted RR	95% CI	p value
Vaccination status								
Not vaccinated	570/1015	Ref	..	..	570/1015	Ref	..	..
Vaccinated ≤2 days before symptom onset	27/99	0·49	0·32–0·70	0·0002	27/99	0·56	0·36–0·82	0·0046
Vaccinated 3–9 days before symptom onset	28/139	0·36	0·24–0·51	<0·0001	28/139	0·44	0·29–0·65	0·0001
Vaccinated ≥10 days before symptom onset	12/68	0·31	0·17–0·53	0·0001	12/68	0·40	0·21–0·69	0·0022
Vaccination date unknown	39/117	0·59	0·42–0·81	0·0016	39/117	0·69	0·48–0·96	0·0341
Unknown status	441/841	0·93	0·82–1·06	0·28	441/841	0·80	0·70–0·91	0·0011
Age group, years								
<5	144/247	1·23	1·02–1·49	0·0286	144/247	1·10	0·90–1·33	0·37
5–14	105/213	1·04	0·84–1·29	0·70	105/213	0·96	0·76–1·19	0·69
15–29	346/748	0·98	0·85–1·13	0·77	346/748	0·96	0·83–1·11	0·59
30–59	437/925	Ref	..	..	437/925	Ref	..	..
≥60	84/144	1·23	0·97–1·55	0·08	84/144	1·06	0·82–1·35	0·66
Sex								
Female	658/1300	Ref	..	..	658/1300	Ref	..	..
Male	459/979	0·93	0·82–1·04	0·21	459/979	0·95	0·84–1·08	0·46
Health-care worker								
Yes	45/130	0·70	0·51–0·94	0·0210	45/130	0·95	0·69–1·28	0·75
No	988/2008	Ref	..	..	988/2008	Ref	..	..
Time from symptom onset to admission								
Per day	1117/2279	1·05	1·03–1·06	<0·0001	1117/2279	1·03	1·02–1·05	<0·0001
Ebola virus disease-specific treatment received								
None	530/693	Ref	..	..	530/693	Ref	..	..
ZMapp	15/38	0·52	0·30–0·83	0·0115	15/38	0·58	0·32–0·97	0·0545
Remdesivir	89/183	0·64	0·50–0·79	0·0001	89/183	0·65	0·51–0·82	0·0005
RCT*	347/910	0·50	0·44–0·57	<0·0001	347/910	0·54	0·47–0·63	<0·0001
mAb114	65/218	0·39	0·30–0·50	<0·0001	65/218	0·44	0·33–0·57	<0·0001
REGN-EB3	71/237	0·39	0·30–0·50	<0·0001	71/237	0·40	0·30–0·52	<0·0001

All variables included in the univariate analysis were included in the multivariate analysis. RR=relative risk. *RCT refers to participation in a randomised controlled trial (ie, patient received either mAb114, REGN-EB3, remdesivir, or ZMapp).

Table 3: **RR of death among patients with confirmed Ebola virus disease**

≥90, and ≥180 days; appendix 2 p 3). Among patients with incomplete data, those with an unknown vaccination date had a CFR of 33·3% (39/117; p<0·0001), whereas those with unknown vaccination status had a CFR similar to patients who were not vaccinated (CFR=52·4% [441/841]; p=0·16). CFR among patients not treated with an Ebola virus disease-specific therapeutic was 76·5% (530/693). However, CFR for patients treated with mAb114 was 29·8% (65/218; p<0·0001) and 30·0% (71/237; p<0·0001) for those treated with REGN-EB3. CFR was 48·6% (89/183; p<0·0001) for patients treated with remdesivir, 39·5% (15/38; p=0·0044) for those treated with ZMapp, and 38·1% (347/910, p=0·0037) for those in the RCT group.

