Effectiveness of rVSV-ZEBOV vaccination during the 2018–20 Ebola virus disease epidemic in the Democratic Republic of the Congo: a retrospective test-negative study

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Summary

Background The recombinant vesicular stomatitis virus–Zaire Ebola virus (rVSV-ZEBOV) vaccine is the only WHO prequalified vaccine recommended for use to respond to outbreaks of Ebola virus (species *Zaire ebolavirus*) by WHO's Strategic Advisory Group of Experts on Immunization. Despite the vaccine's widespread use during several outbreaks, no real-world effectiveness estimates are currently available in the literature.

Methods We conducted a retrospective test-negative analysis to estimate effectiveness of rVSV-ZEBOV vaccination against Ebola virus disease during the 2018–20 epidemic in the Democratic Republic of the Congo, using data on suspected Ebola virus disease cases collected from Ebola treatment centres. Those eligible for inclusion had an available Ebola virus RT-PCR result, available key data, were eligible for vaccination during the outbreak, and had symptom onset aligning with the period in which a ring-vaccination protocol was in use. After imputing missing data, each individual confirmed by RT-PCR to be Ebola virus disease-positive (defined as a case) was matched to one individual negative for Ebola virus disease (control) by sex, age, health zone, and month of symptom onset. Effectiveness was estimated from the odds ratio of being vaccinated (≥10 days before symptom onset) versus being unvaccinated among cases and controls, after adjusting for the matching factors. The imputation, matching and effectiveness estimation, was repeated 500 times.

Findings 1273 (4·8%) of 26 438 eligible individuals were positive for Ebola virus disease (cases) and 25 165 (95·2%) were negative (controls). 40 (3·1%) cases and 1271 (5·1%) controls were reported as being vaccinated at least 10 days before symptom onset. After selecting individuals who reported exposure to an individual with Ebola virus disease within the 21 days before symptom onset and matching, the analysis datasets comprised a median of 309 cases and 309 controls. 10 days or more after vaccination, the effectiveness of rVSV-ZEBOV against Ebola virus disease was estimated to be 84% (95% credible interval 70–92).

Interpretation This analysis is the first to provide estimates of the real-world effectiveness of the rVSV-ZEBOV vaccine against Ebola virus disease, amid the widespread use of the vaccine during a large Ebola virus disease outbreak. Our findings confirm that rVSV-ZEBOV is highly protective against Ebola virus disease and support its use during outbreaks, even in challenging contexts such as in the eastern Democratic Republic of the Congo.

Funding Médecins Sans Frontières.

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Lancet Infect Dis 2024

Published Online
August 20, 2024
https://doi.org/10.1016/S1473-3099(24)00419-5

See Online/Comment
https://doi.org/10.1016/S1473-3099(24)00437-7

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

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Introduction

Ebolaviruses (also known as orthoebolaviruses) are endemic in the Democratic Republic of the Congo; as of March, 2024, the country has had 15 documented outbreaks of Ebola virus disease.[1] The tenth outbreak, confirmed on Aug 1, 2018,[2] was located in the northeastern provinces of North Kivu and Ituri, a region characterised by chronic insecurity and conflict, political instability, mistrust in government, and high population mobility.[3,4] By the end of the outbreak on June 25, 2020, 3470 cases and 2287 deaths were recorded (case-fatality rate 66%), making it the largest reported outbreak in the country, and the second-largest outbreak worldwide, in terms of both number of cases and deaths, after only the 2013–16 epidemic in west Africa.[5]

The recombinant vesicular stomatitis virus–Zaire Ebola virus single-dose vaccine (rVSV-ZEBOV or rVSVΔG-ZEBOV-GP, also known as Ervebo) was prequalified by WHO in November, 2019,[6] and is currently recommended by WHO's Strategic Advisory Group of Experts on Immunization (SAGE) for individuals at risk of exposure during outbreaks of Ebola virus (species *Zaire ebolavirus*, also known as *Orthoebolavirus zairense*).[7,8] In a phase 3 cluster-randomised trial of ring vaccination in Guinea and Sierra Leone (*Ebola Ça Suffit!*) during the 2013–16 Ebola virus disease epidemic in west Africa, vaccine efficacy was estimated to be 100% (95% CI 69–100);[9,10] this is the only efficacy value available to date. The vaccine was deployed

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Research in context

Evidence before this study

We searched PubMed and Google Scholar for studies published between database inception and April 11, 2024, with no language restrictions, using the following terms: (filovirus) OR (Ebola) AND (vaccin*). A single phase 3 trial (n=11 841) evaluated the clinical efficacy of the vaccine using a cluster-randomised design based on identification of people at risk around a newly confirmed case of Ebola virus disease. The study found that a single dose of rVSV-ZEBOV was highly protective against laboratory-confirmed Ebola virus disease (efficacy 100% [95% CI 69–100]). Preliminary analyses from the 2018–20 Ebola virus disease outbreak in the Democratic Republic of the Congo estimated effectiveness to be 98% (95% CI 96–99), but are based only on data from the first third of the epidemic. To our knowledge, more up-to-date estimates are not available at the time of writing, and confirmatory clinical trials to address remaining questions and limitations of the available estimates are constrained by ethical challenges.

