Cochrane Response

Appendices to systematic review of safety, efficacy, immunogenicity, and duration of protection of licensed Ebola virus vaccines

Contents

Protocol: Systematic review of safety, efficacy, immunogenicity, and duration of protection of licensed Ebola virus vaccines

Background

The first Ebola virus vaccine Ervebo (rVSV-ZEBOV) was licensed in November 2019 by the European Medicines Agency (EMA) and prequalified by WHO.(1) The United States Food and Drug Administration (FDA) licensed the vaccine in December 2019. Since then, Burundi, Central African Republic, the Democratic Republic of the Congo, Ghana, Guinea, Rwanda, Uganda, and Zambia have also approved the vaccine. The vaccine is safe and protective against the species Zaire ebolavirus. It is recommended by the Strategic Advisory Group of Experts (SAGE) on Immunization as part as a broader set of Ebola outbreak response tools.(2)

A second vaccine Zabdeno, Mvabea (Ad26.ZEBOV-GP, MVA-BN-Filo) received WHO prequalification in April 2021.(3) It has subsequently been approved in Ghana, Cote d'Ivoire, Rwanda, Uganda and Sierra Leone. The vaccine is delivered in 2 doses: Zabdeno is administered first and Mvabea is given approximately 8 weeks later as a second dose. This prophylactic 2-dose regimen is therefore not suitable for an outbreak response where immediate protection is necessary. For individuals at imminent risk of exposure to Ebola (for example, health care professionals and those living in or visiting areas with an ongoing Ebola virus disease outbreak) who completed the Zabdeno and Mvabea 2-dose vaccination regimen, a Zabdeno booster vaccination should be considered if more than 4 months have passed since the second dose was administered, according to the EMA.(4) It is recommended by the Strategic Advisory Group of Experts (SAGE) on Immunization for pre-emptive vaccination of national response teams e.g., health workers and frontline workers, international responders, laboratory workers who could be exposed, and those working in special Ebola research and treatment units.(2)

Review question

What is the safety, efficacy, immunogenicity, and duration of protection of licensed Ebola virus vaccines in preventive vaccination and outbreak response settings?

Searches

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

We will search the following databases: MEDLINE Ovid (1946-2023), Embase Ovid (1947-2023), and Cochrane Central Register of Controlled Trials (CENTRAL). The Medline search strategy is reported in Appendix 1. We will also search the EMA and FDA website for regulatory documents and additional data for the two vaccines.

A search will also be conducted of these trial registries to identify ongoing studies: ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), and ISRCTN.

Condition

Ebola virus disease.

Participants/Population

We will include any populations or participants, irrespective of age, sex, or setting.

The following populations are of special interest and will be reported separately if data are available:

- Contacts of Ebola virus disease (EVD) cases
- Health care workers (HCWs) and front-line workers (FLWs) in areas with cases
- HCWs and FLWs in countries at risk of EVD outbreak
- General population in countries at risk of EVD outbreak
- HCWs and FLWs in labs working with Ebola virus
- Children and adolescents (<18 years)
- Pregnant and lactating women
- HIV-infected people

Intervention(s)/exposure(s)

Studies assessing three Ebola vaccines will be included:

- rVSV-ZEBOV-GP (Ervebo, Merck): a live-attenuated recombinant viral vaccine
- Ad26.ZEBOV-GP (Zabdeno, Janssen): a recombinant Adenovirus type 26 (Ad26) encoding the glycoprotein (GP) of the Ebola virus Zaire (ZEBOV) Mayinga strain
- MVA-BN-Filo (Mvabea, Janssen): a recombinant DNA vaccine based on modified vaccinia Ankara (MVA)

We will assess the following dose schedules:

- rVSV-ZEBOV-GP administered as one dose.
- Ad26.ZEBOV-GP and MVA-BN-Filo administered together: one dose Ad26.ZEBOV-GP followed by one dose MVA-BN-Filo at recommended interval of 8 weeks.
- Booster dose following primary dose regimen.

We will assess the following doses:

- rVSV-ZEBOV-GP: 1 mL of ≥72 million plaque forming units (pfu) or 2×10^7 pfu, as licensed by the European Medicines Agency (EMA) in 2019 and pre-qualified by the WHO
- Ad26.ZEBOV-GP: not less than 2.5×10^{10} vp (viral particles) translated as not less than 8.75 $\log_{10}$ infectious units (Inf.U) in 0.5 mL, or sometimes expressed as 5×10^{10} vp, as granted marketing authorisation in 2020 by EMA
- MVA-BN-Filo: 1×10^8 infectious units per dose (0.5 mL), as granted marketing authorisation in 2020 by EMA

Comparator(s)/control

Placebo, non-Ebola control vaccine, delayed vaccination, or no intervention.

Types of study to be included

We will include any study design with usable data, including randomised controlled trials irrespective of phase, non-randomised trials, cohort studies, case-control studies, single arm trials and cohorts, case series, and case reports.

Context

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

Main outcome(s)

Ebola virus disease >10 days after vaccination and serious adverse events, measured at the last available follow-up.

Additional outcome(s)

Immunogenicity outcomes: Binding antibody seroresponse; Binding antibody titres; Neutralizing antibody seroresponse; Neutralizing antibody titres. Immunogenicity outcomes will be collected for all reported timepoints to assess duration of protection.

Additional safety outcomes: Adverse events (any severity), measured at up to 30 days follow-up; Local adverse events and Systemic adverse events, measured at up to 7 days follow-up.

Study selection

Results of all searches will be uploaded to DistillerSR to aid sifting and remote teamwork (5). Citations and abstracts will be screened independently, in duplicate by two review authors. A third review author will resolve any disagreements. We will obtain full-text reports for all potentially eligible studies. Two independent review authors will determine the eligibility of studies for inclusion in the review from the full reports according to predefined criteria. A third systematic review author will resolve any disagreements.

We name studies based on the first-named study author, year of publication, and country. Many studies have more than one document associated with them: journal publications (main study reports, reports of long-term follow-up, secondary outcomes and post-hoc analyses), conference abstracts, and study governance documents (protocols, trial registration listings and results, manufacturers' clinical study reports). For each study we grouped these documents together and designated one report as the primary reference for the study.

Data extraction

We will carry out data extraction using pre-tested data extraction forms in DistillerSR (5). Study characteristics and outcome data will be extracted by one reviewer and cross checked by a second reviewer. We will resolve any differences by discussion between the two review authors and referral to the study reports. We will contact study authors for missing data or clarifications.

Outcome data

We will collect outcome definitions and time points for each outcome.

For dichotomous outcomes, we will collect the number of participants experiencing an outcome event and the number analysed in each intervention group. Where only rates are reported, we will collect the number of events and the person-years in each intervention group.

For GMT or GMC immunogenicity data, we will collect the geometric mean and its 95% confidence interval (CI) for each intervention group.

Where data at the arm level are not available, we will extract adjusted or unadjusted effect estimates with their respective measure of variance (standard error (SE), or 95% CI). Data will be collected on the confounding factors considered in the analysis and the methods used to control for confounding.

Study characteristics

From each included study we will extract data on the following study methods, interventions, and population characteristics.

- Methods: study design, duration of follow-up, number of study centres, location, inclusion and exclusion criteria, and date of study.
- Setting: EVD risk area, type of vaccination (e.g., outbreak response, preventive vaccination, or post-exposure prophylaxis)
- Participants: number, age, sex, type of population (general population, contacts of EVD cases or contacts of contacts, HCWs/FLWs, special populations (children, pregnant women, HIV-infected people), lab workers).
- Interventions: type of vaccine, number of doses and schedule, comparison group.
- Outcomes: outcomes, assay characteristics, and time points reported.
- Notes: sponsorship/funding, notable conflicts of interest of study authors, study registry ID numbers.

Risk of bias (quality) assessment

For RCTs we will use version 2 of the Cochrane Risk of Bias tool for RCTs (ROB 2)(6). We will assess the effect of assignment to intervention at baseline (the 'intention-to-treat effect'), regardless of whether the interventions were received as intended. We will assess the risk of bias per outcome and comparison in the following domains: 1) risk of bias arising from the randomization process; 2) risk of bias due to deviations from intended interventions; 3) risk of bias due to missing outcome data; 4) risk of bias in measurement of the outcome; 5) risk of bias in selection of the reported result; 6) overall risk of bias based on the assessments in the five domains(6).

For observational studies, we will use the Cochrane Risk of Bias tool for Non-randomised Studies of Interventions (ROBINS-I) to assess the risk of bias per outcome and comparison. The ROBINS-I tool cover domains relating to confounding, selection bias, information bias, and reporting bias(7).

One reviewer will independently assess the risk of bias of each included study, and a second reviewer will cross-check assessments. If consensus cannot be reached between the two reviewers, referral to a senior reviewer for a final decision will be made.

