# Effectiveness of rVSV-ZEBOV vaccination during the 2018 - 2020 Ebola virus disease epidemic in the Democratic Republic of the Congo: a retrospective observational analysis

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## Abstract

**Background.** The rVSV-ZEBOV vaccine is the only WHO prequalified Ebola vaccine recommended for use to respond to *Zaire ebolavirus* outbreaks by the Strategic Advisory Group of Experts (SAGE). A single ring vaccination trial found the efficacy to be 100%, and despite widespread use during several outbreaks, no effectiveness estimates are currently available in the literature.

**Methods.** We conducted a retrospective test-negative case-control analysis to estimate effectiveness of rVSV-ZEBOV vaccination against EVD during the 2018 - 2020 epidemic in the DRC, using a database of over 60,000 suspected cases from all Ebola treatment

centres. Each EVD-positive case was matched to one EVD-negative control by sex, age, health zone and month of symptom onset, and effectiveness estimated from the odds ratio of being vaccinated vs. unvaccinated among cases and controls, after adjusting for the matching factors. Missing demographic data and vaccination-onset delays were imputed using multivariate imputation.

**Findings.** Among all 26,438 eligible individuals, 4.8% were EVD-positive. 3.1% of cases and 5.1% of controls reported to be vaccinated at least ten days before symptoms onset. Effectiveness of rVSV-ZEBOV vaccination when vaccinated at least ten days before symptom onset was 84% (95% credible interval [70%, 92%]). There was no evidence of a change in effectiveness by age, sex, nor due to change in dosing. Estimates were robust to methodological assumptions.

**Interpretation.** This analysis is the first study to provide estimates of real-world effectiveness of the rVSV-ZEBOV vaccine against EVD, amid the, to date, most widespread use of the vaccine during the second largest EVD outbreak ever recorded. Our findings confirm that rVSV-ZEBOV vaccination is highly protective against EVD and support its use to control EVD outbreaks, even in challenging contexts such as the eastern DRC.

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# Research in context

### Evidence before this study

We searched PubMed and Google Scholar for studies published between database inception and 11 April 2024 using the terms (filovirus) OR (Ebola) AND (vaccin*) with no language restrictions. 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 Ebola virus disease (EVD) case. The study found a single dose of rVSV-ZEBOV was highly protective against laboratory-confirmed EVD (efficacy 100%, 95% confidence interval (CI) [69.9, 100]). Preliminary analyses from the 2018-2020 EVD 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, at the time of writing, not available, 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, to date, the most widespread use of the vaccine during the second largest EVD 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 EVD. We found no evidence of changes in effectiveness following changes in dose, nor by age or sex. Estimates were robust to changes in methodological assumptions.

**Implications of all the available evidence**

We found that vaccination with rVSV-ZEBOV at least ten days before symptom onset was highly protective against developing EVD (84% (95% CrI: [70, 92]). Our findings are compatible with the previously published efficacy estimates from Guinea and Sierra Leone, as well as with a preliminary analysis from the DRC outbreak. Using a large, exhaustive dataset of cases and controls, spanning the entire duration of the tenth DRC EVD 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 EVD outbreaks, in combination with other interventions.

# Introduction

Ebola is endemic in the Democratic Republic of Congo (DRC), and as of March 2024 the country has experienced fifteen documented outbreaks of Ebola virus disease (EVD).[1] The tenth outbreak, confirmed on 1 August 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 25 June 2020, a total of 3,470 cases and 2,287 deaths were recorded (CFR 66%), making it the largest reported outbreak in the country, and the second-largest worldwide (in terms of both number of cases and deaths), after only the 2013-2016 epidemic in West Africa.[5]