Added value of this study

This is the first published study to assess the effectiveness of rVSV-ZEBOV outside a clinical trial and amid the most widespread use of the vaccine to date, during the second-largest Ebola virus disease outbreak ever recorded, addressing uncertainties in the real-world effectiveness of the vaccine left open by previous studies. We use a test-negative design to leverage systematically collected operational data, and our results confirm that a single dose of rVSV-ZEBOV is highly protective against Ebola virus disease 10 days or more after vaccination (84% [95% credible interval 70–92]).

Implications of all the available evidence

Our findings are compatible with the previously published efficacy estimates from Guinea and Sierra Leone, as well as with a preliminary analysis from the Democratic Republic of the Congo outbreak. Using a large, exhaustive dataset of patients with suspected Ebola virus disease, spanning the entire duration of the tenth Democratic Republic of the Congo Ebola virus disease epidemic, we provide the most comprehensive measures of effectiveness of the rVSV-ZEBOV vaccine to date. Our findings reinforce the evidence for vaccinating individuals at risk of exposure to Ebola virus as early as possible during epidemics. Even in challenging settings, such as the eastern Democratic Republic of the Congo, rVSV-ZEBOV vaccination is a highly effective tool to control Ebola virus disease outbreaks, in combination with other interventions.

during the tenth ebolavirus outbreak in the Democratic Republic of the Congo under the Expanded Access framework[11] following the WHO-recommended strategy based on reactive ring vaccination and targeting of at-risk individuals (defined as contacts of people with Ebola virus disease, contacts of contacts, and front-line workers).[7] Vaccination activities began on Aug 8, 2018[12] and over 300 000 individuals were vaccinated during the course of the outbreak using a ring vaccination strategy in which at-risk individuals were targeted for vaccination.[5] Following SAGE guidelines, eligibility for vaccination was revised in mid-June, 2019 to include pregnant and breastfeeding women and infants aged 6–12 months, who were initially ineligible to receive the vaccine; at the same time, the dose was also decreased by half.[8,13]

Real-world effectiveness of rVSV-ZEBOV vaccination is expected to be less than 100%.[14] During the 2018–20 outbreak in the Democratic Republic of the Congo, national and international agencies recorded confirmed cases of Ebola virus disease in vaccinated individuals, including individuals who were reported as having been vaccinated 10 days or more before symptom onset.[15–19] Preliminary, unadjusted analyses estimated vaccine effectiveness to be 98% (95% CI 96–99).[20] Other studies have shown that rVSV-ZEBOV vaccination reduces the risk of death in patients with Ebola virus disease who were vaccinated before and even after exposure.[17–19]

Randomised clinical trials are the gold standard to assess efficacy and effectiveness of a vaccine against disease, symptomatic disease, or severe outcomes.[10] Observational studies can be used to estimate effectiveness using routinely collected data, even when clinical trials are infeasible. Under the test-negative study design, effectiveness is estimated from the odds ratio (OR) of being vaccinated versus unvaccinated among test-positive cases versus test-negative controls who sought care at health facilities and met the suspected case definition. Test-negative studies have been used to estimate the effectiveness of vaccination against influenza,[21–23] symptomatic cholera,[24,25] pneumococcal pneumonia,[26] and COVID-19.[27,28] The primary strengths of this study design are ease of implementation (since cases and controls are passively recruited at health centres) and that the study can be applied retrospectively to sufficiently detailed, systematically collected, operational data.

We aimed to retrospectively estimate the effectiveness of rVSV-ZEBOV vaccination against Ebola virus disease during the 2018–20 Ebola virus disease outbreak in the Democratic Republic of the Congo.

Methods

Study design and data source

We used a test-negative design in which the study population comprised individuals who were reported as having suspected Ebola virus disease across Ebola virus disease facilities (12 treatment, nine transit, and 21 decentralised facilities) in the Democratic Republic of the Congo during the country's tenth Ebola virus disease outbreak, and who met the eligibility criteria described below. Cases were defined as those who tested positive

for Ebola virus disease among this population, while controls were those who tested negative.