The risk of bias assessments will be used for GRADE assessments of the primary outcomes in Summary of findings tables for interpretation of the results.

Strategy for data synthesis

Risk ratios (RR) with 95% confidence intervals will be calculated for dichotomous data (e.g., clinical outcomes, adverse events, seroresponse). Rate ratios will be calculated for dichotomous outcomes reported as incidence rates.

For continuous GMT or GMC data, ratios with 95% CI will be calculated where possible. Initially, the point estimates as well as the lower and upper bound of the 95% CI of GMT or GMC for each group will be transformed into the logarithmic scale to obtain statistically correct standard deviations. Then the mean difference of the compared group will be calculated and results (point estimate and 95% CI) back-transformed to the original scale through exponentiation.

When pooling is feasible, a random-effects meta-analysis will be employed. Feasibility for pooling will be determined based on the outcome definitions and population characteristics, including age, EVD risk status, and special population status.

Appendix 1: Preliminary searches

Ebola Vaccines – MEDLINE Draft Search (Ovid; January 20, 2023)

1. Ebola Vaccines/
2. ((ebola or ebolavirus or EBOV or ZEBOV or EVD) adj10 vaccin*).mp.
3. Hemorrhagic Fever, Ebola/ or Ebolavirus/
4. vaccines/ or viral vaccines/
5. exp vaccination/ or immunization/
6. 4 or 5
7. 3 and 6
8. (Ervebo or rVSV ZEBOV or rVSV EBOV or V920 or rVSV?G ZEBOV or VSV EBOV or Zabdeno* or Ad26?ZEBOV or Mvabea* or MVA BN Filo).mp.
9. 1 or 2 or 7 or 8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. or/10-17
19. exp animals/ not humans.sh.
20. 18 not 19
21. exp cohort studies/ or exp epidemiologic studies/ or exp clinical trial/ or exp evaluation studies as topic/ or exp statistics as topic/
22. ((time and factors) or program or survey* or ci or cohort or comparative stud* or evaluation studies or follow-up*).mp.
23. (control and (group* or study)).mp.
24. or/21-23
25. (animals/ not humans/) or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/
26. hi.fs. or case report.mp.
27. or/25-26
28. 24 not 27
29. 20 or 28
30. 9 and 29

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Table A1. Summary of findings table for safety of Ebola virus vaccines

Patient or population: males and females

Settings: outbreak and preventive settings worldwide

Intervention: rVSV-ZEBOV or Ad26.ZEBOV, MVA-BN-Filo

Comparison: placebo, non-Ebola control vaccine, or no intervention

Effect of interest: effect of assignment to the intervention

Vaccine	Outcome	Illustrative comparative risks*		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
		Control	Ebola virus vaccine				
rVSV-ZEBOV	**Serious adverse events** Follow-up: up to 24 months	18 per 1000	21 per 1000 (14 to 32)	RR 1.16 (0.77 to 1.75)	12,364 (9 RCTs) **	⊕⊕⊕◯ MODERATE [a, b]	See Figure 1 (in main report) and Table A3
		3 more per 1000 (4 fewer to 14 more)					
Ad26.ZEBOV, MVA-BN-Filo	**Serious adverse events** Follow-up: up to 24 months	51 per 1000	59 per 1000 (40 to 87)	RR 1.17 (0.79 to 1.73)	6794 (12 RCTs) ***	⊕⊕⊕◯ MODERATE [b, c]	See Figure 2 (in main report) and Table A4
		9 more per 1000 (11 fewer to 37 more)					

* Illustrative comparative risks are based on rate in control group and relative effect.

** Additional studies considered in GRADE assessment: 6 single arm studies (up to 1 year follow-up, 3914 participants): serious adverse events ranged from 0 to 50 per 1000.

*** Additional studies considered in GRADE assessment: 2 single arm studies (up to 251 days follow-up, 216,163 participants): serious adverse events ranged from 0 to 0.2 per 1000.

[a] Despite some concerns with risk of bias due to lack of blinding, not downgraded as the method of measuring the outcome was deemed appropriate and probably does not differ between groups. Knowledge of intervention status could have influenced outcome assessment, but this was unlikely.

[b] Downgraded one level due to imprecision: 95% CIs include both benefit and harm with the vaccine.

[c] Two studies (EBL2005 infant-AF; EBL3010 pregnant-RWA) were assessed at high risk of overall bias due to unpublished interim results; sensitivity analysis removing these studies from the analysis also showed little to no difference between the groups (RD 1 fewer per 1000, 95% CI 9 fewer to 14 more; RR 0.96, 95% CI 0.56 to 1.67, 10 trials, 4673 participants, I^2= 24%).

Table A2. Serious adverse events reported in rVSV-ZEBOV studies.

Study Country	Population	Follow-up	SAEs/number included participants		Details of SAEs
			rVSV-ZEBOV	Control	
Agnandji 2017 (8) Gabon	Adolescents 13-17 years	1 year	2/20	No control group	Malaria hospitalization; pneumonia hospitalization
	Children 6-12 years	1 year	0/20	No control group	-
Bolay 2018 (9) Liberia	Contacts and contacts of contacts 18-70 years	6 months	0/210	No control group	-
Carnino 2021 (10) Switzerland	FLWs about to be deployed aged 25-70 years	3 days	4/109	No control group	High grade fever (2); vesiculo-papular rash; transient arthritis
Dahlke 2017 (11) Germany	Healthy adults 23-54 years	6 months	0/29**	No control group	-
ElSherif 2017 (12) Canada	Healthy adults 18-62 years	180 days	1/30***	1/10	Cholelithiasis (1); psychotic disorder and major depression (1)
Farooq 2016 (13) USA	Healthy adults 18-50 years	180 days	0/10	0/9	-
Gsell 2017 (14) Guinea	Contacts and contacts of contacts ≥6 years	14 days	3/1510	No control group	Malaria hospitalization (2); stroke hospitalization
Halperin 2017 (15) USA, Spain, Canada	Healthy adults 18-65 years	24 months	35/789	4/133	Conductive deafness (1); autoimmune thyroiditis (2); hyperthyroidism (1); abdominal incarcerated hernia (1); abdominal pain (1); gastrointestinal disorder (1); umbilical hernia (1); cholecystitis (1); hepatic failure (2); appendicitis (1); cellulitis (1); clostridium difficile (1); diverticulitis (2); mastitis (1); pneumonia (1); upper respiratory tract infection (1); urinary tract infection (1); animal bite (1); animal bite (1); arthropod bite (2); craniocerebral injury (1); rib fracture (1); road traffic accident (1); scapula fracture (1); platelet count decreased (1); hyperglycaemic hyperosmolar nonketotic syndrome (1); back pain (1); exostosis (2); foot deformity (1); musculoskeletal chest pain (1); spinal column stenosis (1); basal cell carcinoma (1); breast cancer stage III (1); oropharyngeal squamous cell carcinoma (1); migraine (1); abortion spontaneous (4); nephrolithiasis (1); renal failure (1); menometrorrhagia (1); asthma (1); haemothorax (1); hypoxia (1); pneumothorax

					(1); pulmonary embolism (2); respiratory failure (1); angioedema (1); deep vein thrombosis (1); hypertension (1).
Henao-Restrepo 2015 (16) Guinea (Ebola ça Suffit!)	Adult contacts and contacts of contacts ≥18 years	84 days	Any serious adverse events in vaccinated subjects (immediate or delayed vaccination): 61/5643		See Statistical Safety Report, table 7-3
	Child contacts and contacts of contacts <18 years	84 days	Any serious adverse events in vaccinated subjects (immediate or delayed vaccination): 4/194		
Heppner 2017 (17) USA	Healthy adults 18-61 years	12 months	0/47	0/20	-
Huttner 2015 (18) Switzerland	Healthy adults 20-63 years	12 weeks	0/102****	0/13	-
Juan-Giner 2019 (19) Guinea	HCWs in Ebola-affected areas 18-75 years	250 days	8/2016	No control group	Traffic accident (4); pregnancy-related (2, see below); cerebrovascular accident; acute peritonitis
	Pregnant women HCWs	250 days	2/12	No control group	Miscarriage; stillbirth
Kennedy 2017 (20) Liberia	Adult contacts or HCWs ≥18 years	12 months	47/500	59/500	Malaria (77); gastroenteritis (3); cerebrovascular accident (2); death (3); dehydration (2); pulmonary tuberculosis (3); anaemia (1); malignant hypertension (2); pyrexia (1); typhoid fever (1); foetal death (2); abortion incomplete (1); abortion spontaneous (1); botulism (1); cardiac failure chronic (1); depression (1); diarrhoea haemorrhagic (1); headache (1); hepatic cirrhosis (1); pelvic inflammatory disease (1); plasmodium falciparum infection (1); pneumonia (1); postpartum haemorrhage (1); renal failure (1); respiratory failure (1); seizure (1); sudden death (1); vaginal haemorrhage (1); lower limb fracture (1); pneumocystis jirovecii pneumonia (1); multiple organ dysfunction syndrome (1).
PREVAC 2022 (21) Guinea, Liberia, Sierra Leone, Mali	Adults ≥18 years in countries at risk of EVD outbreaks	12 months	6/395	5/412	Anaemia (1); abdominal pain upper (1); appendicitis (3); cellulitis (1); HIV infection (1); peritonitis (1); pulmonary tuberculosis (1); sepsis (1); head injury (1); humerus fracture (1); ectopic pregnancy (1).
	Children 1-17 years in countries at risk of EVD outbreaks	12 months	9/407	8/389	Sickle cell anaemia with crisis (1); acute abdomen (1); peritoneal haemorrhage (1); death (3); drowning (1); pyrexia (1); appendicitis (3); malaria (1); pneumonia (1); typhoid fever (1); clavicle fracture (1); venom poisoning (1); abortion incomplete (1).