Univariate and adjusted relative risks for death among patients with confirmed Ebola virus disease are presented in table 3. Being vaccinated significantly lowered the risk of death for patients with confirmed Ebola virus disease compared with not being vaccinated, with a progressive increase in the protective effect as more time elapsed from vaccination to symptom onset (those vaccinated ≤2 days before symptom onset had an adjusted relative risk [aRR] of 0·56 [95% CI 0·36–0·82; p=0·0046]; those vaccinated 3–9 days before symptom onset had an aRR of 0·44, 0·29–0·65; p=0·0001); and those vaccinated ≥10 days before symptom onset had an aRR of 0·40 [0·21–0·69; p=0·0022]). Among patients with incomplete data, those with unknown vaccination date had an aRR of 0·69 (0·48–0·96; p=0·0341), whereas those with unknown vaccination status had an aRR of 0·80 (0·70–0·91; p=0·0011). Age group and sex were not significantly associated with the relative risk of death.

Being a health-care worker was significantly associated with the relative risk of death in the univariate analysis (univariate relative risk 0·70, 95% CI 0·51–0·94; p=0·0210), but not in the adjusted analysis (aRR 0·95, 95% CI 0·69–1·28, p=0·75). Longer time from symptom onset to admission significantly increased the risk of death, with an aRR of 1·03 per day [95% CI 1·02–1·05; p<0·0001). Compared with patients with confirmed Ebola virus disease who were not treated, all Ebola virus disease-specific treatments significantly decreased the risk of death, with the greatest protection obtained from mAb114 (aRR 0·44 [95% CI 0·33–0·57; p<0·0001]) and REGN-EB3 (0·40 [0·30–0·52; p<0·0001]).

To explore the potential negative or positive interaction between vaccination and Ebola virus disease-specific treatment, and consequently the possibility of including vaccination as post-exposure prophylaxis, appendix 2 (p 4) presents univariate and adjusted relative risk of death among patients with Ebola virus disease who received Ebola virus disease-specific treatment and were either vaccinated 4 days or less before starting treatment or unvaccinated. The results do not suggest any negative interaction of the vaccine and treatment (administered shortly after vaccination) on the outcome. Compared with those who were not vaccinated and treated, those who were vaccinated and treated with REGN-EB3 or mAb114 had an aRR of 0·29 (95% CI 0·02–1·31; p=0·22), those who were vaccinated and treated with ZMapp or remdesivir had an aRR of 0·73 (0·18–1·99; p=0·60), and those who were vaccinated and treated with any Ebola virus disease-specific treatment (ie, REGN-EB3, mAb114, ZMapp, remdesivir, or RCT) had an aRR of 0·68 (0·35–1·18; p=0·21).

Cycle threshold values for nucleoprotein at admission are shown in table 1, with further details stratified by time from symptom onset to admission provided in appendix 2 (p 5). Cycle threshold values were significantly higher (indicating lower viraemia) among those vaccinated 21 days or more before symptom onset (median 30·0 [IQR 24·6–33·7]) than among patients who were not vaccinated (21·4 [18·4–25·9]; p<0·0001). Cycle threshold values were also significantly higher among those vaccinated 10 days or more before symptom onset than patients who were not vaccinated (p<0·0001). Although lower than the cycle threshold values for patients vaccinated 21 days or more or 10 days or more before symptom onset, cycle threshold values for nucleoprotein at admission were significantly higher and similar (median 25·0 [IQR 20·2–28·0] and 24·9 [21·8–28·1]) for both groups of patients who were probably vaccinated post-Ebola virus disease exposure (ie, ≤2 days and 3–9 days before symptom onset) compared with those who were not vaccinated (p=0·0003 and p<0·0001, respectively). The same conclusions can be drawn for people admitted more than 4 days after symptom onset or earlier, suggesting that the difference compared with patients who were not vaccinated is not due to confounding bias linked to the course of the disease.

Discussion

To our knowledge, our research is the first observational study to describe the protective effect of vaccination with rVSVΔG-ZEBOV-GP against death among patients with confirmed Ebola virus disease admitted to an Ebola health facility. The cases of Ebola virus disease in the Democratic Republic of the Congo that occurred in people who had been vaccinated 10 days or more before symptom onset show that rVSVΔG-ZEBOV-GP protection is inferior to 100%, contrasting the point estimate reported by the first and only available study on rVSVΔG-ZEBOV-GP clinical efficacy.[10,12] Yet, vaccine failure is still compatible with high effectiveness, as shown by the trial. Further research will provide more accurate estimates.