Throughout the outbreak, standardised patient data were recorded on line lists in Microsoft Excel software by data managers at each Ebola virus disease facility. The Excel template was the same for all facilities and was based on the information collected on paper case report forms for suspected Ebola virus disease. Every week, the line lists were compiled into a centralised case management database. This analysis is based on the final version of this compiled database, henceforth referred to as the Ebola treatment centre (ETC) line list, reflecting all patients admitted to an Ebola virus disease facility at any point in the outbreak (July 27, 2018 to June 24, 2020).

This study is a retrospective analysis of data collected for clinical purposes during the emergency response to an Ebola virus disease epidemic, not in the context of research. It 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.

Eligibility criteria

All individuals who met the definition for a suspected cases of Ebola virus disease (appendix 2 p 3) and who were recorded in the ETC line list were assessed for eligibility to be included in the analysis. Individuals were eligible for inclusion if they had an available RT-PCR result (those with inconclusive or missing RT-PCR test results were excluded) and available key data (individuals missing vaccination status, date of symptom onset, or resident health zone were excluded).

Additionally, we excluded those ineligible for vaccination during the outbreak: all children younger than 6 months, in addition to children aged 6–12 months and pregnant or breastfeeding women with symptom onset before June 20, 2019 (7 days after June 13, 2019, when they were first eligible for vaccination under the revised vaccination protocol). Health-care workers, who were vaccinated under a different strategy to the general population and had different risks of exposure to the virus, were also excluded.

We also excluded individuals with a date of symptom onset before Aug 18, 2018 (10 days after Aug 8, 2018, when vaccination started) or after Nov 30, 2019 (when the vaccination protocol changed from ring vaccination only to ring vaccination plus geographically targeted vaccination in areas where ring vaccination was not possible due to security concerns).

Procedures and definitions

Ebola virus disease status was determined by reverse-transcription PCR (RT-PCR) and recorded in the ETC line list as Ebola virus disease-positive (cases) or Ebola virus disease-negative (controls). An individual's vaccination history was self-reported and classified according to vaccination status (vaccinated or unvaccinated) and, for vaccinated individuals, vaccination–onset delay (defined as the time [days] between the date of vaccination and the date of symptom onset [ie, the date on which signs or symptoms of Ebola virus disease first appeared]). Missing data, including missing vaccination–onset delay, were subsequently imputed from observed data (see Statistical analysis and appendix 2 p 5 for imputation methods). Exposure to Ebola virus disease was defined as contact with an individual with Ebola virus disease in the 21 days before symptom onset. Other risk factors for exposure were also recorded, including visiting a health-care facility, visiting a traditional healer, and attending a funeral.

Each case was matched to one control by sex, age group (0–4, 5–14, 15–29, 30–59, and ≥60 years), resident health zone, and calendar month of symptom onset. We matched exactly one control per case so that as many cases as possible could be matched. In each matching strata (defined by values of the matching variables), case and controls were selected uniformly at random from all eligible individuals.

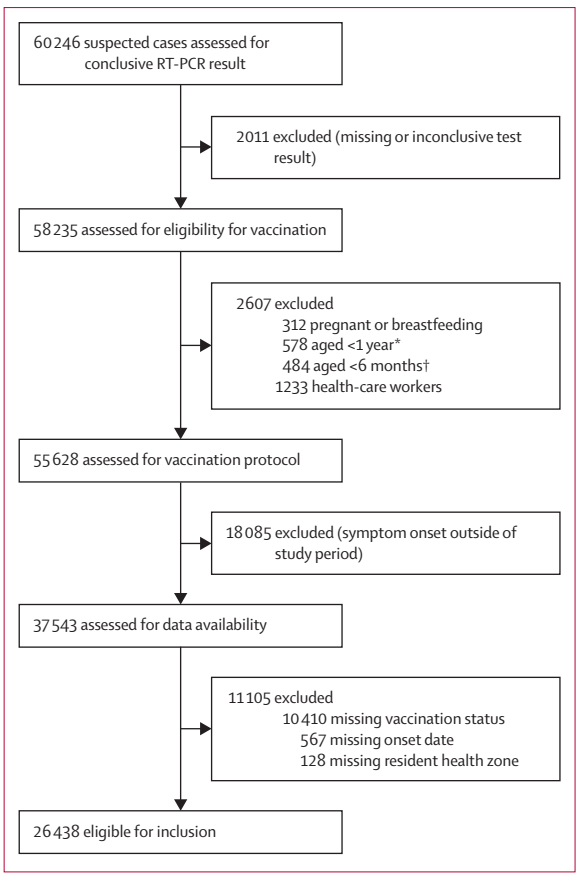

Figure 1: **Assessment of eligibility for study inclusion**
*Onset before June 20, 2019. †Onset from June 20, 2019.

