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Safety, effectiveness, and immunogenicity of Ebola vaccines across virus species and populations: a living systematic review and meta-analysis

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REVIEW TITLE AND BASIC DETAILS

Review title
Safety, effectiveness, and immunogenicity of Ebola vaccines across virus species and populations: a living systematic review and meta-analysis

Condition or domain being studied
Ebola Virus Disease

Rationale for the review
Ebola virus disease (EVD) is a severe, often fatal, viral hemorrhagic fever caused by orthoebolaviruses of the Filoviridae family. Six species are currently recognized within the genus Orthoebolavirus, four of which cause diseases in humans: Zaire Ebola virus (EBOV), Sudan virus (SUDV), Bundibugyo virus (BDBV), and Taï Forest virus. Despite advances in prevention and control, EVD remains a

major public health threat, with recurrent outbreaks causing high morbidity and mortality and placing substantial strain on health systems.

A recent Ebola outbreak in the Democratic Republic of the Congo (DRC) involving Bundibugyo virus highlights an important evidence gap. Unlike EBOV, no vaccines have yet been approved for BDBV or other non-Zaire orthoebolaviruses. This outbreak therefore provides an opportunity to generate and synthesize evidence on candidate vaccines, cross-protective effects of existing platforms, and outcomes across diverse populations.

Recent outbreaks have been classified by the World Health Organization (WHO) as posing a very high public health risk due to ongoing transmission, population mobility, and operational challenges in outbreak containment. Populations at risk include healthcare and frontline workers, close contacts of confirmed or suspected cases, people living in outbreak-affected communities, and those involved in caregiving or funeral practices. Additional subgroups, including pregnant and lactating women, neonates and infants, children, older adults, and immunocompromised individuals may experience increased susceptibility to infection, more severe disease, or distinct vaccine safety and immunogenicity profiles. Case-fatality rates have ranged from 25-90% across documented outbreaks, with particularly severe outcomes reported among pregnant women and children.

Rationale for making this a Living Systematic Review
Vaccination is now a key strategy for Ebola prevention and outbreak response. Two vaccines have been WHO-prequalified targeting EBOV: the single-dose rVSVΔG-ZEBOV-GP (Ervebo®, Merck), and the heterologous two-dose regimen Ad26.ZEBOV (Zabdeno®) followed by MVA-BN-Filo (Mvabea®) (Johnson & Johnson / Bavarian Nordic). In 2024, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) issued the first recommendations for preventive Ebola vaccination among healthcare and frontline workers in high-risk areas, followed byimplenentatio support from GAVI.

Parallel to licensed products, several candidate vaccines are under development for SUDV, BDBV, and multivalent protection, including viral vector–based, DNA, and mRNA platforms. Recent outbreaks in DRC and Uganda have accelerated the deployment of investigational vaccines under emergency protocols, generating a rapidly evolving but fragmented body of evidence spanning clinical trials, observational studies, and real-world programmatic data.

Given the absence of licensed vaccines for Bundibugyo virus and the emergence of new data from ongoing outbreaks—particularly the current DRC context—there is a compelling need for a comprehensive, continuously updated synthesis of evidence on Ebola vaccine safety, effectiveness, and immunogenicity across virus species, vaccine platforms, and populations. evidence on the safety, effectiveness, and immunogenicity of Ebola vaccines remains dispersed across different populations, vaccine platforms, and outbreak contexts. A living systematic review is therefore essential to inform timely policy decisions, guide vaccine deployment strategies, identify critical knowledge gaps, and support preparedness and response efforts for both current and future Ebola outbreaks worldwide.

Review objectives

● Synthesize the available evidence on the safety, effectiveness, and immunogenicity of Ebola vaccines across different diverse populations, virus species, and epidemiologic settings;

● Compare evidence across vaccine platforms, ncluding licensed and investigational products, and across outbreak versus preventive use contexts;

● Identify key evidence gaps, with particular attention to underrepresented populations (e.g., pregnant and lactating women, children, older adults, and immunocompromised individuals) and to non-Zaire orthoebolaviruses such as Bundibugyo virus; and

● Provide timely, continuously updated evidence to inform vaccine development, vaccination strategies, outbreak response, and public health decision-making during the ongoing Ebola outbreak in the Democratic Republic of the Congo and in future outbreak or pandemic preparedness scenarios