It is likely that many of the vaccinated breakthrough cases seen in this cohort would have had sufficient time to mount an immune response against Ebola virus disease. Many of these individuals had been vaccinated 10 days or more before their symptoms occurred (acquiring protective immunity against Ebola virus could require up to a week following vaccination).[10,12] Instead, these cases might have been due to either primary vaccine failure (ie, the patient does not develop an immune response to the vaccination) or perhaps related to cold chain failures, inadequate viral dosing (ie, administering less than prescribed), an inadequate injection administration technique, or host immune factors (eg, immunosuppression).[22,23] Secondary vaccine failure (ie, clinical infection despite a previous immune response to vaccination) after Ebola vaccination is not well understood given the absence of a correlate of protection for the disease and very limited experience with later outbreaks among previously vaccinated populations. Data misclassification—of vaccination status or of an individual's date of vaccination—might potentially also explain these cases.

The goal of vaccination could include protection from infection, severe disease, death, and prevention of onward transmission. In our study, although rVSVΔG-ZEBOV-GP did not protect some individuals against Ebola virus infection, it offered protection against mortality, leading to a CFR of 25·1% in individuals who were vaccinated. This CFR differs largely from the CFR observed in patients who were not vaccinated (56·2%) and from existing data from previous outbreaks that showed high CFR among patients with confirmed Ebola virus disease.[1,2,6,19,24] rVSVΔG-ZEBOV-GP's ability to reduce the CFR could be due, in part, to the fact that patients with Ebola virus disease who were vaccinated showed higher cycle threshold values for nucleoprotein at admission—signifying lower viraemia—than patients who were not vaccinated; this difference increased as the time between vaccination and symptom onset increased.

In our analysis, vaccination was protective against death for all patients, even when adjusted for Ebola virus disease-specific treatment, age group, and time from symptom onset to admission.

Our results reinforce the importance of vaccination and, in the event of vaccine failure, the need for efficient administration of Ebola virus disease-specific treatment. Late vaccination (ie, after Ebola virus disease exposure, even when administered shortly before symptom onset) was significantly protective against death. The question remains whether the combination of Ebola virus disease-specific treatment and vaccination can have antagonistic or synergic effects. In our study, treatment and vaccination were not administered simultaneously; instead, we compared individuals who received both vaccination and treatment within 4 days with those who received treatment but no vaccination, adjusting for confounding factors (appendix 2 p 4). Although the results are not statistically significant, probably due to the small sample size, we did not observe an antagonistic effect. These results highlight the importance of research on post-exposure phrophylaxis strategies that include vaccination in combination with monoclonal antibodies.

As in any observational study, information and selection bias might have affected the findings of this analysis. We believe that the risk of outcome misclassification (ie, living or deceased at discharge) is low. It is possible that some individuals' exposure (ie, vaccination) was misclassified.

Among the few patients who were vaccinated who died, a small proportion were vaccinated more than 21 days before symptom onset and were thus considered to have clearly received the vaccine before being exposed to Ebola virus.[12] To reduce the chance that these rare but notable cases were misclassified, we conducted additional data quality checks by reviewing these patients' medical files. These data checks were ultimately largely consistent with the compiled line list. Interestingly, six of the seven patients who died but had been vaccinated more than 21 days before symptom onset were also admitted to the same Ebola treatment centre, and three of those six patients were vaccinated during the same two-week period, suggesting a non-random effect (eg, a data entry error or primary vaccine failure related to a specific vaccination site). If non-differential misclassification is present, this could have artificially reduced the CFR in the unvaccinated group or artificially increased the CFR in the vaccinated group (if the observed differences are real), thus underestimating the risk difference.