Proches 2023 (22)***** Guinea	Contacts of EVD survivors ≥6 to 18 years	28 days	1/565	No control group	Moderate severity fatigue and muscle pain
	Contacts of EVD survivors ≥18 years		8/1550	No control group	Moderate severity fatigue (2); headache, joint pain, and muscle pain; nausea; dizziness, loss of appetite, buccal inflammation, and itching; joint pain and muscle pain; fatigue, muscle pain, and lower back pain; severe fatigue and moderate headache
Regules 2017 (23) USA	Healthy adults 18-65 years	12 months	0/10	0/9	-
STRIVE (24) Sierra Leone	HCWs and FLWs in EVD outbreak areas	6 months*	54/4172	32/4398	Anaemia, sickle cell anaemia with crisis; abdominal mass; acute abdomen; gastric ulcer haemorrhage; inguinal hernia; inguinal hernia strangulated; inguinal hernia obstructive; pancreatitis; peptic ulcer; peptic ulcer perforation; toothache; umbilical hernia; electrocution; hernia; abscess; abscess limb; appendicitis; cellulitis; encephalitis; HIV wasting syndrome; Ludwig angina; malaria; pelvic inflammatory disease; pulmonary tuberculosis; typhoid fever; urinary tract infection; ankle fracture; clavicle fracture; contusion; femur fracture; foot fracture; forearm fracture; head injury; incisional hernia; jaw fracture; joint dislocation; laceration; lower limb fractur; tibia fracture; diabetes mellitus; chronic myeloid leukaemia; hepatocellular carcinoma; nasopharyngeal cancer; uterine cancer; uterine leiomyoma; aphasia; loss of consciousness; subarachnoid haemorrhage; abortion complete; anxiety; renal failure; adnexal torsion; breast mass; asthma; hematoma; hypertension; hypovolemic shock.

* median follow-up was longer in the vaccine group (180 days vs. 150 days); control group assigned to delayed vaccination; “Enrolment was conducted from April through August 2015 at 7 sites in 5 districts. Participants were individually randomized to either immediate vaccination or deferred (18–24 weeks later) vaccination." "...the deferred group, who were vaccinated from September to December 2015”

**vaccine-related SAEs (study did not report on all SAEs)

***combined vaccine groups $1x10^5$ pfu + $5x10^5$ pfu + $3x10^6$ pfu

****combined vaccine groups $3x10^5$ pfu + $1x10^7$ pfu + $5x10^7$ pfu

*****severe or moderate adverse events

Table A3. Serious adverse events reported in Ad26.ZEBOV, MVA-BN-Filo studies.

Study Country	**Population**	**Follow-up**	**SAEs/number included participants**		**Details of SAEs**
			Ad26, MVA	**Control**	
EBL1001-UK (25)	Healthy adults aged 18–50 years	12 months	1/30	1/12	Bowel perforation following elective colonoscopy; severe gastritis.

EBL2001-EU (26) France, UK	Healthy adults aged 18–65 years	12 months	5/124	1/13	Abortion spontaneous (1); Appendicectomy (1); Cholecystitis acute (1); Hepatitis A (1); Human papilloma virus test positive (1); Miller Fisher syndrome (1).
EBL2002 adult-AF (27) Kenya, Burkina Faso, Cote d'Ivoire, Uganda	Healthy adults 18-70 years old	12 months	20/559	1/109	Abortion spontaneous; acute kidney injury; alcohol poisoning; anembryonic gestation; cataract; cellulitis; congenital, familial, and genetic disorders; dolichocolon; ear and labyrinth disorders; dyspnoea; electrolyte imbalance; eye disorders; gastrointestinal disorders; infections and infestations; glaucoma; injury, poisoning, and procedural complications; inguinal hernia; malaria; ligament sprain; Meniere's disease; metabolism and nutrition disorders; obstruction gastric; pregnancy, puerperium, and perinatal conditions; pulmonary tuberculosis; renal and urinary disorders; respiratory, thoracic, and mediastinal disorders.
	HIV-infected adults 18-50 years	12 months	2/118	0/24	Injury, poisoning, and procedural complications (alcohol poisoning); dyspnoea.
EBL2002 child-AF (28) Kenya, Burkina Faso, Cote d'Ivoire, Uganda	Healthy adolescents 12-17 years old	12 months	0/110	0/21	-
	Healthy children 4-11 years old	12 months	0/108	0/24	-
EBL2005 infant-AF* (29) Guinea, Sierra Leone	Infants 4-11 months	6 months	7/75	1/33	Vaccine group: 6 infections and infestations; 2 metabolism and nutrition disorders; 1 gastrointestinal disorder; Control group: 1 infections and infestations
EBL2011 child boost-SL (30)	Children 4-15 years in countries at risk of EVD outbreak	28 days	0/50	No control group	-
EBL3001 adult-SL (31)	Adults in country at risk of EVD outbreak	2 years	16/298	4/102	Brain abscess (1); gastroenteritis (5); subcutaneous abscess (1); ligament strain (1); skin laceration (1); syncope (1); malaria (3); appendicitis (2); helminthic infection (1); sepsis (1); head injury (2); abortion induced complete (1); chest injury (1); multiple injuries (1); open globe injury (1); radius fracture (1); anaemia (1); anaemia pregnancy (1); abdominal pain (1); dehydration (1); abortion threatened (1); haemorrhage in pregnancy (1); placenta previa (1); premature labour (1); renal hematoma (1); hypovolemic shock (1).
EBL3001 child-SL (32)	Adolescents in country at risk of EVD outbreak	12 months	0/143	1/48	Typhoid fever

	Children 4-11 years in country at risk of EVD outbreak	12 months	5/144	0/48	Gastroenteritis (1); Osteomyelitis chronic (1); Peritonitis (1); Postoperative wound infection (1); Respiratory tract infection (1).
	Children 1-3 years in country at risk of EVD outbreak	12 months	15/144	3/48	Malaria (16); Sepsis (6); Pneumonia (4); Meningitis bacterial (2); Bronchiolitis (1); Subcutaneous abscess (1); Anaemia (4); Iron deficiency anaemia (1); Febrile convulsion (1).
EBL3002-US (33)	Healthy adults, mean age 34 years	12 months	1/150	0/75	Either respiratory disorder or fractured humerus.
EBL3003-US (33)	Healthy adults aged 18–50 years	237 days	4/282	3/47	Death due to chronic prescription drug abuse; death due to the toxic effects of benzodiazepines, cocaine, and opiates; adverse events related to treatment for peripheral arterial occlusive disease; spontaneous abortion; Bell's palsy; pulmonary embolism
EBL3004-US (34)	Healthy adults aged 18–50 years	6 months	11/862	1/48	Injury, poisoning, and procedural complications (5); infections and infestations (2); vascular system disorders (2); nervous system disorders (2); general disorders and administration-site conditions (1); pregnancy, puerperium, and perinatal conditions (1); psychiatric disorders (1)
EBL3008-DRC* (35)	Children and adults (men and non-pregnant women) in country at risk of EVD outbreaks	Not reported	50/19,187	No control group	Most common SAEs: malaria (8 cases), typhoid fever (4 cases), urinary tract infection (4 cases). 1 SAR within 15 minutes of dose 1 (loss of consciousness; treated for anaphylactic shock)
EBL4002 UMURINZI-RWA (36)	Children 2-18 years in areas where EVD is likely to spread	up to 251 days	54/216,113	No control group	Death, vomiting, diarrhoea, ascaris, asphyxiation due to vomiting (1); death, severe malaria (1); death, unknown cause, severe abdominal pain (1); death, acute severe malnutrition and staphylococcal skin infection (1); death, head and abdominal pain (1); death, severe sepsis with suspected leukaemia (1); death, crushing trauma (1); death, food poisoning (1); death, seizures and loss of consciousness (1); death, long history of hypertension and diabetes, recent leg wound debridement, abdominal pain just prior to death (1); death following delivery, COVID-19 (1); death, drowning (1); death, COVID-19 (1); death, 4-y history of seizures and syncope (1); death, history of peptic ulcer disease and hypertension (1); death, post-treatment for gastritis and dry cough (1); death, colon cancer (1); death, road accident (1); death, severe malaria (1); death, cholangiocarcinoma (1); death, gunshot wound (1); cerebral malaria (1); febrile convulsions (8); febrile convulsions, diarrhoea, vomiting (1); febrile convulsions, vomiting (1); fever (3); fever, vomiting, diarrhoea (2); weakness, vomiting (1);