Keywords

Ebola; Ebola virus disease; EVD; Ebola vaccines; Vaccination; Vaccine safety; Vaccine efficacy; Vaccine effectiveness; Immunogenicity; Outbreak preparedness; Outbreak response; Ring vaccination; epidemic preparedness; Filoviruses; Orthoebolavirus; Zaire ebolavirus; Sudan ebolavirus; Bundibugyo virus; Booster vaccination; public health preparedness; Living systematic review; Meta-analysis

Country

Argentina

ELIGIBILITY CRITERIA

Population

Included

Individuals of all ages and populations exposed to or at risk of Ebola virus disease (EVD), including healthy individuals, healthcare workers, outbreak contacts, people living in endemic or outbreak settings, review persons, children, older adults, and immunocompromised populations receiving Ebola vaccine candidates or licensed Ebola vaccines.

Intervention(s) or exposure(s)

Included

We will include Ebola vaccine candidates at all stages of development, including those in preclinical research stages and Ebola vaccine candidates and licensed Ebola vaccines (Table 1), including preventive, outbreak-response, ring vaccination, booster, and heterologous

vaccination strategies across different vaccine platforms, schedules, doses, and routes of administration.

Eligible products include — but are not limited to:

rVSVΔG-ZEBOV-GP (Ervebo®)

Ad26.ZEBOV + MVA-BN-Filo (Zabdeno® + Mvabea®)

Ad5-EBOV

GamEvac-Combi / GamEvac-Lyo

IAVI rVSVΔG-SUDV-GP

Sabin cAd3-SUDV (cAd3-Sudan)

Sabin cAd3-Marburg

ChAd3-EBO-Z ± MVA-BN-Filo

ChAdOx1 biEBOV

cAd3-EBO-Z

INO-4201 (anglobald other DNA candidates)

Multivalent pan-filovirus programme (CEPI/Horizon Europe, 2026)

mRNA filovirus candidate(s)

rVSV pan-filovirus / Marburg candidates (e.g. rVSVΔG-MARV-GP)

Pan-ebolavirus / pan-filovirus candidates

Filovirus vaccine programme

Multivalent Ad26/Ad35 + MVA filovirus vaccine

Ebola VLP vaccine

Inactivated / subunit candidates

Comparator(s) or control(s)

Included
Active or inactive comparators without interventions under study, usual care, or placebo. Non-comparative studies will be included; therefore, a control group will not be mandatory.

Study design

Both randomized and nonrandomized study types will be included.

Included

Randomized controlled trials; non-randomized comparative studies; prospective and retrospective cohort studies; case-control studies; test-negative design studies, and cross-sectional studies, post-marketing safety surveillance reports, technical reports, and regulatory documents, regardless of publication status.

Excluded

1. Editorials, commentaries, or conference abstracts without sufficient data, or opinion pieces without substantive content.

2. Case series with fewer than 10 participants, narrative reviews, editorials, mathematical-modelling studies without primary clinical data, and pre-clinical (animal or in-vitro) studies.

3. Systematic reviews will be excluded and used only as a source to identify primary studies.

Context

There is no context limitation.

LIVING REVIEW METHODS

Living systematic review methods

This review will be conducted as a living systematic review (LSR). Electronic database searches will be updated every two weeks to identify newly published and ongoing studies. Newly identified records will undergo the same screening, data extraction, risk-of-bias assessment, and evidence synthesis procedures as studies included in the initial review.

The review findings, meta-analyses, and certainty-of-evidence assessments will be updated whenever new eligible studies are identified. Updates will be incorporated into the review database and evidence summaries, with particular attention to new evidence that may change effect estimates, certainty ratings, conclusions, or recommendations regarding vaccine safety, effectiveness, or immunogenicity.

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO

02 June 2026

Review timeline
Baseline review start date: 2 June 2026. Baseline review end date: 8 September 2026.

Date of registration in PROSPERO
06 June 2026

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has not been written.

SEARCHING AND SCREENING

Search for unpublished studies
Both published and unpublished studies will be sought.

Main sources that will be searched
The main sources to be searched are *CNKI - China National Knowledge Infrastructure database*, *Clinicaltrials.gov*, *Embase*, *LILACS - Latin American and Caribbean Health Sciences Literature*, *MEDLINE* and *PubMed*.