The recombinant vesicular stomatitis virus–Zaire Ebola virus single-dose vaccine (rVSV-ZEBOV or rVSV∆G-ZEBOV-GP, brand name Ervebo®) was prequalified by WHO in November 2019[6] and is currently recommended by the WHO Strategic Advisory Group of Experts (SAGE) for Immunisation for at-risk individuals during Ebola Zaire outbreaks.[7,8] In a phase 3 cluster-randomised ring vaccination trial in Guinea and Sierra Leone (*Ebola Ça Suffit!*) during the 2013-2016 epidemic in West Africa, vaccine efficacy was estimated to be 100% (95% confidence interval (CI) [69, 100]).[9,10] This is the only efficacy value available to date. The vaccine was deployed during the tenth Ebola outbreak in the DRC under the Expanded Access framework[11] following the WHO-recommended strategy based on reactive ring vaccination and targeting at-risk individuals including, but not limited to, contacts of Ebola cases and contacts of contacts and front line workers.[7] Vaccination activities began on 08 August 2018 [12] and over 300,000 individuals were vaccinated during the course of the outbreak.[5] Following SAGE guidelines, the vaccination strategy was revised in mid-June 2019 to include pregnant and breastfeeding women and infants

between 6 and 12 months old, who were initially ineligible for vaccination; and the dose was also decreased by half.[8,13]

Real-world effectiveness of rVSV-ZEBOV vaccination is expected to be less than 100%.[14,15] During the 2018-2020 DRC outbreak, national and international agencies recorded confirmed EVD cases in vaccinated individuals, including among individuals who were reported as having been vaccinated ten or more days before symptom onset.[16–19] Preliminary, unadjusted analyses estimated vaccine effectiveness as 98% (95% CI [96, 99]).[20] Other studies have shown that rVSV-ZEBOV vaccination reduces the risk of dying among EVD patients who were vaccinated before and even after exposure.[18,19,21]

Randomised clinical trials are the gold standard to assess efficacy and effectiveness of a vaccine against infection, symptomatic disease, or severe outcomes.[10] When clinical trials are infeasible, observational studies can be used to estimate effectiveness using routinely collected data. Under the test-negative study design, effectiveness is estimated from the odds ratio of being vaccinated vs. unvaccinated among test-positive cases versus test-negative controls who sought care at health facilities and met the suspected case definition. Recently, the test-negative studies have been used to estimate the effectiveness of vaccination against influenza,[22–26] symptomatic cholera,[27–29] pneumococcal pneumonia hospitalisation,[30] and symptomatic COVID-19 infection or hospitalisation.[31,32] The primary strengths of the 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.

In this analysis we used a test-negative study design to retrospectively estimate effectiveness of rVSV-ZEBOV vaccination against EVD during the tenth EVD outbreak in the DRC.

# Methods

## Data

Throughout the tenth EVD outbreak in the DRC, standardised patient data were recorded on Excel line lists by the data managers of each EVD facility (12 treatment, 9 transit, and 21 decentralised facilities). The Excel template was the same for all facilities and was based on the information collected on the paper case report forms for suspected EVD. Every week, the Excel 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 ETC line list, reflecting all patients admitted to an EVD facility at any point in the outbreak (27 July 2018 – 24 June 2020).

EVD infection status was determined by reverse transcription polymerase chain reaction (RT-PCR) and recorded in the ETC line list as EVD-positive or EVD-negative. Individuals' vaccination history was self-reported and defined according to vaccination status (vaccinated or unvaccinated) and, for vaccinated individuals, the time (days) between date of vaccination and date of symptom onset (the date on which signs or symptoms of EVD

first appeared), henceforth referred to as vaccination-onset delay. Missing data, including missing vaccination-onset delays, were subsequently imputed from observed data. Exposure to EVD was defined as contact with an Ebola case in the 21 days before symptom onset. Other risk factors for exposure were also recorded, including visiting a healthcare facility, visiting a traditional healer and attending a funeral.

## Eligibility

All individuals who met the definition for a suspected Ebola case (given in the supplementary information) and were recorded in the ETC line list were assessed for eligibility to be included in the analysis according to the following criteria:

**Positive or negative RT-PCR result.** Individuals with inconclusive or missing RT-PCR test results were excluded.

**Eligibility for vaccination.** Some individuals were not eligible to receive the rVSV-ZEBOV vaccine during the outbreak; these individuals were therefore excluded from subsequent analyses. We excluded all children less than six months old, plus children 6 - 12 months old and pregnant or breastfeeding women with symptom onset before 20 June 2019 (seven days after 13 June 2019, when they were first eligible for vaccination under the revised vaccination protocol). Additionally, we excluded healthcare workers, who were vaccinated under a different strategy to the general population and had different risks of exposure to the virus.