					fever, diarrhoea, vomiting, weakness (1); pharyngitis in pregnancy (1); UTI (1); UTI and vomiting in pregnancy (2); UTI in pregnancy (1); DVT in pregnancy (1); generalized arthralgia with prior history (1); severe lower back pain (1); seizure (1).
PREVAC 2022-AF (21) Guinea, Liberia, Sierra Leone, Mali	Adults ≥18 years in countries at risk of EVD outbreaks	12 months	14/396	5/412	Blood and lymphatic system (1); gastrointestinal (4); general and administration site (1); infections and infestations (11); injury, poisoning, procedural (4); musculoskeletal, connective tissue (1); pregnancy, puerperium, perinatal (1); reproductive system and breast (1); skin and subcutaneous tissue (1).
	Children 1-17 years in countries at risk of EVD outbreaks	12 months	5/403	8/389	Blood and lymphatic system (1); congenital, familial, genetic (1); general and administration site (1); infections and infestations (8); injury, poisoning, procedural (3).

EVD= Ebola virus disease; SAE= serious adverse events; SAR= serious adverse reaction

* preliminary data: unpublished confidential data from presentation to SAGE 2022

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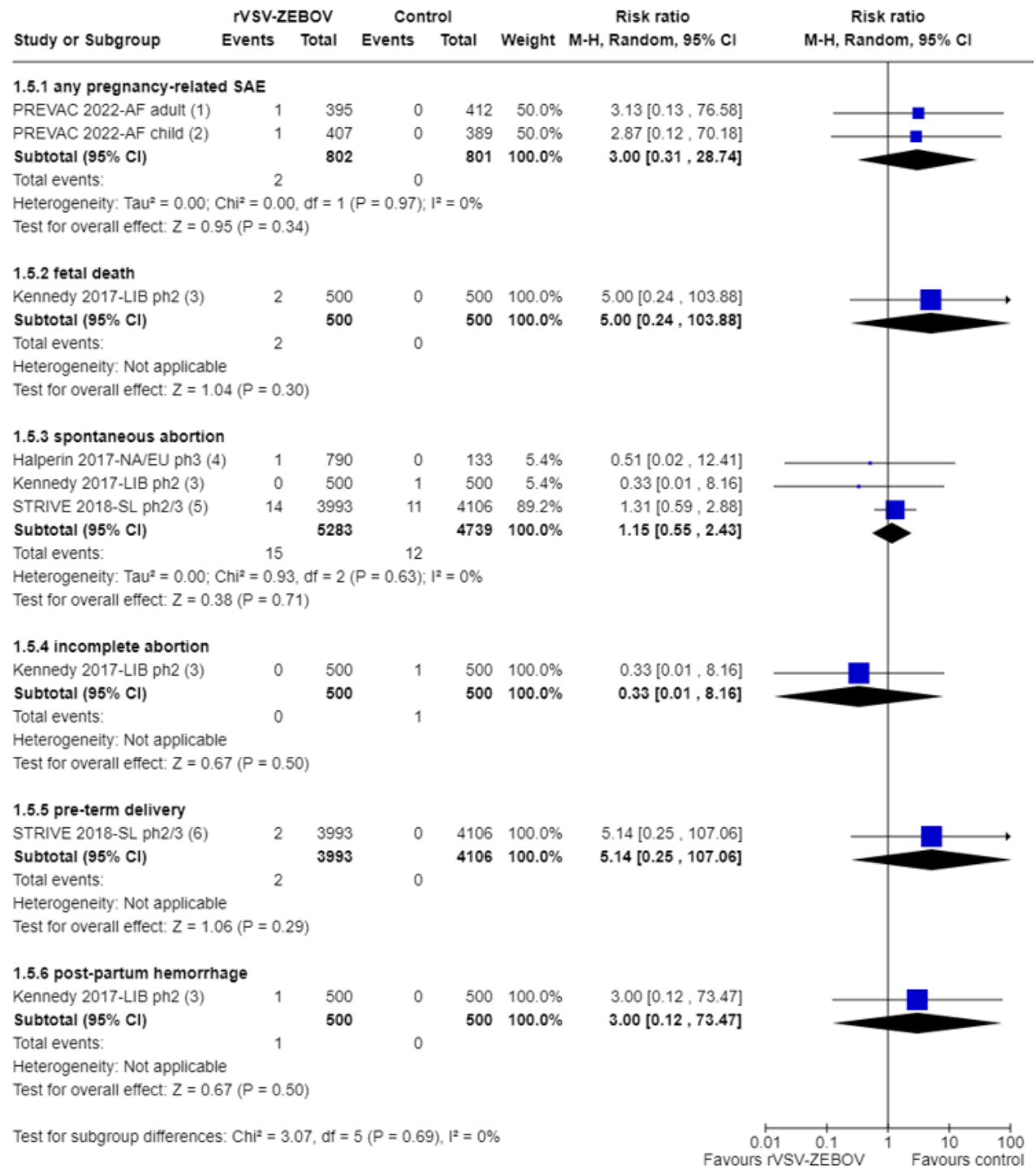
Figure A1. Pregnancy outcomes in rVSV-ZEBOV RCTs



Footnotes

(1) 12 months follow-up; PREVAC 2022, Table S6
(2) 12 months follow-up; PREVAC 2022, Table S7
(3) 12 months follow-up; Kennedy 2017, Table S2
(4) 6 months follow-up; Halperin 2017, Supplemental Table 1
(5) pregnancy loss (spontaneous abortion and stillbirth); Legardy-Williams 2020, Table 1
(6) Legardy-Williams 2020, Table 1

Table A4. Pregnancy outcomes reported in rVSV-ZEBOV studies.

Study Country	Population	Outcome	Follow-up	Events / participants	
				rVSV-ZEBOV	Control
Halperin 2017 (37) USA, Spain, Canada	Healthy adults 18-65 years	Spontaneous abortion	42 days	1/790	0/133
Henao-Restrepo 2015 (38) Guinea (Ebola ça Suffit!)	Adult contacts and contacts of contacts ≥18 years, vaccinated subjects (immediate or delayed vaccination)	Malaria in pregnancy	84 days	1/5643	
		Spontaneous abortion	84 days	2/5643	
Juan-Giner 2019** (19) Guinea	Subgroup: pregnant women	Live birth	180 days	10/11	-
		Miscarriage		1/11	-
		Stillbirth		1/11	-
		Caesarean section		1/11	-
		Any pregnancy-related SAE		2/12	-
Kennedy 2017 (20) Liberia	Adult contacts or HCWs ≥18 years	Incomplete abortion	12 months	0/500	1/500
		Spontaneous abortion		0/500	1/500
		Foetal death		2/500	0/500
		Post-partum haemorrhage		1/500	0/500
PREVAC 2022 (21) Guinea, Liberia, Sierra Leone, Mali	Adults ≥18 years in countries at risk of EVD outbreaks, one dose	Any pregnancy-related SAE	12 months	1/395	0/412
	Children and adolescents 1-17 years in countries at risk of EVD outbreaks, one dose			1/407	0/389
	Adults ≥18 years in countries at risk of EVD outbreaks, two doses			0/197	0/412
	Children and adolescents 1-17 years in countries at risk of EVD outbreaks, two doses			0/202	0/389
STRIVE (39) Sierra Leone	HCWs and FLWs in EVD outbreak areas	Live birth	6 months*	17/3993	22/4106
		Preterm delivery		2/3993	0/4106
		Pregnancy loss (stillbirth; spontaneous abortion)		14/3993	11/4106
	Subgroup: pregnancies with known outcome	Live birth		17/31	22/33
		Preterm delivery		2/31	0/33
		Pregnancy loss (stillbirth; spontaneous abortion)		14/31	11/33
Ring vaccination (40)*** DRC, North Kivu, Ituri 08/08/2018-16/05/2020	Pregnancies during an EVD outbreak	Live birth	Not reported	1654/1663	-
		Caesarean section		72/1663	-
		Spontaneous abortion		5/1663	-
		Stillbirth		3/1663	-
		Maternal death		1/1663	-

