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[Intervention Protocol]

Vaccines for preventing Ebola virus disease

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of vaccines to prevent Ebola virus disease in people who have been, or have potentially been, exposed to Ebola virus.

BACKGROUND

Ebola virus disease (EVD), previously known as Ebola haemorrhagic fever, was first reported in 1976 in Zaire (now the Democratic Republic of the Congo). EVD has been responsible for tens of thousands of cases across multiple outbreaks, with case fatality rates ranging from 25% to 90% (WHO 2023). The largest known outbreak of EVD in history was the 2013 to 2016 outbreak in West Africa, which saw nearly 29,000 cases (confirmed, probable, or suspected cases), and resulted in over 11,000 deaths.

The impact of outbreaks includes wider effects on communities, healthcare systems, healthcare-seeking behaviour, society, and the economy (Elston 2017; McMahon 2016). Resources may be diverted from other essential services, such as TB, HIV, and maternal and infant health care (Malvy 2019). Adverse mental health effects have also been recognised in survivors, their families, and communities.

Infection prevention and control (IPC) practices, including hand hygiene, waste segregation and management, burial procedures, and the use of personal protective equipment are currently used to control the spread of EVD. Safe and effective vaccination, in addition to IPC strategies could greatly reduce mortality and the economic burden of EVD outbreaks, by protecting people exposed to the virus and their contacts from infection.

Description of the condition

The Ebola virus is one of over 30 viruses responsible for viral haemorrhagic fevers. The organism belongs to the family Filoviridae and the genus Orthoebolavirus. Four species of the genus Orthoebolavirus cause disease in humans: *Sudan ebolavirus* (SUDV), *Bundibugyo ebolavirus* (BDBV), *Taï Forest ebolavirus* (TAFV), and *Zaire ebolavirus* (EBOV).

The Ebola virus can spread from an animal host (often bats and monkeys) to humans through direct contact with infected body fluids or tissues (such as through handling, killing, and consumption of wild animal meat). This is termed a spillover event (CDC 2023; Goeijenbier 2014). The virus can then spread from human to human through contact (including through broken skin, or mucous membranes in the eyes, nose, or mouth) with blood or body fluids (urine, saliva, sweat, faeces, vomit, breast milk, amniotic fluid, and semen) of a person who has symptomatic EVD, or who has died from EVD (Goeijenbier 2014; West 2014). Transmission from human to human only occurs after the exposed person develops signs and symptoms of EVD. Objects, such as clothes, bedding, needles and other medical equipment that are contaminated with body fluids from an infected person can also transmit disease between humans (CDC 2023).

The incubation period is between 2 and 21 days. In the early stages of EVD, commonly observed clinical features include fever, pharyngitis, bilateral conjunctival injection, and several non-specific symptoms, such as malaise, anorexia, nausea, vomiting, and diarrhoea (Bah 2015; Goeijenbier 2014). Early Ebola infection in infants and children can be non-specific (West 2014). Later findings include bleeding from mucus membranes or puncture sites (all infected persons show some degree of coagulopathy), decreased liver and renal function, myocarditis, or pulmonary oedema (Bah 2015). In severe cases, tachypnoea, hypotension, anuria, and coma may be seen.

The gold standard for diagnosis is reverse-transcriptase polymerase chain reaction and tissue culture. Enzyme-linked immunosorbent assay may be reliable in people who live long enough to develop antibodies. A complete blood count, serum electrolytes, urea and creatinine, liver function tests, and arterial blood gases may be taken to assess the impact of the virus on body systems. The differential diagnoses of EVD in endemic settings include malaria, dengue fever, Marburg virus disease, Lassa fever, and typhoid fever (West 2014).

The mainstay of treatment for EVD is supportive care, which includes correcting hydration and electrolyte derangement, managing fever and pain, and treating any concurrent infections (Lamontagne 2018). Monoclonal antibody medications for EVD include inmazeb (atoltivimab + maftivimab + odesivimab) and ansuvimab- zykl (Ebenga (Gao 2022)). A randomised controlled trial (RCT) reported disease attenuation with monoclonal antibody therapeutics (Mulangu 2019). Isolation of suspected and confirmed cases, barrier nursing, regular disinfection of surfaces, proper use of personal protective equipment, and safe burial procedures are important components of outbreak management.