See **Online** for appendix 2

Statistical analysis

We used multivariate imputation to replace missing data (sex, age, and vaccination–onset delay) with estimated

	Ebola virus disease-positive (n=1273)	Ebola virus disease-negative (n=25 165)
Sex		
Female	742 (58·3%)	12 132 (48·2%)
Male	531 (41·7%)	13 013 (51·8%)
Missing data	0	20
Age, years		
0–4	104 (8·2%)	3654 (14·5%)
5–14	122 (9·6%)	5510 (21·9%)
15–29	443 (34·8%)	8579 (34·1%)
30–59	522 (41·0%)	6344 (25·2%)
≥60	81 (6·4%)	1071 (4·3%)
Missing data	1	7
Health zone*		
Beni	282 (22·2%)	8080 (32·1%)
Butembo	116 (9·1%)	3150 (12·5%)
Kalunguta	87 (6·8%)	639 (2·5%)
Katwa	209 (16·4%)	3361 (13·4%)
Komanda	23 (1·8%)	793 (3·2%)
Mabalako	184 (14·5%)	1496 (5·9%)
Mambasa	43 (3·4%)	748 (3·0%)
Mandima	156 (12·3%)	1305 (5·2%)
Vuhovi	31 (2·4%)	195 (0·8%)
Other	142 (11·2%)	5398 (21·5%)
Month of symptom onset		
August, 2018	2 (0·2%)	8 (<0·1%)
September, 2018	10 (0·8%)	36 (0·1%)
October, 2018	28 (2·2%)	114 (0·5%)
November, 2018	43 (3·4%)	342 (1·4%)
December, 2018	51 (4·0%)	667 (2·7%)
January, 2019	68 (5·3%)	1276 (5·1%)
February, 2019	29 (2·3%)	868 (3·4%)
March, 2019	84 (6·6%)	1309 (5·2%)
April, 2019	147 (11·5%)	1568 (6·2%)
May, 2019	166 (13·0%)	1807 (7·2%)
June, 2019	184 (14·5%)	2002 (8·0%)
July, 2019	195 (15·3%)	2595 (10·3%)
August, 2019	130 (10·2%)	2695 (10·7%)
September, 2019	62 (4·9%)	2949 (11·7%)
October, 2019	47 (3·7%)	3748 (14·9%)
November, 2019	27 (2·1%)	3181 (12·6%)
Vaccination status		
Unvaccinated	940 (73·8%)	20 310 (80·7%)
Vaccinated		
0–2 days before symptom onset	73 (5·7%)	210 (0·8%)
3–9 days before symptom onset	142 (11·2%)	261 (1·0%)
≥10 days before symptom onset	40 (3·1%)	1271 (5·1%)
Unknown time before symptom onset	55 (4·3%)	3044 (12·1%)
After symptom onset	23 (1·8%)	69 (0·3%)

Data are n (%); denominators are non-missing data. *Only the nine health zones that had the most confirmed or probable Ebola virus disease cases are shown, and the category "Other" includes all other health zones.

Table 1: **Characteristics of all eligible individuals**

values, assuming that these data were missing at random but could be inferred from observed data. To account for uncertainty in the missing values, we made 50 imputations. To account for variation arising when randomly selecting cases and controls in each matching strata, we sampled ten case–control matched datasets from each imputed dataset, resulting in 500 samples.

Vaccine effectiveness was estimated using a multivariable Bayesian logistic regression model as (1–OR) × 100%, where OR was the adjusted OR of testing positive for Ebola virus disease after being vaccinated at least 10 days before symptom onset versus being unvaccinated in cases compared with controls, adjusting for the matching variables as fixed effects. We fitted the model independently to each of the 500 imputed-matched population samples using the Markov chain Monte Carlo method. The final estimate of vaccine effectiveness was obtained by pooling the posterior parameter samples across all model fits. We summarised the posterior distribution for vaccine effectiveness by the median and 95% credible interval (CrI) calculated from the posterior 2·5% and 97·5% quantiles. To ensure that cases and controls had a similar risk of exposure to the Ebola virus, in our primary analysis, we considered only individuals who reported contact with an individual with Ebola virus disease; in sensitivity analyses, we considered alternative definitions of Ebola virus disease exposure, by including either additional known risk factors for exposure (visiting a hospital or traditional healer, or attending a funeral), or by using a definition based on whether there were reported cases in the individuals resident health area (admin-3) or health zone (admin-2) in the 21 days before symptom onset. Full details of this sensitivity analysis are given in appendix 2 (p 25).

All analyses were done in R version 4.2.2. Imputation of missing data was done using the R package mice (multivariate imputation by chained equations) version 3.15.0;[29] Bayesian regression models were implemented in the R package brms (Bayesian regression models in stan) version 2.19.0.[30–32] Full details of the statistical methodology, including imputation, matching, and model fitting, are given in appendix 2 (pp 5, 9, 18–19).