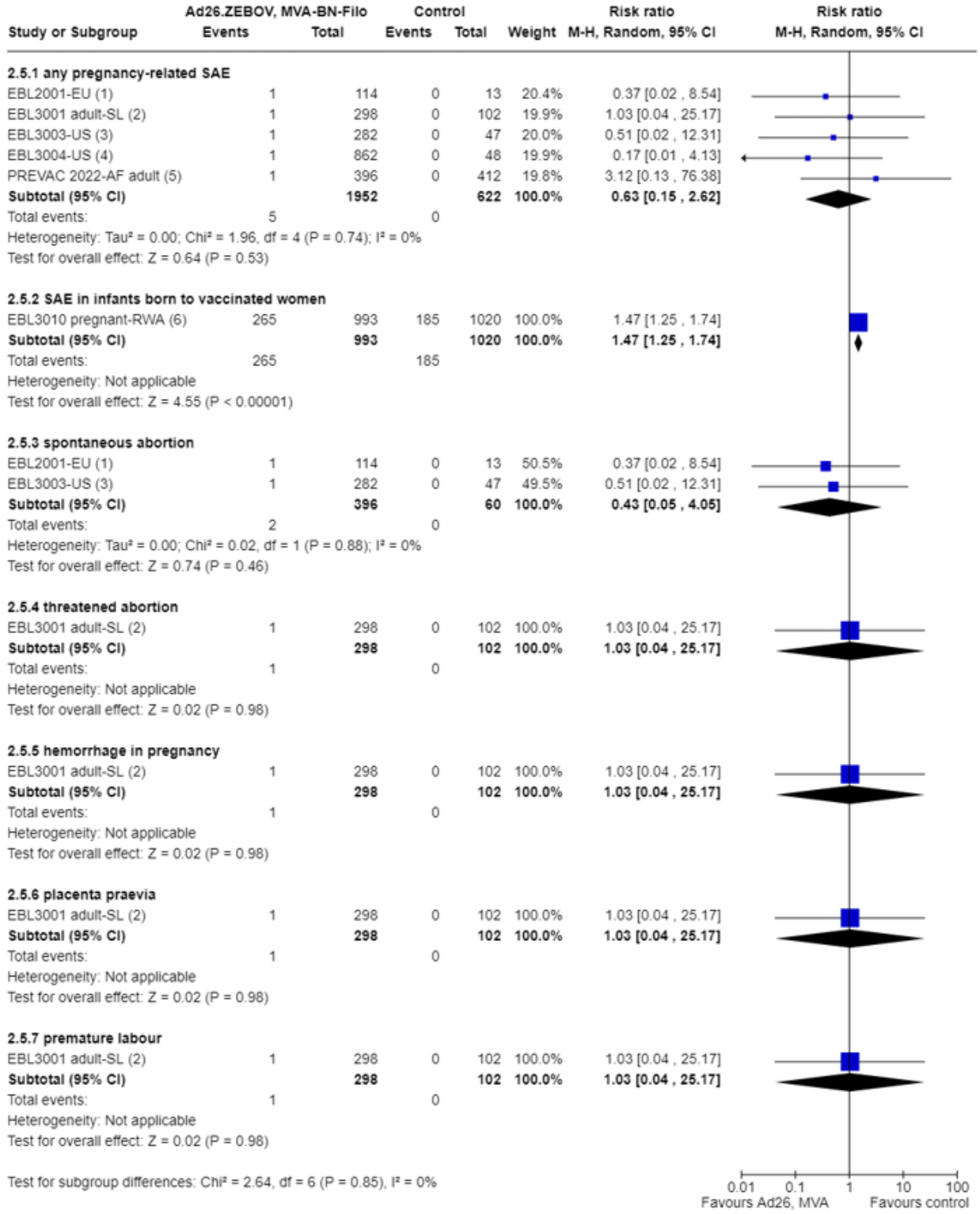
Ring vaccination (40)*** DRC, North Kivu 12/02/2021-31/03/2021, 13/10/2021-16/11/2021	Pregnancies during an EVD outbreak	Live birth	Not reported	10/10	-
		Caesarean section		0/10	-
		Spontaneous abortion		0/10	-
		Stillbirth		0/10	-
		Maternal death		0/10	-
Ring vaccination (40)*** DRC, Equator 05/06/2020-22/11/2020	Pregnancies during an EVD outbreak	Live birth	Not reported	236/236	-
		Caesarean section		2/236	-
		Spontaneous abortion		0/236	-
		Stillbirth		0/236	-
		Maternal death		0/236	-
Ring vaccination (40)*** Guinea, N'Zerekore 23/02/2021-04/04/2021	Pregnancies during an EVD outbreak	Live birth	Not reported	39/40	-
		Caesarean section		8/40	-
		Spontaneous abortion		0/40	-
		Stillbirth		0/40	-
		Maternal death		1/40	-

* median follow-up was longer in the vaccine group (180 days vs. 150 days); control group assigned to delayed vaccination; "Enrolment was conducted from April through August 2015 at 7 sites in 5 districts. Participants were individually randomized to either immediate vaccination or deferred (18–24 weeks later) vaccination." "...the deferred group, who were vaccinated from September to December 2015"

**11 women reported 12 pregnancies. One woman had a spontaneous abortion followed by a healthy live birth.

***Data from unpublished presentation to SAGE on ring vaccination campaigns.

Figure A2. Pregnancy outcomes in Ad26.ZEBOV, MVA-BN-Filo RCTs



Footnotes

(1) 1 year follow-up; Pollard 2021, Table 3 in Appendix 2
(2) 2 years follow-up; Ishola 2022, Table S5
(3) 237 days follow-up; Bockstal 2021, p. 157
(4) 6 months follow-up; Goldstein 2022, poster
(5) 1 year follow-up; PREVAC 20200, Table S6
(6) Date 2022, presentation [confidential]

Table A5. Pregnancy outcomes reported in Ad26.ZEBOV, MVA-BN-Filo studies.

Study Country	Outcome	Population	Follow-up	Events / participants	
				Ad26, MVA	Control
EBL2001-EU (41) France, UK	Spontaneous abortion	Healthy adults aged 18–65 years	1 year	1/114	0/13
	Any pregnancy-related SAE			1/114	0/13
EBL3001 adult-SL (31)	Threatened abortion	Adults in country at risk of EVD outbreak	2 years	1/298	0/102
	Haemorrhage in pregnancy			1/298	0/102
	Placenta praevia			1/298	0/102
	Premature labour			1/298	0/102
	Any pregnancy-related SAE			1/298	0/102
EBL3003-US (33) USA	Spontaneous abortion	Healthy adults aged 18–50 years	237 days	1/282	0/47
	Any pregnancy-related SAE			1/282	0/47
EBL3004-US (34) USA	Any pregnancy-related SAE	Healthy adults aged 18–50 years	6 months	1/862	0/48
EBL3008-DRC* (35)	SAEs in pregnant women	Pregnant women in country at risk of EVD outbreak	Not reported	371/1221	-
	Caesarean section			258/1221	-
	Miscarriage	Pregnancies with known outcomes in women in country at risk of EVD outbreak		55/1238	-
	Stillbirth			30/1238	-
	Live birth			1100/1238	-
	Preterm birth	Infants with known gestational age born to vaccinated women in country at risk of EVD outbreak		188/891	-
	Low birth weight	Infants with known birth weight born to vaccinated women in country at risk of EVD outbreak		79/1032	-
	Early neonatal death (up to 7 days)	Live born infants born to vaccinated women in country at risk of EVD outbreak		11/1100	-
	Congenital abnormalities	Live born infants born to vaccinated women in country at risk of EVD outbreak		5/1100	-
EBL3010 pregnant-RWA* (29)	SAEs in pregnant women**	Pregnant women and their infants	Not reported	125/993	91/1020
	SAEs in infants born to vaccinated women**			265/781	185/801
EBL4002 UMURINZI-RWA (36)	Any pregnancy-related SAE	Women aged 18 years and older in areas where EVD is likely to spread (UMURINZI vaccination campaign)	22 months	5/63,742	-
	UTI (with or without vomiting) in pregnancy			3/63,742	-
	DVT in pregnancy			1/63,742	-