Mortality rates vary according to virus species, with an overall mortality rate of 44% (CDC 2023; Goeijenbier 2014). Pregnant women and children under five years are likely to have higher mortality rates. People who survive EVD may develop myalgia, arthralgia, hearing loss, and persistent body weakness. Survivors may also experience ocular complications, such as photophobia, ophthalmalgia, decreased visual acuity, and uveitis (Vetter 2016). Survivors are considered to have some protective immunity to the species of Ebola virus that infected them. The duration of any protective immunity in humans is unknown, as is whether it provides protection against a different species of Ebola virus.

Description of the intervention

The following are currently licenced vaccines, in one or more countries, for EVD. A number of other vaccine candidates are under development (Woolsey 2021).

rVSV-ZEBOV (Ebola Zaire vaccine or Ervebo)

rVSV-ZEBOV is also known by the brand name Ervebo. The vaccine contains an attenuated recombinant vesicular stomatitis virus modified to contain glycoprotein from the *Zaire ebolavirus*.

It is approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA (EMA 2024; FDA 2023)).

rVSV-ZEBOV vaccine is a replication competent virus vaccine (sometimes termed a live vaccine), administered as a single dose intramuscular injection. The vaccine is licenced for persons aged one year and older (EMA 2024; FDA 2023). As such, it could be used in an acute Ebola outbreak setting for eligible, immunocompetent people.

Adverse reactions following vaccination include injection site pain, headaches, fever, and muscle pain.

Ad26.ZEBOV/MVA-BN-Filo vaccine (Zabdeno/Mvabea)

Ad26.ZEBOV is known by the brand name Zabdeno. It consists of Adenovirus type 26, modified to include glycoprotein from the *Zaire ebolavirus* (Mayinga strain (EMA 2023a)).

MVA-BN-Filo is known by the brand name Mvabea. It consists of Vaccinia Ankara Bavarian Nordic Virus, modified to include glycoprotein from the *Zaire ebolavirus* (Mayinga strain), the *Sudan ebolavirus* (Gulu strain), Marburg Musoke strains, and the nucleoprotein from the *Taï Forest ebolavirus* (EMA 2023b).

Both vaccines are licenced for individuals one year and older, by the EMA.

The Ad26.ZEBOV/MVA-BN-Filo vaccine (Zabdeno/Mvabea) is a two-dose regimen. Ad26.ZEBOV (Zabdeno) is administered first, and MVA-BN-Filo (Mvabea) is given approximately eight weeks later, as a second dose. As such, this vaccine regimen is not ideal when immediate protection is required, such as during an outbreak. For people at imminent risk of exposure to Ebola (for example, healthcare professionals and those living in or visiting areas with an ongoing EVD outbreak) who completed the Zabdeno and Mvabea two-dose vaccination regimen, a Zabdeno booster vaccination should be considered if more than four months have passed since the second dose was administered.

Common reported adverse reactions following vaccination with Zabdeno/Mvabea include pain or swelling at the injection site, headache, arthralgia and myalgia, chills, fatigue, and depressed appetite.

Ad5-EBOV

The Ad5-EBOV vaccine contains the human adenovirus serotype-5 vector, modified to include glycoprotein from the *Zaire ebolavirus* (Makona strain).

Most adverse reactions have been reported as mild and self-limiting, arising and resolving within 48 hours of vaccination, and include pain and swelling at the injection site (Zhu 2017). Fever, headache, and fatigue were noted up to seven days after vaccination. No serious vaccine-attributable event was reported (Zhu 2017).

It is approved as a single intramuscular dose in people aged 18 years to 60 years, by the China Food and Drug Administration (Zhu 2015).

rVSV/Ad5 (GamEvac Combi)

rVSV/Ad5 is a replication competent virus vaccine, with recombinant vesicular stomatitis virus and the adenovirus serotype-5, expressing the *Zaire ebolavirus* glycoprotein.

In healthy recipient volunteers, most adverse events have been reported as mild or moderate, generally resolving within three days of vaccination. They include pain at the injection site, fever, headache, myalgia, and fatigue. It was noted that liver and kidney function indicators, including alanine aminotransferase, aspartate amino transferase, creatinine, and creatine phosphokinase, were affected up to seven days following vaccination. Study authors also reported that urticarial and anaphylactic allergic reactions were variable, and concluded that no serious adverse events were reported (Dolzhikova 2017).