**Vaccination strategy**. We excluded individuals with a date of symptom onset before 18 August 2018 (10 days after 08 August 2018 when vaccination started) or after 30 November 2019 (when the vaccination strategy changed and wider geographically targeted vaccination was introduced in some areas where ring vaccination wasn't possible due to security concerns).

**Availability of key data.** Individuals missing any of the following key variables were excluded: vaccination status, date of symptom onset, or resident health zone.

## Study design

We used a test-negative design in which the study population comprised individuals who were reported as suspected EVD cases on the ETC line list and met the eligibility criteria described above. Effectiveness of rVSV-ZEBOV vaccination against infection was estimated from the odds ratio of being vaccinated at least ten days before symptom onset vs. unvaccinated among individuals who were confirmed EVD-positive compared to those who were confirmed EVD-negative. 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 EVD case; in sensitivity analyses, we considered alternative definitions of EVD exposure.

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 only matched 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.

## Statistical methods

Vaccine effectiveness was estimated using a multivariable Bayesian logistic regression model, as VE = (1 - OR) x 100%, where OR was the adjusted odds ratio of testing positive for EVD after being vaccinated at least ten days before symptom onset vs. being unvaccinated. We adjusted for the matching variables as fixed-effects. We used multivariate imputation to replace missing data (sex, age, and vaccination-onset delay) with estimated values, assuming that these data are missing at random but can be inferred from observed data. To account for uncertainty in the missing values we made 50 imputations. Then, from each of the imputed data sets, we sampled ten case-control matched data sets, and fit our model independently to each imputed-matched population sample using Markov-chain Monte Carlo (MCMC). Full details of the statistical methodology, including imputation, matching, and model fitting, are given in the supplementary information. 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.

# Results

## Study population

A total of 60,246 suspected cases were assessed for eligibility, of which 26,438 were eligible for inclusion (supplementary Figure S8). Among all eligible individuals, 1,273 were EVD-positive and 25,165 were EVD-negative, henceforth referred to as cases and controls, respectively. Cases and controls differed by sex, age, resident health zone, and calendar month of symptom onset (supplementary Table S1 and Figure S9). Approximately one quarter (26%) of cases were reported as being vaccinated, of which the majority were vaccinated less than ten days before symptom onset: only 3.1% of cases were vaccinated at least ten days before symptom onset. Conversely, 19% of controls were reported as being vaccinated, of which 5.1% were vaccinated at least ten days before symptom onset. Date of vaccination was missing for only 4.3% of cases, but for 12% of controls. Unsurprisingly, EVD exposure was also significantly different between cases and controls: 52% of cases reported contact with an EVD case during the 21 days before symptom onset, compared to only 10% of controls (supplementary Table S2).

Our primary study population comprised individuals who were unvaccinated, or vaccinated at least ten days before symptom onset, and who reported contact with an EVD case. These constraints, along with the case-control matching process, substantially reduced the size of the study population. Each imputed-matched sample of the primary study population comprised on average 309 cases and controls (range 302 - 315), of which 15 cases (4.9%; range 3.6 – 7.4%) and 65 controls (21%; range 16 – 26%) were vaccinated at

least ten days before symptom onset (Table 1 and supplementary Figure S10). The primary study population was majority female, between 15 and 59 years old, from Beni, Katwa, and Mabalako health zones and had symptom onset between April and August 2019 inclusive (Table 1 and supplementary Figure S11).