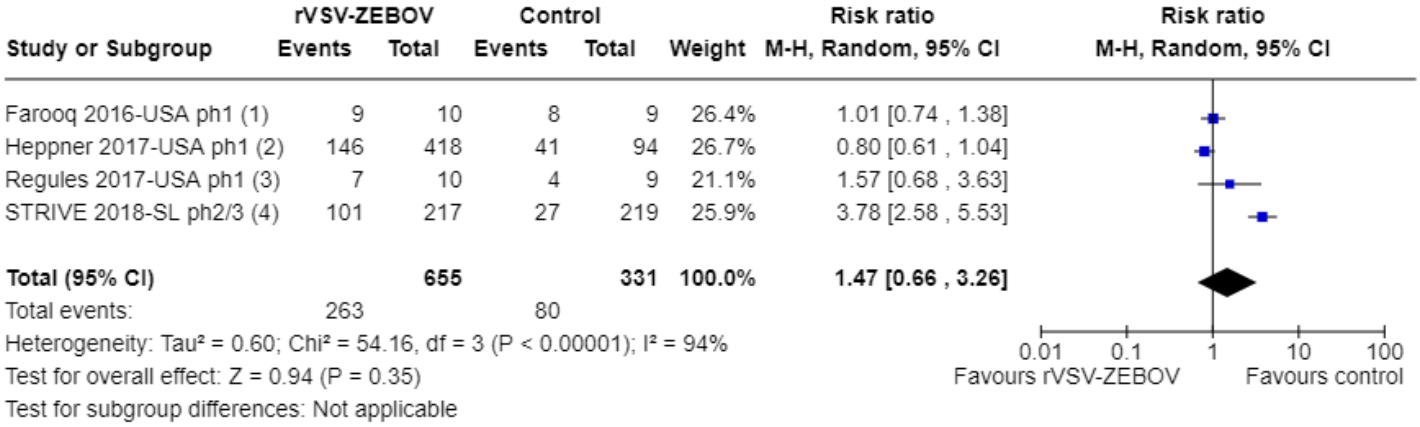
	Pharyngitis in pregnancy			1/63,742	-
PREVAC 2022-AF (21) Guinea, Liberia, Sierra Leone, Mali	Any pregnancy-related SAE	Adults ≥18 years in countries at risk of EVD outbreaks	12 months	1/396	0/412
		Children and adolescents 1-17 years in countries at risk of EVD outbreaks		0/403	0/389

DVT= deep vein thrombosis; EVD= Ebola virus disease; SAE= serious adverse event; UTI= urinary tract infection

*preliminary data: unpublished confidential data from presentation to SAGE 2022

** pregnant women: 3 related: 1 vomiting-post dose 1; 1 headache & 1 fever-post dose 2; infants: none related

Figure A3. Unsolicited adverse events in rVSV-ZEBOV RCTs



Footnotes

(1) 28 days follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02269423

(2) 28 days follow-up; combined doses; Heppner 2017, p 861

(3) 28 days follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02280408

(4) 28 days follow-up; safety substudy: https://clinicaltrials.gov/ct2/show/results/NCT02378753

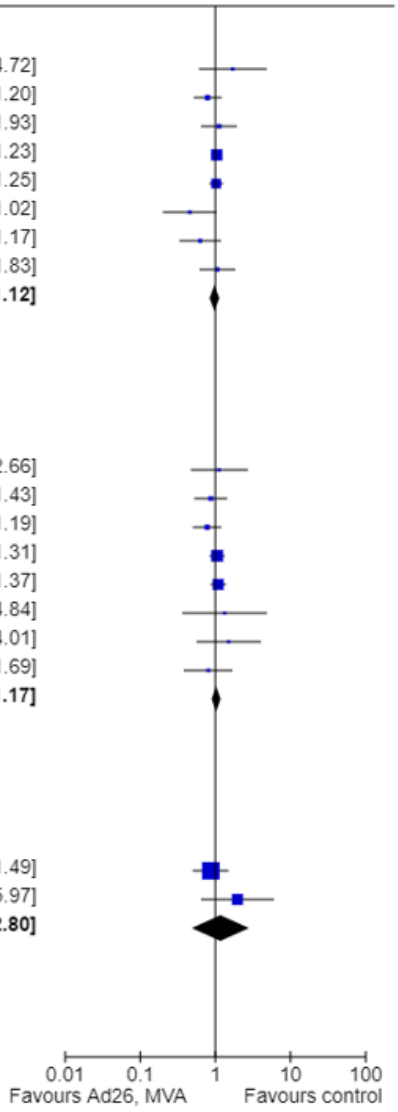
Table A6. Unsolicited adverse events reported in rVSV-ZEBOV studies.

Study Country	**Population**	**Follow-up**	**AEs/number included participants**	
			rVSV-ZEBOV	**Control**
Farooq 2016 (13) USA, phase 1	Healthy adults 18-50 years	28 days	9/10	8/9
Henao-Restrepo 2015 (38) Guinea (Ebola ça Suffit!)	Adult contacts and contacts of contacts ≥18 years	14 days	Any unsolicited adverse events in vaccinated subjects (immediate or delayed vaccination): 658/5643	
	Child contacts and contacts of contacts ≥18 years	14 days	Any unsolicited adverse events in vaccinated subjects (immediate or delayed vaccination): 8/194	
Heppner 2017 (42) USA, phase 1	Healthy adults 18-61 years (combined doses)	28 days	146/418	41/94
Proches 2023 (22) Guinea	Contacts of EVD survivors ≥6 to 18 years	14 days	193/1550	No comparison group
	Contacts of EVD survivors ≥18 years		71/565	No comparison group

Regules 2017 (23) USA, phase 1	Healthy adults 18-65 years	28 days	7/10	4/9
STRIVE (43) Sierra Leone, phase 2/3	HCWs and FLWs in EVD outbreak areas (safety sub-study)	28 days	101/217	27/219

Figure A4. Unsolicited adverse events in Ad26.ZEBOV, MVA-BN-Filo RCTs

Study or Subgroup	Ad26.ZEBOV, MVA-BN-Filo Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI
2.2.1 After first dose						
EBL2002 adult HIV-AF (1)	25	59	3	12	2.0%	1.69 [0.61 , 4.72]
EBL2002 adult-AF (1)	68	224	17	44	10.4%	0.79 [0.52 , 1.20]
EBL2002 child-AF (2)	50	109	9	22	6.7%	1.12 [0.65 , 1.93]
EBL3001 adult-SL (3)	198	298	65	102	36.5%	1.04 [0.88 , 1.23]
EBL3001 child-SL (4)	202	431	66	144	29.7%	1.02 [0.83 , 1.25]
EBL3002-US (5)	10	150	11	75	3.2%	0.45 [0.20 , 1.02]
EBL3003-US (6)	36	270	10	47	5.1%	0.63 [0.33 , 1.17]
FLV1001-US (7)	9	15	13	23	6.6%	1.06 [0.61 , 1.83]
Subtotal (95% CI)		**1556**		**469**	**100.0%**	**0.97 [0.84 , 1.12]**
Total events:	598		194			
Heterogeneity: Tau² = 0.01; Chi² = 8.65, df = 7 (P = 0.28); I² = 19%						
Test for overall effect: Z = 0.39 (P = 0.69)						
2.2.2 After second dose						
EBL2002 adult HIV-AF (1)	22	59	4	12	2.4%	1.12 [0.47 , 2.66]
EBL2002 adult-AF (1)	58	200	13	39	7.4%	0.87 [0.53 , 1.43]
EBL2002 child-AF (2)	48	108	12	21	10.0%	0.78 [0.51 , 1.19]
EBL3001 adult-SL (3)	145	246	48	86	39.1%	1.06 [0.85 , 1.31]
EBL3001 child-SL (4)	187	428	57	142	34.8%	1.09 [0.87 , 1.37]
EBL3002-US (8)	8	145	3	72	1.1%	1.32 [0.36 , 4.84]
EBL3003-US (9)	36	270	4	45	1.9%	1.50 [0.56 , 4.01]
FLV1001-US (7)	5	11	13	23	3.3%	0.80 [0.38 , 1.69]
Subtotal (95% CI)		**1467**		**440**	**100.0%**	**1.02 [0.89 , 1.17]**
Total events:	509		154			
Heterogeneity: Tau² = 0.00; Chi² = 3.59, df = 7 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.2.3 After any dose						
EBL2001-EU (10)	58	124	7	13	64.1%	0.87 [0.51 , 1.49]
EBL3004-US (11)	106	862	3	48	35.9%	1.97 [0.65 , 5.97]
Subtotal (95% CI)		**986**		**61**	**100.0%**	**1.16 [0.48 , 2.80]**
Total events:	164		10			
Heterogeneity: Tau² = 0.24; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Chi² = 0.37, df = 2 (P = 0.83), I² = 0%						



Footnotes

(1) follow-up: 28 days; Barry 2021, table 2
(2) follow-up: 28 days; Anywaine 2022, supplement table A
(3) follow-up: 28 days; Ishola 2022, Table S3
(4) follow-up: 28 days; Afolabi 2022, Table S4
(5) follow-up: 55 days; Bockstal 2021, Table 5
(6) follow-up: 55 days; combined batches; Bockstal 2021, Table 5
(7) follow-up: 28 days; Bockstal 2022, Table 3
(8) follow-up: 42 days; Bockstal 2021, Table 5
(9) follow-up: 42 days; combined batches; Bockstal 2021, Table 5
(10) follow-up: 126 days; https://clinicaltrials.gov/ct2/show/results/NCT02416453
(11) follow-up: 28 days after any dose; Goldstein 2022, poster

Cochrane Response

Table A7. Unsolicited adverse events reported in Ad26.ZEBOV, MVA-BN-Filo studies.