It is a two-dose intramuscular regimen, licenced in Russia for emergency use for people aged 18 years to 55 years (Dolzhikova 2017).

How the intervention might work

Vaccines aim to generate an immune response that prevents EVD, or reduces the risk of severe disease or death on subsequent exposure to the Ebola virus. To achieve this, the vaccine must contain antigens that are either derived from the pathogen (Ebola virus), or produced synthetically to represent components of the Ebola virus. All current vaccines for EVD express Ebola virus glycoprotein antigen (the sole surface protein of the Ebola virus virion) to stimulate an immune response in the recipient (Woolsey 2021).

The ability of the vaccine components to stimulate an immune response (immunogenicity), is critical to confer protection against the development of EVD upon exposure to the Ebola virus. Prior to clinical trials in humans exposed to the Ebola virus, vaccines were trialled in healthy human volunteers to gather data on safety, undesirable effects, and early efficacy data, most often through markers of immunogenicity (Phase I trials). Protection against EVD conferred by a vaccine can subsequently be measured in clinical trials of people exposed, or potentially exposed to the disease, which relate immune responses following vaccination to clinical outcomes, such as how many cases of EVD were prevented, or a reduction in disease severity. A recent retrospective cohort analysis reported improved survival in people vaccinated with rVSV-ZEBOV in the Democratic Republic of the Congo between 2018 and 2020 (Coulborn 2024). The nature of EVD is such that outbreaks are sporadic and unpredictable, limiting the opportunities for human trials on vaccine efficacy.

Overall, vaccination strategies must balance harms and benefits for recipients, in addition to implementation considerations and cost. Based on 90% vaccine efficacy and an estimated basic reproductive number value (R_0; number of secondary cases that result from an individual infection) of four, an estimated 80% vaccine coverage is required to establish herd immunity (Masterson 2018). Population-level vaccination against the Ebola virus is not considered a feasible goal, as endemic regions in Central and West Africa include over half a billion people, presenting considerable financial and logistical challenges (CDC 2023). The strategy of ring vaccination (immunising contacts of people with confirmed disease) can also face logistical barriers, as contacts of people with EVD, and their contacts, may refuse vaccination, or be impossible to find. Different strategies for each outbreak situation may need to be considered. Isolated cases or small outbreaks could benefit from early contact tracing and ring vaccination. Large outbreaks may require community-based, population-based, or region-based vaccination to adequately control an outbreak. To protect healthcare workers and support staff (such as ambulance drivers, hospital cleaners and administrators, security staff, and burial teams), their immunisation is essential.

Why it is important to do this review

Since its discovery, the Ebola virus has shown ongoing outbreak potential that could threaten global health security. The Ebola virus has been exported to non-endemic countries (CDC 2023). Whilst historically, outbreaks have impacted relatively small numbers of people on a global scale, they have caused great suffering, and caused a significant economic toll in affected countries. Health system disruption from disease outbreaks, and the subsequent impact on illness and death from non-EVD pathologies can ensue. In addition, the Ebola virus has bioweapon potential. Thus, it is

critical to understand the benefits and harms of currently available vaccines to inform clinical and health policy decisions in any future outbreak scenario, and inform further vaccine development.

OBJECTIVES

To assess the effects of vaccines to prevent Ebola virus disease in people who have been, or have potentially been, exposed to Ebola virus.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs), quasi-RCTs, or cluster-RCTs in which participants have been randomised to receive either an Ebola virus disease (EVD) vaccine or no vaccine, placebo, or a different EVD vaccine.

We will define quasi-RCTs as RCT study designs that lack a true randomisation technique, but do include a systematic approach to participant allocation, such as alternate allocation.

This review aims to capture studies in which vaccines are used in real-world populations impacted by EVD, to achieve the most clinically relevant evidence for stakeholders. As such, we will exclude studies investigating only adverse effects, which do not concurrently investigate clinical efficacy. This means, for example, that studies focussing on vaccine safety and tolerability in healthy volunteers will not be eligible.

Types of participants

Human participants who have been, or have potentially been exposed to EVD and participated in an Ebola virus vaccine trial.

There will be no specific exclusion criteria relating to age, sex, or setting. Pregnant and lactating women are eligible for inclusion.

We will include studies in any country or setting, including preventive vaccination, outbreak response, and post-exposure prophylaxis.