Role of the funding source

Employees of the study funder, Médecins Sans Frontières, and its research affiliate, Epicentre, were involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

60 246 suspected cases were assessed for eligibility, of which 26 438 were eligible for inclusion (figure 1). Among all eligible individuals, 1273 (4·8%) were Ebola virus disease-positive (cases) and 25 165 (95·2%) were Ebola virus disease-negative (controls). Cases and controls differed by sex, age, resident health zone, and

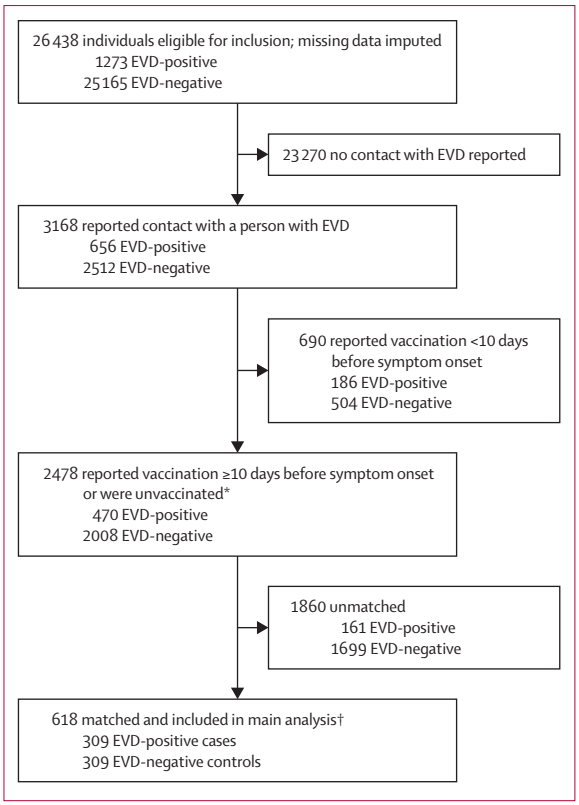

Figure 2: **Selection of cases and controls for primary analysis**
EVD=Ebola virus disease. *Median values reported; values reported vary as a result of imputation of missing data. †Median values reported; values reported vary as a result of imputation of missing data and case–control matching.

calendar month of symptom onset (table 1; appendix 2 p 13). 333 (26·2%) of 1273 cases were reported as being vaccinated, with most vaccinated less than 10 days before symptom onset; only 40 (3·1%) cases were vaccinated at least 10 days before symptom onset. Conversely, 4855 (19·3%) of 25 165 controls were reported as being vaccinated, with 1271 (5·1%) vaccinated at least 10 days before symptom onset. Date of vaccination was missing for 55 (4·3%) cases and for 3044 (12·1%) controls. Ebola virus disease exposure was significantly different between cases and controls: 656 (51·5%) cases reported contact with an individual with Ebola virus disease during the 21 days before symptom onset, compared with only 2512 (10·0%) controls (appendix 2 p 15).

Our primary study population comprised matched cases and controls (matched by sex, age group, residence health zone, and month of symptom onset) who reported contact with an Ebola virus disease case, and were unvaccinated, or vaccinated at least 10 days before symptom onset. These constraints substantially reduced the size of the study population (figure 2). Each imputed-matched sample of the primary study population comprised a median of 309 cases and 309 controls (range 302–315), of which 15 cases (4·9% [IQR 4·6–5·4;

	Ebola virus disease-positive (n=309)	Ebola virus disease-negative (n=309)
Sex		
Female	171 (55·3%)	171 (55·3%)
Male	138 (44·7%)	138 (44·7%)
Age, years		
0–4	20 (6·5%)	20 (6·5%)
5–14	29 (9·4%)	29 (9·4%)
15–29	110 (35·6%)	110 (35·6%)
30–59	138 (44·7%)	138 (44·7%)
≥60	12 (3·9%)	12 (3·9%)
Health zone*		
Beni	128 (41·4%)	128 (41·4%)
Butembo	23 (7·4%)	23 (7·4%)
Kalunguta	21 (6·8%)	21 (6·8%)
Katwa	60 (19·4%)	60 (19·4%)
Komanda	4 (1·3%)	4 (1·3%)
Mabalako	35 (11·3%)	35 (11·3%)
Mambasa	6 (1·9%)	6 (1·9%)
Mandima	15 (4·9%)	15 (4·9%)
Vuhovi	5 (1·6%)	5 (1·6%)
Other	12 (3·9%)	12 (3·9%)
Month of symptom onset		
August, 2018	1 (0·3%)	1 (0·3%)
September, 2018	0	0
October, 2018	5 (1·6%)	5 (1·6%)
November, 2018	11 (3·6%)	11 (3·6%)
December, 2018	10 (3·2%)	10 (3·2%)
January, 2019	17 (5·5%)	17 (5·5%)
February, 2019	7 (2·3%)	7 (2·3%)
March, 2019	11 (3·6%)	11 (3·6%)
April, 2019	35 (11·3%)	35 (11·3%)
May, 2019	54 (17·5%)	54 (17·5%)
June, 2019	45 (14·6%)	45 (14·6%)
July, 2019	71 (23·0%)	71 (23·0%)
August, 2019	26 (8·4%)	26 (8·4%)
September, 2019	9 (2·9%)	9 (2·9%)
October, 2019	4 (1·3%)	4 (1·3%)
November, 2019	3 (1·0%)	3 (1·0%)
Vaccination status		
Unvaccinated	294 (95·1%)	244 (79·0%)
Vaccinated (≥10 days before symptom onset)	15 (4·9%)	65 (21·0%)