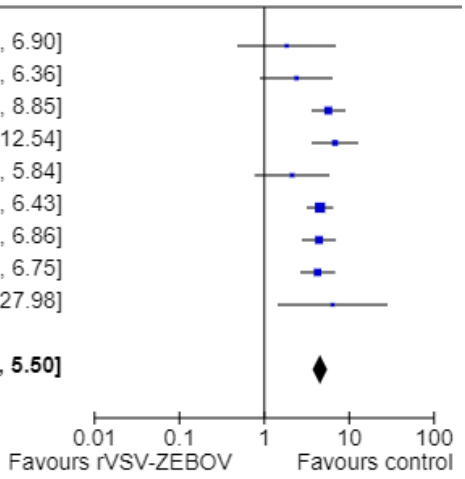
Study Country	Population	Follow-up	AEs/number included participants	
			Ad26, MVA	Control
EBL1001-UK (25)	Healthy adults aged 18–50 years	15 days after first dose	14/15	Not reported in control group
		21 days after second dose	8/12	
EBL1003-KEN (44)	Healthy adults 18-50 years in country at risk of EVD outbreak	28 days after any Ad26.ZEBOV dose	20/30	16/24
		28 days after any MVA-BN-Filo dose	26/30	16/24
EBL2001-EU (26) France, UK	Healthy adults aged 18–65 years	126 days	58/124	7/13
EBL2002 adult-AF (27) Kenya, Burkina Faso, Cote d'Ivoire, Uganda	Healthy adults 18-70 years old	28 days after first dose	68/224	17/44
		28 days after second dose	58/200	13/39
	HIV-infected adults 18-50 years	28 days after first dose	25/59	3/12
		28 days after second dose	22/59	2/12
EBL2002 child-AF (28) Kenya, Burkina Faso, Cote d'Ivoire, Uganda	Healthy adolescents 12-17 years old	28 days after first dose	31/55	5/10
		28 days after second dose	26/54	4/10
	Healthy children 4-11 years old	28 days after first dose	19/54	4/12
		28 days after second dose	22/54	8/11
EBL2011 child boost-SL (30)	Children 4-15 years in countries at risk of EVD outbreak	28 days after booster	32/50	No control group
EBL3001 adult-SL (31)	Adults in country at risk of EVD outbreak	28 days after first dose	198/298	65/102
		28 days after second dose	145/246	48/86
EBL3001 child-SL (32)	Adolescents 12-17 years in country at risk of EVD outbreak	28 days after first dose	54/143	20/48
		28 days after second dose	49/142	13/46
	Children 4-11 years in country at risk of EVD outbreak	28 days after first dose	60/144	18/48
		28 days after second dose	46/143	13/48
	Children 1-3 years in country at risk of EVD outbreak	28 days after first dose	88/144	28/48
		28 days after second dose	92/143	31/48
EBL3002-US (33)	Healthy adults, mean age 34 years	56 days after first dose	10/150	11/75

		42 days after second dose	8/145	3/72
EBL3003-US (33)	Healthy adults aged 18–50 years (combined batches)	56 days after first dose	36/270	10/47
		42 days after second dose	36/270	4/45
EBL3004-US (34)	Healthy adults aged 18–50 years	28 days after any dose	106/862	3/48
EBL4002 UMURINZI-RWA (36)	Children 2-18 years in areas where EVD is likely to spread	up to 251 days	1343/216,113	No control group
FLV1001-US (45)	Healthy adults aged 18–50 years	28 days after first dose	9/15	13/23
		28 days after second dose	5/11	13/23

Figure A5. Local adverse events in rVSV-ZEBOV RCTs

Study or Subgroup	rVSV-ZEBOV Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI
ElSherif 2017-CAN ph1 (1)	11	30	2	10	2.2%	1.83 [0.49 , 6.90]
Farooq 2016-USA ph1 (2)	8	10	3	9	4.0%	2.40 [0.91 , 6.36]
Halperin 2017-NA/EU ph3 (3)	572	790	17	133	17.6%	5.66 [3.63 , 8.85]
Heppner 2017-USA ph1 (4)	34	47	10	94	9.9%	6.80 [3.69 , 12.54]
Huttner 2015-EU ph1/2 (5)	50	102	3	13	3.8%	2.12 [0.77 , 5.84]
Kennedy 2017-LIB ph2 (6)	153	495	34	498	26.7%	4.53 [3.19 , 6.43]
PREVAC 2022-AF adult (7)	133	592	21	412	17.8%	4.41 [2.83 , 6.86]
PREVAC 2022-AF child (7)	126	609	19	389	16.3%	4.24 [2.66 , 6.75]
Regules 2017-USA ph1 (8)	10	10	1	9	1.8%	6.36 [1.45 , 27.98]
Total (95% CI)		**2685**		**1567**	**100.0%**	**4.51 [3.70 , 5.50]**
Total events:	1097		110			

Heterogeneity: Tau² = 0.01; Chi² = 8.58, df = 8 (P = 0.38); I² = 7%
Test for overall effect: Z = 14.88 (P < 0.00001)
Test for subgroup differences: Not applicable



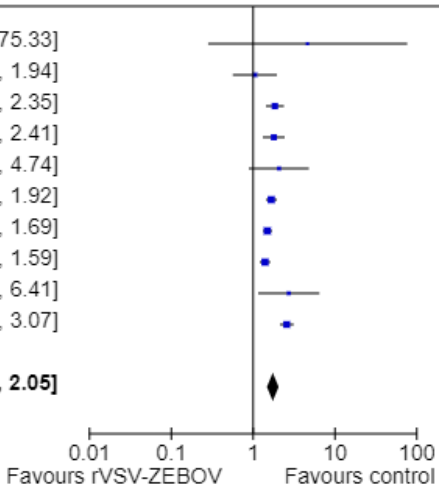
Footnotes

(1) 14 days follow-up; combined dose groups; injection-site pain proxy; ElSherif 2017, p E823
(2) 14 days follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02269423
(3) 42 days follow-up; Halperin 2017, Table 3
(4) 14 days follow-up; Heppner 2017, Table S2
(5) 14 days follow-up; combined doses; pain at injection-site proxy; Huttner 2015, Table S3
(6) 7 days follow-up; Kennedy 2017, Table 2
(7) 7 days follow-up; PREVAC 2022, Table 2
(8) 14 days follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02280408

Figure A6. Systemic adverse events in rVSV-ZEBOV RCTs

Study or Subgroup	rVSV-ZEBOV Events	rVSV-ZEBOV Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
ElSherif 2017-CAN ph1 (1)	6	30	0	10	0.3%	4.61 [0.28 , 75.33]
Farooq 2016-USA ph1 (2)	7	10	6	9	5.2%	1.05 [0.57 , 1.94]
Halperin 2017-NA/EU ph3 (3)	493	791	45	133	13.0%	1.84 [1.44 , 2.35]
Heppner 2017-USA ph1 (4)	35	47	39	94	11.5%	1.79 [1.34 , 2.41]
Huttner 2015-EU ph1/2 (5)	65	102	4	13	3.3%	2.07 [0.90 , 4.74]
Kennedy 2017-LIB ph2 (6)	288	495	174	498	16.0%	1.67 [1.45 , 1.92]
PREVAC 2022-AF adult (7)	390	592	182	412	16.5%	1.49 [1.32 , 1.69]
PREVAC 2022-AF child (7)	363	609	166	389	16.2%	1.40 [1.22 , 1.59]
Regules 2017-USA ph1 (8)	10	10	3	9	3.1%	2.73 [1.16 , 6.41]
STRIVE 2018-SL ph2/3 (9)	187	205	82	231	14.9%	2.57 [2.15 , 3.07]
Total (95% CI)		**2891**		**1798**	**100.0%**	**1.74 [1.47 , 2.05]**
Total events:	1844		701			

Heterogeneity: Tau² = 0.04; Chi² = 37.56, df = 9 (P < 0.0001); I² = 76%
Test for overall effect: Z = 6.56 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

(1) 14 days follow-up; combined dose groups; arthralgia proxy; ElSherif 2017, p E823
(2) 14 days follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02269423
(3) 42 days follow-up; EMA Ervebo assessment report, Table 20
(4) 14 days follow-up; Heppner 2017, Table S2
(5) 14 days follow-up; combined doses; fatigue proxy; Huttner 2015, Table S3
(6) 7 days follow-up; Kennedy 2017, Table 2
(7) 7 days follow-up; PREVAC 2022, Table 2
(8) 14 days follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02280408
(9) 7 days follow-up; Samai 2018, table 3

Table A8. Local and systemic adverse events reported in rVSV-ZEBOV studies.