Types of interventions

Interventions

We will include studies assessing any licenced Ebola vaccine.

There are no restrictions on the timing of delivery, dose, or frequency of delivery of an intervention vaccine. It is expected the intervention vaccines will be administered in trials, as per the licencing manufacturers' advice.

The currently licenced vaccines for EVD are:

- r-VSV-ZEBOV-GP (Ervebo)
- Ad26.ZEBOV-GP (Zabdeno) in a combined schedule with MVA-BN-Filo (Mvabea)
- Ad5-EBOV
- rVSV/Ad5

As noted, Ad26.ZEBOV-GP and MVA-BN-Filo are licenced for use in a combined schedule, so they will be considered together as an intervention, rather than considering each of the individual vaccines alone as an intervention.

We will capture ongoing trials for vaccines that meet the inclusion criteria.

Comparator

Placebo, a different Ebola virus vaccine, the intervention vaccine administered at a different frequency or dose, or no intervention.

Types of outcome measures

There are no published core outcomes sets on this topic.

We selected outcomes of high relevance to clinical and policy decision-making.

We will include eligible studies regardless of outcomes reported.

Primary outcomes

1. Ebola virus disease presenting more than 10 days after vaccination: measured as the total number of participants in each arm at the last available follow-up
2. All-cause mortality: defined as death from any cause occuring within 30 days of vaccination, measured as an absolute number

Secondary outcomes

1. Serious adverse events or complications: defined as those requiring admission to hospital or are a threat to life
2. Minor adverse events or complications: all other events not captured by serious adverse events.

Secondary outcomes will be measured by the number of participants experiencing the outcome until the last available point of follow-up.

Search methods for identification of studies

We will attempt to identify all potential studies, regardless of publication status (published, unpublished, in press, or in progress). We will use the Cochrane sensitivity-maximising RCT filter for MEDLINE Ovid, and adapt it for the other databases, except CENTRAL (Lefebvre 2024).

Electronic searches

We will search the following databases using the search terms and strategy described in Appendix 1

1. Central Register of Controlled Trials (CENTRAL; current issue), published in the Cochrane Library;
2. MEDLINE Ovid (1946 to present);
3. Embase Ovid (1974 to present);
4. Science Citation Index-Expanded, Conference proceedings citation index on Web of Science platform (1900 to present);
5. World Health Organization (WHO) Global Index Medicus (2012 to present).

Using "Ebola" and “vaccines” or “vaccination” as search terms, we will search two trial registers for trials in progress.

1. WHO International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/; 2006 to present);

2. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home; 2000 to present).

Searching other resources

We will check the reference lists of included studies and contact experts in the field to identify any additional references.

To identify any post-publication amendments on included or eligible studies, we will undertake a search on the Retraction Watch Database (https://retractionwatch.com/). Post-publication amendedments will be noted in the systetmatic search for studies. The topic expert review authors also remain abreast of amendments and changes to trials in this field.

We will exclude retracted RCTs. We will consider RCTs with an expression of concern, depending on the nature of the concern. These studies will either be excluded, assigned to the awaiting classification category, or included in the review (for example, if the concerns do not affect the validity of the data).

Data collection and analysis

Selection of studies

Two review authors will independently screen the titles and abstracts of the search results using Covidence software (Covidence). The full-text articles of all potentially relevant trials will be retrieved. Two review authors will independently review the full-text reports against the review inclusion criteria. We will examine each report to ensure that we include multiple publications from the same trial only once. We plan to contact trial authors for clarification if the eligibility of a trial is unclear. Any disagreements will be resolved through discussion or with a third review author as necessary.

We will list the excluded studies and the reasons for their exclusion in the characteristics of excluded studies table. The study selection process will be illustrated using a PRISMA diagram (Page 2021).

Data extraction and management

Two review authors will independently use a piloted data extraction form to extract data on study setting and characteristics, participant characteristics, EVD vaccine, other treatments given, and study funding sources. They will extract information on study outcomes (EVD, all-cause mortality, and adverse effects). Any disagreements will be resolved through discussion. We will contact the corresponding trial author in the case of unclear or missing data.