| | **EVD-pos**, N = 309[1] | **EVD-neg**, N = 309[1] |
|---|---|---|
| **Sex** | | |
| Female | 171 (55%) | 171 (55%) |
| Male | 138 (45%) | 138 (45%) |
| **Age (years)** | | |
| 0-4 | 20 (6.5%) | 20 (6.5%) |
| 5-14 | 29 (9.4%) | 29 (9.4%) |
| 15-29 | 110 (36%) | 110 (36%) |
| 30-59 | 138 (45%) | 138 (45%) |
| 60+ | 12 (3.9%) | 12 (3.9%) |
| **Health zone** | | |
| Beni | 128 (41%) | 128 (41%) |
| Butembo | 23 (7.4%) | 23 (7.4%) |
| Kalunguta | 21 (6.8%) | 21 (6.8%) |
| Katwa | 60 (19%) | 60 (19%) |
| Komanda | 4 (1.3%) | 4 (1.3%) |
| Mabalako | 35 (11%) | 35 (11%) |
| 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 symptom onset** | | |
| 2018-08 | 1 (0.3%) | 1 (0.3%) |
| 2018-09 | 0 (0%) | 0 (0%) |
| 2018-10 | 5 (1.6%) | 5 (1.6%) |
| 2018-11 | 11 (3.6%) | 11 (3.6%) |
| 2018-12 | 10 (3.2%) | 10 (3.2%) |
| 2019-01 | 17 (5.5%) | 17 (5.5%) |
| 2019-02 | 7 (2.3%) | 7 (2.3%) |
| 2019-03 | 11 (3.6%) | 11 (3.6%) |
| 2019-04 | 35 (11%) | 35 (11%) |
| 2019-05 | 54 (17%) | 54 (17%) |
| 2019-06 | 45 (15%) | 45 (15%) |
| 2019-07 | 71 (23%) | 71 (23%) |
| 2019-08 | 26 (8.4%) | 26 (8.4%) |
| 2019-09 | 9 (2.9%) | 9 (2.9%) |
| 2019-10 | 4 (1.3%) | 4 (1.3%) |
| 2019-11 | 3 (1.0%) | 3 (1.0%) |
| **Vaccination status** | | |
| Unvaccinated | 294 (95%) | 244 (79%) |
| Vaccinated (10+ days) | 15 (4.9%) | 65 (21%) |

[1] n (%)

**Table 1: Characteristics of the matched primary study population by EVD infection status.** The primary study population comprises eligible individuals who were either unvaccinated, or vaccinated at least ten days before symptom onset, and reported contact with an Ebola case during the 21 days before symptom onset. Each case was matched to one control by sex, age group, health zone, and month of symptom onset. We report counts and proportions by sex, age group (years), resident health zone, month of symptom onset, and vaccination status, disaggregated by EVD infection status. Since exact counts for each characteristic can vary across each imputed-matched population sample, Table 1 shows values for a single imputed-matched sample in which the number of cases and controls, and the number that reported being vaccinated at least ten days before symptom onset, are all equal to the median values across all imputed-matched samples. See the supplementary information for details of the imputation and matching processes, and for details on the variation in each characteristic across all imputed-matched samples.

## Vaccine effectiveness

We estimated that the effectiveness of rVSV-ZEBOV vaccination against EVD for individuals who were vaccinated at least ten days before symptom onset was 84% (95% posterior credible interval (CrI): [70, 92]) (Figure 1). We found no clear evidence of difference in effectiveness by sex (Figure 1 and SI section 6.2.2), although estimated effectiveness was marginally lower for females (median 80%; 95% CrI [57, 91]) versus males (median 86%; 95% CrI [66, 94]). Similarly, there was no clear difference in effectiveness for children (under five or under fifteen years old) compared to adults (at least fifteen years old), although point estimates decreased slightly with age (83% for adults; 80% for children under fifteen years old; 71% for children under five years old: Figure 1 and SI section 6.2.3). Sample size and statistical power to estimate effectiveness in under five year olds were low, resulting in a posterior credible interval including zero. Vaccine effectiveness under the original protocol was 79% (95% CrI [58, 90]), compared to 71% (95% CrI [14, 91]) under the revised protocol (i.e. decreased dose) (Figure 1); again, sample size and statistical power for the revised protocol population were low, hence the very wide uncertainty (SI section 6.2.1). Finally, effectiveness of rVSV-ZEBOV vaccination against EVD infection when vaccinated between three and nine days before symptom onset was 16% (95% CrI [-35, 48]) (SI section 6.2.4).