Data are n (%). Since exact counts for each characteristic can vary across each imputed-matched population sample, this table shows values for a single imputed-matched sample in which the number of cases and controls, and the number who reported being vaccinated ≥10 days before symptom onset, are all equal to the median values across all imputed-matched samples. See appendix 2 (pp 5–6, 9–10, 15–17) for details of the imputation and matching processes, and for details on the variation in each characteristic across all imputed-matched samples. *Only the nine health zones that had the most confirmed or probable Ebola virus disease cases are shown, and the category "Other" includes all other health zones.

Table 2: **Characteristics of the matched primary study population by Ebola virus disease status**

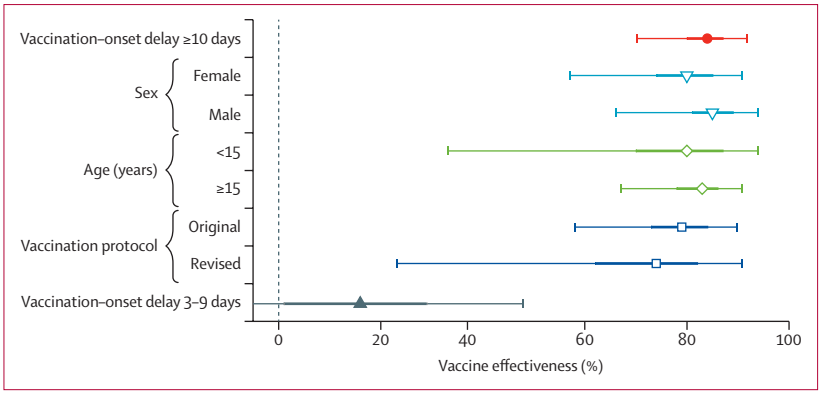

Figure 3: **Effectiveness of rVSV-ZEBOV vaccination against Ebola virus disease**
Estimated effectiveness against Ebola virus disease of rVSV-ZEBOV vaccination after at least 10 days (primary analysis) is shown in red, with stratification by sex, age, and vaccination protocol shown below. Estimated effectiveness against Ebola virus disease 3–9 days after vaccination is shown in grey. All estimates are median estimate, 50% posterior credible intervals (thick lines), and 95% posterior credible intervals (thin lines). Estimates were adjusted for sex, age group, and time-place strata (defined by month of symptom onset and resident health zone). The x-axis is truncated at zero for clarity; values are reported in the main text and appendix 2 (p 21).

range 3·6–7·4]) and 65 controls (21·1% [IQR 20·1–22·0; range 15·6–25·7]) were vaccinated at least 10 days before symptom onset (table 2; appendix 2 p 16). The primary study population was mostly female, aged 15–59 years, from Beni, Katwa, and Mabalako health zones, and had symptom onset between April and August, 2019, inclusive (table 2; appendix 2 p 17).

We estimated that 10 or more days after vaccination, the effectiveness of rVSV-ZEBOV vaccination against Ebola virus disease was 84% (95% CrI 70 to 92; figure 3; appendix 2 p 21). When stratified by sex, effectiveness was 80% for females (57 to 91) and 86% for males (66 to 94; figure 3; appendix 2 p 22). Stratified by age, effectiveness was 80% (33 to 94) for children younger than 15 years, and 83% (67 to 91) for adults (aged ≥15 years; figure 3; appendix 2 p 22). Stratified estimates of effectiveness for children younger than 5 years were very limited by sample size (only 21 matched, out of 31 possible cases and 324 possible controls), resulting in wide uncertainty (median 71% [–9 to 92]; appendix 2 p 22). When stratified by vaccination protocol, effectiveness was 79% (58 to 90) under the original protocol, and 71% (14 to 91) under the revised protocol (including both broader eligibility and halved dose; figure 3; appendix 2 p 23). Finally, after 3 to 9 days, effectiveness of rVSV-ZEBOV vaccination against Ebola virus disease was 16% (–35 to 48; appendix 2 p 24).