For our dichotomous outcomes, we will record the number of participants who experienced the event, and the number of participants randomised to each treatment group. We will record the number of participants analysed in each arm, and use the discrepancy between the figures to calculate the number of participants lost to follow-up, allowing us to perform sensitivity analyses to investigate the effect of missing data if necessary.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias for each outcome, in each study, using Cochrane's RoB 2 tool (Higgins 2019; Sterne 2019). This tool addresses risks of bias relating to five domains: the randomisation process; deviations from intended interventions; missing outcome data; measurement of outcomes; and selection of reported outcomes. The tool provides a series of signalling questions for each domain, mapped via an algorithm to a proposed risk-of-bias judgement. The outcomes assessed will be all primary and secondary review outcomes: EVD presenting more than ten days after vaccination, all-cause mortality, serious adverse events, and minor adverse events.

We will provide a risk of bias judgement for each outcome in each of the five domains, which could be low risk of bias, some concerns, or high risk of bias. We will use the judgements across the five domains to reach an overall risk of bias judgement for each outcome (low risk of bias, some concerns, or high risk of bias). We will refer to the guidance for the application of the tool when reaching judgements of the overall risk of bias for each outcome (Higgins 2023b). For each outcome, we will consider the implications of the judgements in each domain for the overall risk-of-bias judgement, asking whether the problems identified are likely to affect the ability to draw reliable conclusions from the study. We will consider the overall risk of bias to be low if all domains are at low risk; some concerns if at least one domain is of some concern and no domain is at high risk; and high risk of bias if there is at least one domain considered to be at high risk, or several domains with some concerns.

For cluster-RCTs, we will use the version of the tool tailored to this trial design (Eldridge 2021), with an additional domain to assess bias associated with timing and recruitment of participants.

We will assess the effect of assignment to the intervention (intention-to-treat analysis). We will use the purpose-built Excel tool to manage the data generated during the risk of bias assessment, and will store the full RoB 2 data (e.g. completed Excel tool) in an online repository.

Study authors will be contacted for any missing information required to inform the risk of bias judgements.

Any disagreements will be resolved through discussion and consultation with a third review author if necessary.

Measures of treatment effect

We will present dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CIs).

There are no included outcomes involving continuous data.

Unit of analysis issues

For cluster-randomised studies, we plan to extract adjusted measures of effect (where available) from the trial reports. If only unadjusted data are available, we will adjust them ourselves, using the intracluster correlation coefficient (ICC). If the ICC is not reported, we will contact the study authors to obtain it, or borrow an ICC value from a similar study, or estimate the ICC. If we do estimate the ICC, we will perform sensitivity analyses to investigate the robustness of our analyses.

If we identify multi-arm trials, we will select relevant arms for our analyses. If more than two arms are relevant to this review, we will either combine intervention arms so that there is one comparison, or split the control group between multiple comparisons so that participants are not double-counted in the meta-analysis.

Adverse effects will be measured by the number of participants experiencing an adverse event, not the number of adverse events.

Dealing with missing data

We will attempt to contact the study authors to request missing data when necessary.

If we are unable to obtain missing individual data, we plan to conduct a complete case analysis in the first instance, and we may perform sensitivity analyses to investigate the impact of missing data on the primary outcomes. For example, we may vary the event rate for missing individuals from intervention and control groups within plausible limits, or we may exclude studies, thought to be at risk of bias, from our meta-analyses.

We will assess the risk of bias due to missing outcome data in the RoB 2 tool (Sterne 2019). We will take into consideration the extent of missing data, whether data can be considered to be missing at random, imbalances between arms, and the results of sensitivity analyses.

Where measures of variability are not reported for effect estimates, we will use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 6.3.1 and 6.3.2 to derive standard errors from CIs or P values (Higgins 2023a).

Assessment of heterogeneity

We plan to assess clinical and methodological heterogeneity by appraising the included studies following data extraction. When there is a high degree of clinical and methodological heterogeneity between studies, we will not combine them in a meta-analysis. Some sources of clinical heterogeneity are listed in Subgroup analysis and investigation of heterogeneity. For studies included in a meta-analysis, we will assess statistical heterogeneity by inspecting the forest plot to determine how close point estimates are to each other, and the degree of overlap of CIs. We will use the Chi^2 test with P = 0.10 to indicate statistical significance, and the I^2 statistic to quantify heterogeneity, using the thresholds outlined in the *Cochrane Handbook*, Chapter 10.10.2 to interpret this result (Deeks 2023).