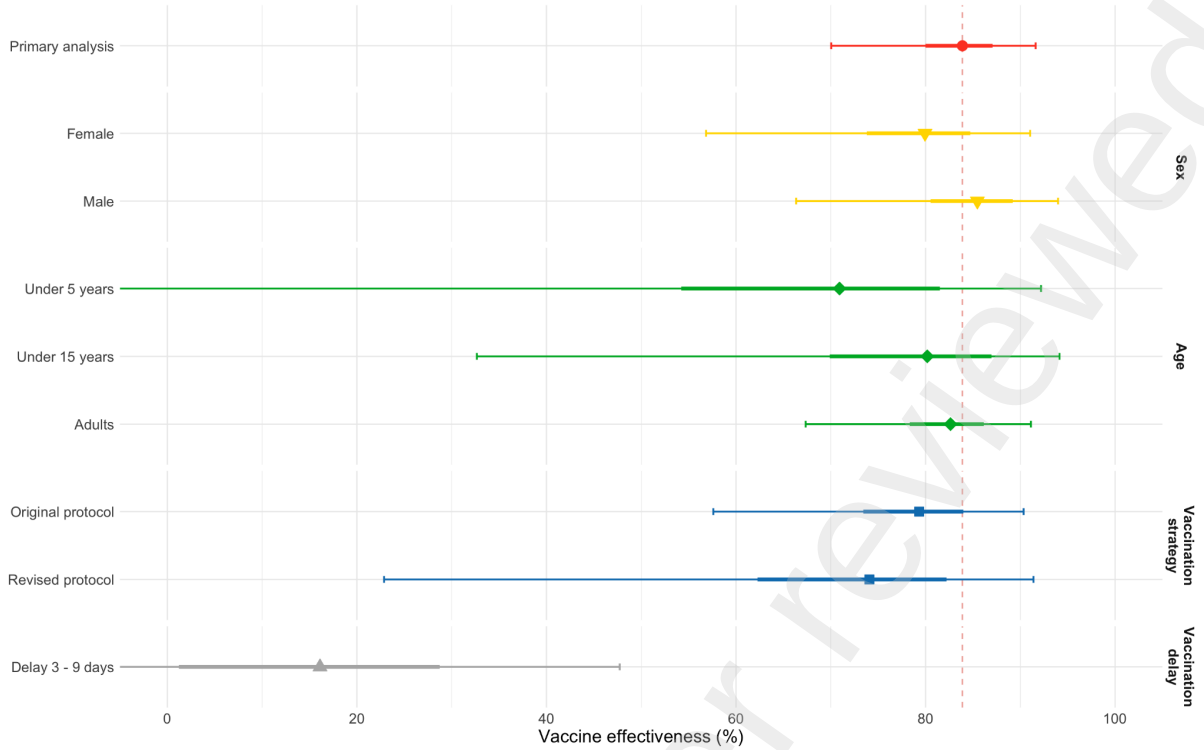


**Figure 1: Effectiveness of rVSV-ZEBOV vaccination against Ebola virus disease.** Estimated effectiveness of rVSV-ZEBOV vaccination when vaccinated at least ten days before symptom onset (primary analysis) is shown in red. Estimated effectiveness stratified by age (under five years, under fifteen years, and at least fifteen years), and vaccination protocol (original protocol before 13 June 2019; revised protocol from 13 June 2019 onwards, including decreased dose) are shown in green and blue, respectively. Estimated effectiveness when vaccinated between three and nine days before symptom onset is shown in grey. For all estimates we show the median (point) estimate and 50% and 95% posterior credible intervals (thick and thin lines, respectively). All 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 in the supplementary information section 6.2.

Misreporting of individuals' vaccination statuses could result in both under- and over-estimation of vaccine effectiveness, depending on their EVD infection status and original vaccination status, and how often misreporting occurred (SI section 7). When simulating the potential effect of misreporting, the largest unilateral effect occurred for misreporting among unvaccinated cases: if 5% of unvaccinated cases were actually vaccinated, then estimated effectiveness would be 67% (95% CrI [44, 73]). Estimated effectiveness was robust to technical assumptions and methodological choices assessed in sensitivity analyses, including: handling of missing data (SI section 2.3), matching criteria between cases and controls (SI section 3.2), the prior distribution used for effectiveness (SI section 5.2), the definition of EVD exposure (SI section 6.3), and the suspected case definition (SI section 6.4).

# Discussion

Our results show that vaccination with rVSV-ZEBOV at least ten days before symptom onset was highly protective against developing EVD (84% effectiveness, 95% CrI [70, 92]).