Other sources that will be searched
SciELO, WHO regional indexes (AIM, IMSEAR, WPRIM), Web of Science, Global Health, WHO ICTRP, PACTR, EU Clinical Trials Register (EU-CTR/CTIS), ISRCTN, WHO IRIS, CDC, FDA and EMA grey-literature repositories; WHO SAGE working-group documents, Chinese Biomedical Literature Database (CBM), Chinese Science Journal Database, EPPI-Centre evidence maps on epidemic-prone diseases

Search language restrictions
There are no language restrictions.

Search date restrictions
There are no search date restrictions.

Other methods of identifying studies
Other studies will be identified by: *contacting authors or experts*, *looking through all the articles that cite the papers included in the review ("snowballing" or forward citation searching)*, *reference list checking (backward citation searching)*, *searching conference*

proceedings, *searching dissertation and thesis databases* and *searching trial or study registers*.

Additional information about identifying studies
Contacting authors and content experts, including experts involved in Ebola vaccine development, backward and forward citation tracking ("snowballing") of included studies and of recent relevant systematic reviews, reference-list checking, hand-searching of conference proceedings, searching trial and study registers, and consultation with the WHO Ebola vaccines technical group and CEPI.

Link to search strategy
A full search strategy has been uploaded to PROSPERO. The PDF may be accessed through this link https://www.crd.york.ac.uk/PROSPEROFILES/5b3cb5a08a549841b37e341a880eef68.pdf.

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
Pairs of reviewers will independently screen each title and abstract and any potentially relevant full-text studies and reports will be retrieved. These will be independently selected, and any exclusion criteria will be documented for ineligible studies, in both study phases. Any disagreements will be resolved through review team discussions and documented. This process will be performed using the web-based software Nested Knowledge (https://nested-knowledge.com/).

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will be asked to provide any required data not available in published reports.

Study risk of bias or quality assessment
Risk of bias will be assessed using: *Cochrane RoB-2* and *ROBINS-I*

For non-comparative studies we will use NIH Quality Assessment tools.

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment

Risk of bias due to missing results will not be assessed

Certainty assessment

The certainty of evidence for each critical and important outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

OUTCOMES TO BE ANALYSED

Main outcomes

1. Safety outcomes

a. Local and systemic adverse events within 7–14 days post-vaccination following Ebola vaccination, including reactogenicity outcomes such as injection-site reactions, fever, fatigue, headache, myalgia, arthralgia, and other solicited or unsolicited within 28 days adverse events.

b. Serious adverse events (SAEs) and all-cause mortality temporally associated with Ebola vaccination.

c. Hospitalization related to adverse events following vaccination.

d. Adverse events relevant to all populations of special interest (AESI) following Ebola vaccination, including neurological, immunological, cardiovascular, musculoskeletal, ophthalmologic, dermatologic, hematological, or other clinically significant events as defined by study authors, regulatory agencies, and AESI lists from the Safety Platform for Emergency vaccines (SPEAC) Project, funded by CEPI. (Preliminary list: Thrombosis with Thrombocytopenia Syndrome (TTS), Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), myocarditis, pericarditis, acute aseptic arthritis, single organ cutaneous vasculitis, Anaphylaxis, Acute multiple organ dysfunction, Transverse myelitis, Generalized convulsion, Guillain-Barré Syndrome, Ophthalmologic Acute intraocular inflammation, Single organ cutaneous vasculitis).

e. Maternal, obstetric, neonatal, and infant/pediatric safety outcomes including (but not limited to):

Maternal: stillbirth, spontaneous abortion/miscarriage, antenatal bleeding, postpartum hemorrhage, hypertensive disorders of pregnancy (preeclampsia/eclampsia) and maternal death

Neonatal: congenital anomalies, preterm birth, fetal infection, neonatal infection, low birth weight and neonatal death.

Pediatric: Febrile seizure

f. For breastfeeding women: lactation-related events and any evidence of vaccine-vector or antibody transfer via human milk.

Additional outcomes

2. Efficacy/effectiveness outcomes

a. Vaccine efficacy / effectiveness against laboratory-confirmed Ebola virus infection.