1. 0% to 40%: might not be important
2. 30% to 60%: may represent moderate heterogeneity
3. 50% to 90%: may represent substantial heterogeneity
4. 75% to 100%: considerable heterogeneity

We will consider the number of studies, and the magnitude and direction of effects when interpreting the I^2 statistic. We will not pool outcomes with considerable heterogeneity in a meta-analysis.

Assessment of reporting biases

We will attempt to identify all research that meets our predefined eligibility criteria. Missing studies can introduce bias to the analysis. We will search for completed, non-published trials in trial registers, and contact trial authors to seek information on publication plans. We plan to classify these studies as 'awaiting classification' until the results are reported. We will report the number of completed, non-published trials.

If there are 10 or more studies pooled in a meta-analysis, we plan to investigate the risk of reporting bias (publication bias) using visual assessment of funnel plots. If funnel plot asymmetry is suggested by a visual assessment, we will perform further exploratory analysis, as guided by our statistician. We do not anticipate more than 10 relevant studies within a meta-analysis. In the final review, we will report all the methods used.

Data synthesis

We will perform a meta-analysis of data from RCTs if there are at least two studies with outcome data that can be pooled, and it is meaningful to pool the data across studies; that is, if the interventions, participants, and the underlying clinical measures are similar. Our decision to perform a meta-analysis will be determined by the clinical and methodological heterogeneity, and by the comparability of outcomes. Our primary analysis will include all eligible studies, and we will not exclude studies based on risk of bias assessment. We will perform sensitivity analyses to explore the impact of risk of bias on the meta-analysis. We assume that studies will be functionally different from one another, and will not produce a common effect size. Therefore, we will use the Mantel-Haenszel random-effects model in RevMan for meta-analysis (RevMan 2024).

If it is inappropriate to combine the data in a meta-analysis (because of insufficient studies or data, or if pooling does not make sense), we will report the effect sizes with 95% CI or standard errors of individual studies, and provide a narrative, rather than quantitative, summary of the findings, addressing the direction and size of the effect, and consistency of the effect across studies, using the study-level reported data. We will use Synthesis Without Meta-analysis (SWiM) guidance in the event of narrative synthesis of findings (Campbell 2020).

If there are sufficient data, we will stratify analyses by different vaccines.

Subgroup analysis and investigation of heterogeneity

In this first review version, we do not expect numerous trials, and no subgroups are planned.

In future updates, if there are sufficient data, and in the event of heterogeneity within our planned meta-analyses, we will consider stratifying the data to explore the heterogeneity in intervention effects as follows:

1. Participants under the age of 16 years. For the purposes of this review, children are defined as younger than 16 years. Vaccines may have different impacts on children, and the potential risk-benefit consideration of receiving the vaccine may differ.
2. Pregnant and lactating women. A vaccine may work differently in pregnant and lactating women, due to different body physiological processes, and the potential risk-benefit consideration of having the vaccine may be different.
3. Target Ebola virus species (*Zaire ebolavirus*, *Sudan ebolavirus*, *Taï Forest ebolavirus*, *Bundibugyo ebolavirus*). A vaccine may work differently in different virus species.

Sensitivity analysis

If meta analyses are undertaken, we will explore the impact of missing data and risk of bias on the summary effect estimates, by conducting sensitivity analyses.

Our main analysis will focus on available evaluable data. In the event of considerable missing outcome data from participants, we will first compare the proportion of missing data in the intervention and control groups to explore the potential impact of different dropout rates between groups on the effect estimate for the outcome. If there are disproportionate missing data in one group compared to the other, we will explore the assumption that all missing data was from participants who experienced the outcome compared to assuming all missing data was from participants who did not experience the outcome. In the Discussion section, we will discuss how potentially the risk of the event among the missing participants may have differed from the risk of the event among the observed participants in these different scenarios, and the possible influence on the overall effect estimate.

To explore the impact of risk of bias, we will re-analyse the data after removing studies at high risk of bias, comparing this result with the result of the main analysis.

Additional sensitivity analyses may be required if particular issues related to the studies under review arise.

Summary of findings and assessment of the certainty of the evidence

We will present the main results of the review in summary of findings tables that include a rating of the certainty of evidence based on the GRADE approach. We will follow current GRADE guidance, recommended in the *Cochrane Handbook* (Schünemann 2024).

We will judge the certainty of the evidence of the effect estimate for all primary review outcomes (EVD case at the last available follow-up point, all-cause mortality within 30 days of vaccination), and secondary review outcomes (serious and minor adverse effects at the last available follow-up point).