This is, 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 vaccine.

Our estimate of effectiveness was compatible with the *Ebola Ça Suffit!* ring vaccination trial (100% efficacy, 95% CI [69, 100]).[10] While this result ultimately led to the licensure and use of the rVSV-ZEBOV vaccine in outbreak response, 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 to efficacy were expected, due to operational factors such as: vaccine failure as a result of cold-chain failure; inadequate dosing; inadequate vaccine administration technique, and; immunosuppression or due to the observational nature of the study and associated incomplete documentation.

Our results are lower than preliminary estimates from the 2018-2020 EVD outbreak in the DRC (98% effectiveness; 95% CrI [96, 99]);[20] however, the majority of breakthrough infections occurred from June 2019 onwards, whereas these preliminary analyses are based on data until March 2019 only. Differences may additionally be due to contrasting analysis approaches: the preliminary estimate was derived by directly comparing incidence in vaccinated and unvaccinated at-risk individuals.

We also carried out a series of analyses to estimate effectiveness by sex, age, and vaccination strategy (supplementary information section 6.2). While we found no clear difference in effectiveness between subgroups, some comparisons were ultimately limited by sample size and statistical power: Our result for individuals vaccinated between three and nine 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 EVD 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 (SI Section 6.4). To ensure that cases and controls had a similar risk of exposure to the Ebola virus,[35] our analysis included only individuals who reported contact with an EVD case during the 21 days before symptom onset. This exposure was reported in only half of cases, indicating some limitations in identifying or reporting EVD exposure: as a result, half of the otherwise eligible cases were not included in our analysis, in addition to an unknown number of controls (EVD-negative individuals who did have contact with an EVD case, 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 (SI section 6.3). Confounding due to differences between cases and controls was addressed by matching on participant age, sex, home location, and time; using alternative matching criteria had little effect on estimated effectiveness (SI Section 3.2).

Estimates of vaccine effectiveness under the test-negative design can be biased by misclassification of individuals' infection and/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 consider only individuals vaccinated ten 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 under- or over-estimation of effectiveness (SI Section 7.2), depending on for whom the misclassification occurred and how frequently. Hypothetical unilateral misreporting among unvaccinated cases had the largest absolute effect on estimated effectiveness: for example, if 5% of reportedly unvaccinated cases were actually vaccinated at least ten days before symptom onset, estimated effectiveness would be 67%, compared to 84% for no misreporting. In reality, misreporting of individuals' vaccination history may have occurred at different rates according to their infection 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 EVD outbreak ever recorded. Our results indicate that rVSV-ZEBOV is highly protective against EVD and support its reactive, targeted use in at-risk people during EVD outbreaks. While randomised controlled trials are considered the gold standard for estimating vaccine efficacy, their reliance on an unvaccinated or delay-vaccinated control group presents ethical concerns; 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 preemptive 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 particularly vulnerable populations such as children and pregnant women is warranted.

# Declarations

## Ethical considerations

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. It was conducted with the approval and collaboration of the Ministry of Health of the Democratic Republic of the Congo. As data were deidentified, the risk to patients was minimal.

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## Authors' contributions

Authors listed alphabetically. **Steve Ahuka-Mundeke:** conceptualisation (equal); writing - review and editing (equal). **Anton Camacho:** conceptualisation (equal); methodology (equal); writing - review and editing (equal). **Rebecca M. Coulborn:** conceptualisation (equal); writing - review and editing (equal). **Flavio Finger:** conceptualisation (equal); methodology (equal); writing - original draft (supporting); writing - review and editing (equal); project administration (lead). **Etienne Gignoux:** conceptualisation (equal); methodology (equal); writing - review and editing (equal). **John Johnson:** conceptualisation (equal); writing - review and editing (equal). **Richard Kitenge:** conceptualisation (equal); writing - review and editing (equal). **Sophie Meakin:** conceptualisation (equal); methodology (equal); statistical analysis and implementation (lead); writing - original draft (lead); writing - review and editing (equal). **Elisabeth Mukamba Musenga:** conceptualisation (equal); writing - review and editing (equal). **Stephane Hans Bateyi Mustafa:** conceptualisation (equal); writing - review and editing (equal). **Justus Nsio:** conceptualisation (equal); writing - review and editing (equal). **Esther Sterk:** conceptualisation (equal); writing - review and editing (equal). All authors, including members of the Epicentre-MSF EVD Working Group, contributed to data curation, interpreted the results, and approved the work for publication.