Estimated effectiveness was robust under alternative definitions of possible Ebola virus disease exposure (appendix 2 p 25). When defined as any reported risk (among contact with an Ebola virus disease case, visiting a health facility, visiting a traditional healer, and attending a funeral), estimated effectiveness at 10 or more days after vaccination was 82% (95% CrI 67–91). When defined as any Ebola virus disease cases in the resident health zone or health area, estimated effectiveness at 10 or more days after vaccination was 79% (66–87). Effectiveness was also robust when the suspected case definition was applied post hoc (median 82% [64–91]; appendix 2 p 26) or when inclusion was restricted to patients with at least one symptom of severe Ebola virus disease (median 83% [68–91]; appendix 2 p 27).

Misreporting of individuals' vaccination statuses could result in both underestimation and overestimation of vaccine effectiveness, depending on their Ebola virus disease status and original vaccination status, and how often misreporting occurred (appendix 2 p 33). When simulating the potential effect of misreporting, the largest unilateral effect was found for misreporting among unvaccinated cases: if 5% of cases reported as unvaccinated were actually vaccinated, then estimated effectiveness would be 67% (95% CrI 44–73; appendix 2 p 33).

Finally, estimates were robust to methodological choices, namely matching criteria between cases and controls (appendix 2 p 10), and the choice of prior distribution for effectiveness (appendix 2 p 19).

Discussion

Our results show that vaccination with rVSV-ZEBOV was highly protective against developing Ebola virus disease at 10 or more days after vaccination (effectiveness 84% [95% CrI 70–92]). This is, at the time of writing and to our knowledge, the only published estimate of the real-world effectiveness of the vaccine and is based on the, to date, most widespread use of the rVSV-ZEBOV vaccine outside of a clinical trial.

Our estimate of effectiveness was compatible with the findings of the *Ebola Ça Suffit!* ring vaccination trial (100% efficacy [95% CI 69–100]).[10] While this earlier result ultimately led to prequalification and use of the rVSV-ZEBOV vaccine in outbreak responses, the study and its interpretation had some limitations. In particular, some experts have expressed uncertainties about the magnitude of the vaccine's efficacy, but have noted that, in a confirmatory controlled trial, it would be unethical to deny the vaccine to anyone at risk.[13,14] The observational study design allowed us to estimate effectiveness without the same ethical challenges. Lower central estimates of effectiveness compared with efficacy were expected due to operational factors such as vaccine failure resulting from cold-chain failure; inadequate dosing; inadequate vaccine administration technique; immunosuppression; or due to the observational nature of the study and associated incomplete documentation.

Our results are lower than preliminary estimates from the 2018–20 Ebola virus disease outbreak in the Democratic Republic of the Congo (effectiveness 98% [95% CrI 96–99]);[20] however, the majority of breakthrough cases occurred from June, 2019 onwards, whereas these preliminary analyses were based on data only until March, 2019. Differences might additionally be due to contrasting analysis approaches: the preliminary estimate was derived by directly comparing incidence in vaccinated and unvaccinated individuals at risk.

We also did a series of stratified analyses to estimate effectiveness by sex, age, and vaccination strategy (appendix 2 p 21). Although there was no clear evidence of difference in effectiveness between subgroups, some comparisons, such as between children and adults, were limited by sample size and statistical power. As such, further research is required to more concretely ascertain whether there are any differences in effectiveness by age. Our result for individuals vaccinated 3–9 days before symptom onset, similarly limited by a small sample size, indicates a possible mild protective effect, but is also compatible with no effect.

Our study comes with a number of limitations, mainly originating from its observational, retrospective nature and known shortcomings of the test-negative design.[33–36] Cases and controls were selected from a population of suspected Ebola virus disease cases, thus minimising selection bias;[36] despite reports of difficulties adhering to the clinical suspected case definition, retrospectively applying the case definition based on reported signs and symptoms had little effect on estimated effectiveness (appendix 2 p 26). Eligibility criteria decreased the primary study population from initially over 60 000 suspected Ebola cases to 26 438 eligible individuals, with symptom onset outside of the study period and missing key data the main reasons for exclusion. Further limiting our analysis to individuals reporting contact with an individual with Ebola virus disease, who were unvaccinated or were vaccinated more than 10 days before symptom onset, in addition to matching, decreased the sample size to a median of 309 cases and 309 controls. Our analysis included only individuals who reported contact with a person with Ebola virus disease during the 21 days before symptom onset to ensure that cases and controls had a similar risk of exposure to Ebola virus.[35] This exposure was reported in only half of cases, indicating limitations in identifying or reporting Ebola virus disease exposure: as a result, half of the otherwise eligible cases were not included in our analysis, in addition to an unknown number of controls (individuals negative for Ebola virus disease who did have contact with someone with Ebola virus disease, but for whom this was not identified or reported). Although it is impossible to retrospectively classify exposure risk in cases and controls, we found that our estimate of effectiveness was robust to variations in the proxy that we used for exposure (appendix 2 p 25). Differences between demographic characteristics of cases and controls were addressed by matching on participant age, sex, home location, and time; relaxing matching criteria had little effect on estimated effectiveness (appendix 2 p 10). We used multivariate imputation to account for imbalances in missing key data between cases and controls. A complete-case analysis led to compatible but lower vaccine effectiveness estimates (appendix 2 p 7).