Regarding selection bias, the non-random allocation of the main exposure in this analysis (ie, vaccination) could have produced a differential baseline risk of death between vaccinated or unvaccinated individuals due to the frequency of comorbidities or differential health-seeking behaviour. Selection bias could also apply to the treatment received by the patient with confirmed Ebola virus disease. We tried to mitigate any potential bias by conducting stratified analyses and multivariate regression.

Another limitation of this analysis is the presence of missing data. For some patients with confirmed Ebola virus disease, it was not possible to retrieve their vaccination status. Additionally there were some patients with confirmed Ebola virus disease documented as having been vaccinated, but the date of vaccination was not recorded. However, the mortality rates for these two categories are consistent with the results for the other categories. Indeed, we would expect the majority of patients with unknown vaccination status not to have been vaccinated, and a minority to have been vaccinated; we observe a risk of death similar to that of unvaccinated patients, but slightly lower. Patients who had recorded vaccination but did not have a vaccination date (indicating probable vaccination, but with lower reliability) had a risk of death similar to that of patients who were vaccinated. In addition, cycle threshold value for nucleoprotein at admission was missing for 369 (16%) of the 2279 patients with confirmed Ebola virus disease included in this analysis.

Higher cycle threshold values at admission among those who were vaccinated could be related to better active surveillance of cases, contacts of cases, and contacts-of-contacts of cases, or to greater acceptance of care by these patients. Better surveillance or greater acceptance of care could have led to earlier admission at an Ebola treatment centre in individuals who received rVSVΔG-ZEBOV-GP compared with those who were not vaccinated. The time from symptom onset to admission could potentially confound the protective effect of vaccination against death. However, when we adjusted for the different potential counfounding risk factors, including the time between symptom onset and admission, the protective effect of the vaccine—although slightly reduced—remained significant.

Vaccination with rVSVΔG-ZEBOV-GP greatly reduced the risk of death, even when adjusted for Ebola virus disease-specific treatment, age group, and time from symptom onset to admission. Vaccination was also associated with an increase in cycle threshold values for nucleoprotein. Both of these benefits increased with greater elapsed time between vaccination and infection. Our results reinforce the importance of vaccinating populations who are at risk of exposure to Ebola virus to reduce the risk of infection and—if infection occurs—the risk of death.

Contributors

MB, NP, EG, and FL contributed to the conceptualisation and design of the work. MB and EG accessed and verified all data. MB performed the analysis with the support of EG and FL. RMC, MB, NP, EG, and FL interpreted the data and wrote the Article. All authors substantially contributed to the acquisition of data, had full access to all study data, contributed to the early and final drafts of the manuscript, and accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All data belong to the Ministry of Health of the Democratic Republic of the Congo, who—in accordance with an established Memorandum of Understanding between Epicentre and the Ministry of Health—authorised access to the dataset for this collaborative research. Further request for data access and analyses of data must be presented to and approved by the Ministry of Health.

Acknowledgments

We thank Janet Ousley, from Médecins Sans Frontières Operational Centre Paris (Paris, France), for providing medical editing and copyediting. Médecins Sans Frontières funded the research.