## Competing interests

The authors declare they have no competing interests.

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## Availability of data and materials

All analyses were carried out in R version 4.2.2. Imputation of missing data were performed using the R package mice v3.15.0 (Multivariate Imputation by Chained Equations); Bayesian regression models are implemented in the R package brms v2.19.0 (Bayesian Regression Models in Stan). Code is available online at github.com/epicentre-msf/ebola-rvsv-effectiveness.

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.

# References


1 Democratic Republic of Congo declares new Ebola outbreak in Mbandaka. World Health Organisation, 2022 https://www.afro.who.int/countries/democratic-republic-of-congo/news/democratic-republic-congo-declares-new-ebola-outbreak-mbandaka.

2 2018 - Democratic Republic of the Congo. World Health Organisation, 2018 https://www.who.int/emergencies/disease-outbreak-news/item/4-august-2018-ebola-drc-en.

3 Ilunga Kalenga O, Moeti M, Sparrow A, Nguyen V-K, Lucey D, Ghebreyesus TA. The Ongoing Ebola Epidemic in the Democratic Republic of Congo, 2018–2019. *N Engl J Med* 2019; **381**: 373–83.

4 Jombart T, Jarvis CI, Mesfin S, *et al.* The cost of insecurity: from flare-up to control of a major Ebola virus disease hotspot during the outbreak in the Democratic Republic of the Congo, 2019. *Eurosurveillance* 2020; **25**: 1900735.

5 Ebola virus disease - African Region (AFRO), Democratic Republic of the Congo. World Health Organisation, 2020 https://www.who.int/emergencies/disease-outbreak-news/item/2020-DON284.

6 WHO prequalifies Ebola vaccine, paving the way for its use in high-risk countries. World Health Organisation, 2019 https://www.who.int/news/item/12-11-2019-who-prequalifies-ebola-vaccine-paving-the-way-for-its-use-in-high-risk-countries.

7 Ebola virus disease. World Health Organisation, 2023 https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease.

8 Strategic Advisory Group of Experts on Immunization. Interim Recommendations on Vaccination against Ebola Virus Disease (EVD). 2019 https://cdn.who.int/media/docs/default-source/immunization/ebola/interim-ebola-recommendations-may-2019.pdf?sfvrsn=c54ce264_9.

9 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. *The Lancet* 2015; **386**: 857–66.

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!). *The Lancet* 2017; **389**: 505–18.

11 Strategic Advisory Group of Experts on Immunization. Meeting of the Strategic Advisory Group of Experts on Immunization, April 2017: conclusions and recommendations. 2017: 301–20.

12 Ebola vaccination begins in North Kivu. World Health Organisation, 2018 https://www.who.int/news-room/detail/08-08-2018-ebola-vaccination-begins-in-north-kivu.

13 SAGE Ebola Vaccines – Session 7: Overview of the evidence and recommendations. World Health Organisation, 2019.

14 Committee on Clinical Trials During the 2014-2015 Ebola Outbreak, Board on Global Health, Board on Health Sciences Policy, Health and Medicine Division, National Academies of Sciences, Engineering, and Medicine. Integrating Clinical Research into Epidemic Response: The Ebola Experience. Washington, D.C.: National Academies Press, 2017.

15 Metzger WG, Vivas-Martínez S. Questionable efficacy of the rVSV-ZEBOV Ebola vaccine. *The Lancet* 2018; **391**: 1021.

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 Mbala-Kingebeni P, Pratt C, Mutafali-Ruffin M, *et al.* Ebola Virus Transmission Initiated by Relapse of Systemic Ebola Virus Disease. *N Engl J Med* 2021; **384**: 1240–7.