Estimates of vaccine effectiveness under the test-negative design can be biased by misclassification of disease or vaccination status. False-positive RT-PCR results have previously been observed in individuals shortly after vaccination,[37] but are unlikely to affect our main findings given that we considered only individuals vaccinated 10 days or more before symptom onset. However, misreporting of an individual's vaccination history is more likely, since vaccination status and date were mostly self-reported; very few were recorded as confirmed by vaccination card. In hypothetical scenarios, we showed that misreporting of vaccination history could result in underestimation or overestimation of effectiveness (appendix 2 p 32), depending on for whom the misclassification occurred and how frequently. Hypothetical unilateral misreporting among unvaccinated cases had the largest absolute effect on estimated effectiveness. In reality, misreporting of vaccination histories might have occurred at different rates according to an individual's disease status, vaccination status, or other factors, and so the magnitude and direction of potential bias cannot be quantified with certainty.

To our knowledge, this is the first published study to assess the effectiveness of rVSV-ZEBOV outside a clinical trial and amid, to date, the most widespread use of the vaccine during the second-largest Ebola virus disease outbreak ever recorded. Our results indicate that rVSV-ZEBOV is highly protective against Ebola virus disease and support its reactive, targeted use in people at risk of exposure during Ebola virus disease outbreaks. While randomised controlled trials are considered the gold standard for estimating vaccine efficacy, ethical concerns are presented by their reliance on control groups consisting of unvaccinated individuals or those vaccinated with a delay following a reported exposure, whereas observational studies such as ours permit vaccine effectiveness to be assessed during outbreak response. Further work on the duration of protection to understand the potential pre-emptive and preventive use of rVSV-ZEBOV during outbreaks and in endemic areas, its potential use as post-exposure prophylaxis, as well as its efficacy in populations particularly susceptible to severe disease and outcomes, such as children and pregnant women, is warranted.

Contributors

SA-M: conceptualisation, writing (review and editing), supervision. AC: conceptualisation, methodology, writing (review and editing). RMC: conceptualisation, writing (review and editing). FF: conceptualisation, methodology, writing (original draft), writing (review and editing), supervision, project administration (lead). EG: conceptualisation, methodology, writing (review and editing), supervision. JJ: conceptualisation, writing (review and editing). RK: conceptualisation, writing (review and editing). SM: conceptualisation, methodology, software (lead), formal analysis (lead), visualisation (lead), writing (original draft; lead), writing (review and editing). EMM: conceptualisation, writing (review and editing). SHBM: conceptualisation, writing (review and editing). JN: conceptualisation, writing (review and editing). ES: conceptualisation, writing (review and editing). AC, RMC, FF, EG, JJ, SM, ES: data curation and interpretation of results as part of the Epicentre-MSF EVD Working Group. All authors had full access to all the data in the study and had final responsibility for the decision to

submit for publication. SM and FF accessed and verified the data underlying the study.

Declaration of interests

We declare no competing interests.

Data sharing

For the **code used in study analyses** see https://github.com/epicentre-msf/ebola-rvsv-effectiveness

Code used in the analyses is available online at GitHub. 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; requests should be addressed to Steve Ahuka-Mundeke (amstev04@yahoo.fr; amstev4@gmail.com).

Acknowledgments

This work was funded by Médecins Sans Frontières (MSF). The following people were part of the Epicentre-MSF EVD Working Group and made valuable contributions to data curation and interpretation of the results: Patrick Barks, Anais Broban, Kerry Dierberg, Francesco Grandesso, Emmanuel Grellety, Gaston Musemakweli Komanda, Pascale Lissouba, Rachel Mahamba, Guyguy Manangama, Germain Mweha, Aminata Laat Sen Ndiaye, Klaudia Porten, and Julien Potet. The authors are thankful for the work performed by numerous members of the Ministry of Health, Epicentre, MSF, and other partner organisations to collect the line list data that made this analysis possible.

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