References

1 WHO. Ebola virus disease fact sheet. 2023. https://www.who.int/en/news-room/fact-sheets/detail/ebola-virus-disease (accessed July 7, 2023).
2 Coltart CEM, Lindsey B, Ghinai I, Johnson AM, Heymann DL. The Ebola outbreak, 2013–2016: old lessons for new epidemics. *Philos Trans R Soc Lond B Biol Sci* 2017; **372:** 20160297.
3 European Medicines Agency. Ervebo, INN-Ebola Zaire vaccine [rVSVΔG-ZEBOV-GP, live]: EPAR—medicine overview. https://www.ema.europa.eu/en/documents/overview/ervebo-epar-medicine-overview_en.pdf (accessed Aug 10, 2023).
4 European Medicines Agency. Ervebo, INN-Ebola Zaire vaccine (rVSVΔG-ZEBOV-GP, live). Annex 1. Summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/ervebo-epar-product-information_en.pdf (accessed Aug 10, 2023).
5 WHO. SAGE Ebola vaccines—session 7. Overview of the evidence and recommendations. 2019. https://terrance.who.int/mediacentre/data/sage/SAGE_Docs_Ppt_Oct2019/7_session_ebola/Oct2019_Session7_R_DBlueprint_recommendation.pdf (accessed Aug 10, 2023).
6 Centers for Disease Control and Prevention. History of Ebola virus disease (EVD) outbreaks. 2023. https://www.cdc.gov/vhf/ebola/history/chronology.html (accessed July 7, 2023).
7 WHO. Meeting of the Strategic Advisory Group of Experts on immunization, April 2017—conclusions and recommendations. *Wkly Epidemiol Rec* 2017; **92:** 301–20.
8 Minister of Health Democratic Republic of the Congo. Epidemiological situation in North Kivu and Ituri provinces, press release, 10 February 2019. https://mailchi.mp/sante.gouv.cd/ebola_kivu_10fev19?e=bd21be675e (accessed July 7, 2023).
9 Strategic Advisory Group of Experts. SAGE interim recommendations on vaccination against Ebola virus disease. 2019. https://cdn.who.int/media/docs/default-source/immunization/ebola/interim-ebola-recommendations-may-2019.pdf?sfvrsn=c54ce264_9 (accessed July 7, 2023).
10 Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet* 2017; **389:** 505–18.
11 Lévy Y, Lane C, Piot P, et al. Prevention of Ebola virus disease through vaccination: where we are in 2018. *Lancet* 2018; **392:** 787.
12 Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet* 2015; **386:** 857–66.
13 Longini IM, Røttingen JA, Kieny MP, Edmunds WJ, Henao-Restrepo AM. Questionable efficacy of the rVSV-ZEBOV Ebola vaccine—Authors' reply. *Lancet* 2018; **391:** 1021–22.
14 Metzger WG, Vivas-Martínez S. Questionable efficacy of the rVSV-ZEBOV Ebola vaccine. *Lancet* 2018; **391:** 1021.
15 WHO. Preliminary results on the efficacy of rVSV-ZEBOV-GP Ebola vaccine using the ring vaccination strategy in the control of an Ebola outbreak in the Democratic Republic of the Congo: an example of integration of research into epidemic response. 2019. https://cdn.who.int/media/docs/default-source/ebola/ebola-ring-vaccination-results-12-april-2019.pdf?sfvrsn=b9cca6aa_1&download=true (accessed Oct 27, 2020).
16 Mulangu S, Dodd LE, Davey RT, et al. A Randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med* 2019; **381:** 2293–303.
17 Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159:** 702–06.
18 Schieffelin JS, Shaffer JG, Goba A, et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N Engl J Med* 2014; **371:** 2092–100.
19 WHO Ebola Response Team. Ebola virus disease in west Africa—the first 9 months of the epidemic and forward projections. *N Engl J Med* 2014; **371:** 1481.
20 Bah EI, Lamah M-C, Fletcher T, et al. Clinical presentation of patients with Ebola virus disease in Conakry, Guinea. *N Engl J Med* 2015; **372:** 40–47.
21 Gignoux E, Azman AS, de Smet M, et al. Effect of artesunate–amodiaquine on mortality related to Ebola virus disease. *N Engl J Med* 2016; **374:** 23–32.
22 Marzi A, Engelmann F, Feldmann F, et al. Antibodies are necessary for rVSV/ZEBOV-GP-mediated protection against lethal Ebola virus challenge in nonhuman primates. *Proc Natl Acad Sci USA* 2013; **110:** 1893–98.
23 Pinski AN, Messaoudi I. Therapeutic vaccination strategies against EBOV by rVSV-EBOV-GP: the role of innate immunity. *Curr Opin Virol* 2021; **51:** 179–89.
24 Rosello A, Mossoko M, Flasche S, et al. Ebola virus disease in the Democratic Republic of the Congo, 1976-2014. *Elife* 2015; **4:** 1976–2014.