18 Rupani N, Ngole ME, Lee JA, *et al.* Effect of Recombinant Vesicular Stomatitis Virus–Zaire Ebola Virus Vaccination on Ebola Virus Disease Illness and Death, Democratic Republic of the Congo - Volume 28, Number 6—June 2022 - Emerging Infectious Diseases journal - CDC. *Emerg Infect Dis* 2022. DOI:10.3201/eid2806.212223.

19 Coulborn RM, Bastard M, Peyraud N, *et al.* 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. *Lancet Infect Dis* 2024; published online Feb 7. DOI:10.1016/S1473-3099(23)00819-8.

20 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. Institut National pour la Recherche Biomedicale (INRB) and World Health Organisation (WHO), 2019 https://www.who.int/publications/m/item/preliminary-results-on-the-efficacy-of-rvsv-zebov-gp-ebola-vaccine-using-the-strategy-in-the-control-of-an-ebola-outbreak.

21 Kasereka MC, Ericson AD, Conroy AL, Tumba L, Mwesha OD, Hawkes MT. Prior vaccination with recombinant Vesicular Stomatitis Virus – Zaire Ebolavirus vaccine is associated with improved survival among patients with Ebolavirus infection. *Vaccine* 2020; **38**: 3003–7.

22 Foppa IM, Haber M, Ferdinands JM, Shay DK. The case test-negative design for studies of the effectiveness of influenza vaccine. *Vaccine* 2013; **31**: 3104–9.

23 Sullivan S, Feng S, Cowling B. Potential of the test-negative design for measuring influenza vaccine

effectiveness: A systematic review. *Expert Rev Vaccines* 2014; **13**. DOI:10.1586/14760584.2014.966695.
24 Cowling BJ, Chan K-H, Feng S, *et al.* The effectiveness of influenza vaccination in preventing hospitalizations in children in Hong Kong, 2009–2013. *Vaccine* 2014; **32**: 5278–84.
25 Bond HS, Sullivan SG, Cowling BJ. Regression approaches in the test-negative study design for assessment of influenza vaccine effectiveness. *Epidemiol Infect* 2016; **144**: 1601–11.
26 Fukushima W, Hirota Y. Basic principles of test-negative design in evaluating influenza vaccine effectiveness. *Vaccine* 2017; **35**: 4796–800.
27 Azman AS, Parker LA, Rumunu J, *et al.* Effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. *Lancet Glob Health* 2016; **4**: e856–63.
28 Ali M, You YA, Sur D, *et al.* Validity of the estimates of oral cholera vaccine effectiveness derived from the test-negative design. *Vaccine* 2016; **34**: 479–85.
29 Franke MF, Jerome JG, Matias WR, *et al.* Comparison of two control groups for estimation of oral cholera vaccine effectiveness using a case-control study design. *Vaccine* 2017; **35**: 5819–27.
30 Heo JY, Seo YB, Choi WS, *et al.* Effectiveness of Pneumococcal Vaccination Against Pneumococcal Pneumonia Hospitalization in Older Adults: A Prospective, Test-Negative Study. *J Infect Dis* 2022; **225**: 836–45.
31 Lopez Bernal J, Andrews N, Gower C, *et al.* Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med* 2021; **385**: 585–94.
32 Stowe J, Andrews N, Kirsebom F, Ramsay M, Bernal JL. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation, a test negative case-control study. *Nat Commun* 2022; **13**: 5736.
33 Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. *Am J Epidemiol* 2016; **184**: 345–53.
34 Dean NE, Hogan JW, Schnitzer ME. Covid-19 Vaccine Effectiveness and the Test-Negative Design. *N Engl J Med* 2021; **385**: 1431–3.
35 Pearson CAB, Edmunds WJ, Hladish TJ, Eggo RM. Potential test-negative design study bias in outbreak settings: application to Ebola vaccination in Democratic Republic of Congo. *Int J Epidemiol* 2022; **51**: 265–78.
36 Sullivan SG, Khvorov A, Huang X, *et al.* The need for a clinical case definition in test-negative design studies estimating vaccine effectiveness. *Npj Vaccines* 2023; **8**: 1–5.
37 Cnops L, Gerard M, Vandenberg O, *et al.* Risk of Misinterpretation of Ebola Virus PCR Results After rVSV ZEBOV–GP Vaccination. *Clin Infect Dis* 2015; **60**: 1725–6.