Two review authors will independently assess the certainty of the body of evidence using the five GRADE considerations (the overall judgement of risk of bias for the outcome, consistency of effect, imprecision, indirectness, and publication bias). They will reach a consensus view on any downgrading decision through discussion following their independent assessment. A third and fourth review author will be involved in discussion as necessary, in the event of any disagreement to reach consensus. In the event of strongly differing views on a judgement, we will report these reasons, for transparency.

We will rate the certainty of evidence for each outcome effect estimate as described by Balshem and colleagues as (Balshem 2011):

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
3. Low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The summary of findings tables will present the findings for all outcomes with their associated follow-up time point.

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Toby Lasserson, Cochrane Evidence Production and Methods Directorate;
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Hannah Payne, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Victoria Pennick, Cochrane Central Production Service;
- Peer-reviewers (provided comments and recommended an editorial decision): Houreratou Barry, Centre MURAZ/Institut National de Santé Publique, Burkina Faso (clinical/content review); Armand Sprecher, Médecins Sans Frontières - Brussels (clinical/content review); Clare Miles, Evidence Production and Methods Directorate (methods review); Ina Monsef, Cochrane Haematology, Institute of Public Health, Faculty of Medicine and University Hospital Cologne, University of Cologne, Germany (search review); Jo Platt, Central Editorial Information Specialist (search review).

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Balshem 2011

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APPENDICES

Appendix 1. Draft search strategy - MEDLINE Ovid

Ovid MEDLINE(R) ALL <1946 to present>

1 Hemorrhagic Fever, Ebola/

2 Ebolavirus/

3 Ebola.tw.

4 1 or 2 or 3

5 Vaccines/

6 Vaccination/

7 (vaccin* or toxoid* or immuni* or immune or conjugate* or inocula* or booster* or revaccin*).tw.

8 5 or 6 or 7

9 4 and 8

10 Ebola Vaccines/

11 (Ervebo or "rVSV-ZEBOV" or "recombinant vesicular stomatitis virus" or Zabdeno or Mvabea or "Ad26.ZEBOV-GP" or "MVA-BN-Filo" or "Ad5-EBOV" or "adenovirus serotype5 vector" or "cAd3-EBOZ" or "Glycoprotein vaccine*").tw.

12 9 or 10 or 11

13 randomized controlled trial.pt.

14 controlled clinical trial.pt.

15 (randomized or placebo or randomly or trial or groups).ti,ab.

16 drug therapy.sh.

17 13 or 14 or 15 or 16

18 animals/ not humans/

19 17 not 18

20 12 and 19

This is the preliminary search strategy for MEDLINE Ovid; it will be adapted for other databases.

CONTRIBUTIONS OF AUTHORS

TF, STJ, and HR were involved in the conceptualisation, design, and planning of the protocol.

RK, HR, and SG contributed to co-ordination of the protocol development.

RK, HR, SG, MC, MR, LT, and KCO contributed to the writing of the protocol.

All authors reviewed the protocol prior to submission.

DECLARATIONS OF INTEREST

RK has no known conflicts of interest.

HR has no known conflicts of interest. She is employed by the Liverpool University Hospitals NHS Foundation Trust.

KCO has no known conflicts of interest. KCO has worked as a clinician, managing viral haemorrhagic fevers in Nigeria.

SG has no known conflicts of interest.

MC has no known conflicts of interest. She is a Cochrane Editor and was not involved in the editorial process of this protocol.

MR has no known conflicts of interest.

LT has a share of a patent on a Zika vaccine, and is an Independent Contractor Consultant for AstraZeneca and Synairgen. Travel, accommodation, and registration (2024 only) for ECCMID 2023 and 2024 were covered by AstraZeneca.

STJ has worked as a consultant with the Clinical Unit of the World Health Organization (WHO) Health Emergencies Programme, in which capacity his roles included deployment to support the response to Filovirus disease outbreaks across sub-Saharan Africa. He is affiliated with the Wellcome Trust (Grant/Contract) and is a WHO Independent Contractor - Consultant.

TF has worked as a consultant with the Clinical Unit of the WHO Health Emergencies Programme, in which capacity his roles included deployment to support the response to global Filovirus disease outbreaks. He is a WHO Independent Contractor - Consultant.

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