Laboratory-confirmed EVD (RT-PCR detection of orthoebolavirus RNA in clinical specimens or other recognized confirmatory test) in vaccinated vs. comparator groups, reported as vaccine efficacy (VE) or vaccine effectiveness with 95% confidence intervals, overall and by age stratum (neonates/infants <1 y; 1–4 y; 5–11 y; 12–17 y; adults; pregnant women).

b. Vaccine efficacy / effectiveness against Symptomatic EVD.

c. Vaccine efficacy / effectiveness against Severe EVD, including hospitalization, intensive care admission, hemorrhagic manifestations, organ failure, or death.

d. Vaccine efficacy / effectiveness against Ebola-related mortality.

e. Secondary transmission and outbreak-related outcomes when available, including ring vaccination effectiveness and outbreak containment indicators.

3. Immunogenicity outcomes

a. Humoral immune responses following Ebola vaccination, including IgG, neutralizing antibodies, seroconversion rates, and duration of immunity.

b. Immune responses according to vaccine platform, dose schedule, booster strategies, and prior Ebola exposure.

c. Maternal and neonatal immunogenicity outcomes, including antibody persistence, placental antibody transfer, umbilical cord blood antibodies, and breastmilk-mediated antibody transfer when available.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

If data are available and methodologically appropriate, we will undertake aggregate meta-analyses for each comparison according to the Cochrane Handbook for Systematic Reviews of Interventions and use random-effects meta-analysis for the primary analyses. We will also perform proportion meta-analyses to summarize frequencies from single-arm or non-comparative studies.

We will use R statistical software to analyze the data. The main packages selected for data analyses will be Meta, Metafor, and Tidyverse. We will estimate hazard ratios (HRs), risk ratios (RRs), odds ratios (ORs), mean differences (MDs), or standardized mean differences (SMDs) with 95% confidence intervals (95% CIs). We will also estimate proportions with 95% CIs for non-comparative studies.

To report efficacy/effectiveness outcomes, we will transform outcome measures into vaccine efficacy/effectiveness (VE) estimates whenever possible by calculating the percentage reduction in disease risk among vaccinated individuals relative to comparator groups. Adjusted effect measures will be prioritized over unadjusted estimates whenever available.

Heterogeneity will be assessed using the I^2 statistic, and potential sources of heterogeneity will be explored through subgroup and sensitivity analyses. When meta-analysis is not appropriate because of substantial clinical or methodological heterogeneity, findings will be summarized descriptively and presented in structured tables.

We will provide a frequently updated online and interactive platform to present available data and the main findings of this living systematic review.

Analysis of subgroups or subsets

Pre-specified subgroup analyses will include age group, sex, pregnancy status, newborn/infant status, country income level (high-income versus low- and middle-income countries), geographic region, vaccine platform, individual Ebola vaccine, dose schedule, booster use, route of administration, outbreak versus non-outbreak setting, immunocompromised status, healthcare worker status, and baseline exposure risk. Additional sensitivity analyses will be undertaken excluding studies at high risk of bias.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification		
Screening search results against inclusion criteria		
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Baseline review status

The baseline review is currently planned or ongoing.

Living review status

The living review is currently ongoing.

Publication of review results

Results of the review will be published.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

Dr Jamile Ballivian (review guarantor and contact) Instituto de Efectividad Clínica y Sanitaria. Argentina.

No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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No conflict of interest declared.

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Review affiliation

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Funding source

Additional non-commercial funding information
CEPI

Peer review

There has been no peer review of this planned review.

ADDITIONAL INFORMATION

Review conflict of interest

Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings
Ebola Vaccines; Ebolavirus

SIMILAR REVIEWS

Check for similar records already in PROSPERO
PROSPERO identified a number of existing PROSPERO records that were similar to this one (last check made on 2 June 2026). These are shown below along with the reasons given by that the review team for the reviews being different and/or proceeding.

- A systematic review of the effects of Ebola vaccines [published 7 October 2018] [CRD42018110505]. The review was acknowledged as **similar** but the authors opted to continue because *there are differences in population*, *there are differences in intervention or comparator*, *the review looks at additional or different outcomes*, *the review will be more up to date*, *the review uses improved methods*
- Fifty years of Ebola virus disease outbreaks in the Democratic Republic of Congo: a systematic review and meta-analysis of epidemiology, mortality and response evolution [published 27 May 2026] [CRD420261405955]. The review was judged **not to be similar**
- Chikungunya vaccines for neglected tropical disease control: a systematic review and meta-analysis of immunogenicity, safety, and evidence gaps for real-world implementation [published 19 May 2026] [CRD420261399890]. The review was judged **not to be similar**

PROSPERO version history

- Version 1.0, published 06 Jun 2026

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