Study Country	Population	Follow-up	Local AEs/number included participants		Systemic AEs/number included participants	
			rVSV-ZEBOV	control	rVSV-ZEBOV	control
Agnandji 2017 (8) Gabon	Adults ≥18 years	28 days	9/16	No control group	8/16	No control group
	Adolescents 13-17 years		11/20	No control group	10/20	No control group
	Children 6-12 years		10/20	No control group	13/20	No control group
Bolay 2018 (9) Liberia	Contacts and contacts of contacts 18-70 years	1 month	-	-	106/189	No control group
Carnino 2021 (10) Switzerland	FLWs about to be deployed aged 25-70 years	3 days	99/117	No control group	32/109	No control group
Cnops 2015 (46) Belgium	Case report of needlestick injury (PPE)	2 days	-	-	1/1	No control group

Dahlke 2017 (11) Germany	Healthy adults 23-54 years	14 days	9/10	No control group	-	-
Davis 2019 (47) Scotland	Contacts aged 24-67 years	12 months	18/26*	No control group	18/26**	No control group
ElSherif 2017 (12) Canada	Healthy adults 18-62 years (combined dose groups)	14 days	11/30*	2/10*	6/30***	0/10***
Farooq 2016 (13) USA, phase 1	Healthy adults 18-50 years	14 days	8/10	3/9	7/10	6/9
Ficko 2022 (48) DRC	HCWs, mean age 39 years	"immediate"	111/246	No control group	11/246	No control group
Gunther 2011 (49) Germany	Case report of lab needlestick injury (PPE)	14 days	0/1	No control group	1/1	No control group
Halperin 2017 (37, 50) USA, Spain, Canada phase 3	Healthy adults 18-65 years	42 days	572/790	17/133	493/791	45/133
Henao-Restrepo 2015 (38) Guinea (Ebola ça Suffit!)	Adult contacts and contacts of contacts ≥18 years	14 days	Any solicited local or systemic adverse events in vaccinated subjects (immediate or delayed vaccination): 3078/5643			
	Child contacts and contacts of contacts ≥18 years	14 days	Any solicited local or systemic adverse events in vaccinated subjects (immediate or delayed vaccination): 71/194			
Heppner 2017 (42) USA, phase 1	Healthy adults 18-61 years	14 days	34/47	10/94	35/47	39/94
Huttner 2015 (18) Switzerland	Healthy adults 20-63 years (combined dose groups)	14 days	50/102*	3/13*	65/102****	4/13****
Juan-Giner 2019 (19) Guinea	HCWs in Ebola-affected areas 18-75 years	6 days	234/2002	No control group	-	-
Kennedy 2017 (20) Liberia, phase 2	Adult contacts or HCWs ≥18 years	7 days	153/495	34/498	288/495	174/498
PREVAC 2022 (21) Guinea, Liberia, Sierra Leone, Mali	Adults ≥18 years in countries at risk of EVD outbreaks	7 days	133/592	21/412	390/592	182/412
	Children 1-17 years in countries at risk of EVD outbreaks	7 days	126/609	19/389	363/609	166/389
Proches 2023 (22) Guinea	Contacts of EVD survivors ≥6 to 18 years	28 days	38/565*	No control group	216/565**	No control group
	Contacts of EVD survivors ≥18 years		52/1550*	No control group	526/1550**	No control group
Regules 2017 (23) USA, phase 1	Healthy adults 18-65 years	14 days	10/10	1/9	10/10	3/9
STRIVE (24)	HCWs and FLWs in EVD outbreak areas	7 days	166/205	Not reported in control group	187/205	82/231

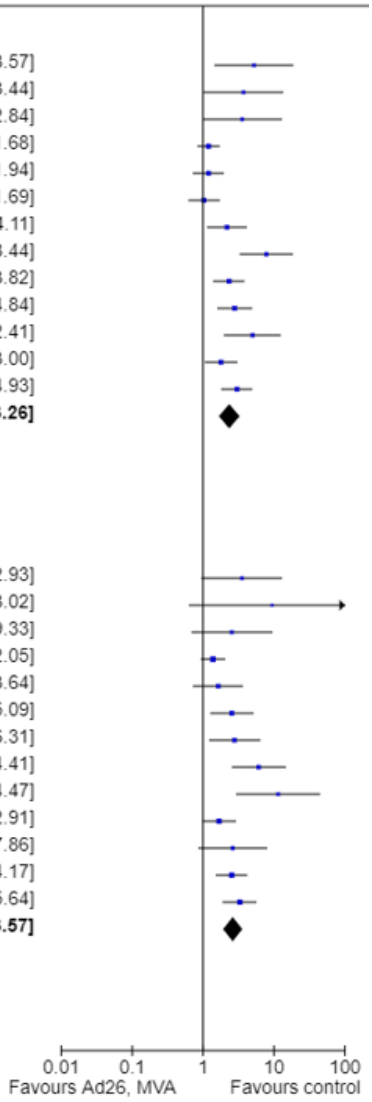
Sierra Leone, phase 2/3						
Wong 2016 (51) Sierra Leone, USA	Adults with occupational exposure aged 36-45 years	21 days	3/5*	No control group	4/5**	No control group

*injection-site pain as proxy; **headache as proxy; ***arthralgia as proxy; ****fatigue as proxy

EVD= Ebola virus disease; FLW= front line worker; HCW= health care worker; PPE= post-exposure prophylaxis

Figure A7. Local adverse events in Ad26.ZEBOV, MVA-BN-Filo RCTs

Study or Subgroup	Ad26.ZEBOV, MVA-BN-Filo Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI
2.3.1 After first dose						
EBL1001-UK (1)	26	30	2	12	4.4%	5.20 [1.46 , 18.57]
EBL2001-EU (2)	71	124	2	13	4.3%	3.72 [1.03 , 13.44]
EBL2002 adult HIV-AF (3)	35	59	2	12	4.3%	3.56 [0.99 , 12.84]
EBL2002 adult-AF (3)	121	224	20	44	10.4%	1.19 [0.84 , 1.68]
EBL2002 child-AF (4)	59	109	10	22	9.4%	1.19 [0.73 , 1.94]
EBL3001 adult-SL (5)	51	298	17	102	9.3%	1.03 [0.62 , 1.69]
EBL3001 child-SL (6)	65	431	10	144	8.2%	2.17 [1.15 , 4.11]
EBL3002-US (7)	78	150	5	75	6.6%	7.80 [3.30 , 18.44]
EBL3003-US (8)	167	282	12	47	9.3%	2.32 [1.41 , 3.82]
EBL3004-US (9)	499	862	10	48	8.9%	2.78 [1.60 , 4.84]
FLV1001-US (10)	13	15	4	23	6.3%	4.98 [2.00 , 12.41]
PREVAC 2022-AF adult (11)	36	396	21	412	9.2%	1.78 [1.06 , 3.00]
PREVAC 2022-AF child (11)	59	403	19	389	9.3%	3.00 [1.82 , 4.93]
Subtotal (95% CI)		**3383**		**1343**	**100.0%**	**2.33 [1.67 , 3.26]**
Total events:	1280		134			
Heterogeneity: Tau² = 0.25; Chi² = 44.75, df = 12 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 4.93 (P < 0.00001)						
2.3.2 After second dose						
EBL1001-UK (12)	17	29	2	12	4.3%	3.52 [0.96 , 12.93]
EBL2001-EU (2)	54	92	0	7	1.3%	9.38 [0.64 , 138.02]
EBL2002 adult HIV-AF (3)	25	59	2	12	4.3%	2.54 [0.69 , 9.33]
EBL2002 adult-AF (3)	113	200	16	39	13.5%	1.38 [0.93 , 2.05]
EBL2002 child-AF (4)	42	108	5	21	8.1%	1.63 [0.73 , 3.64]
EBL3001 adult-SL (5)	58	246	8	86	9.3%	2.53 [1.26 , 5.09]
EBL3001 child-SL (6)	50	428	6	142	7.8%	2.76 [1.21 , 6.31]
EBL3002-US (7)	61	145	5	72	7.4%	6.06 [2.55 , 14.41]
EBL3003-US (8)	137	270	2	45	4.0%	11.42 [2.93 , 44.47]
EBL3004-US (9)	295	756	10	43	11.2%	1.68 [0.97 , 2.91]
FLV1001-US (10)	5	11	4	23	5.5%	2.61 [0.87 , 7.86]
PREVAC 2022-AF adult (11)	49	380	20	392	11.9%	2.53 [1.53 , 4.17]
PREVAC 2022-AF child (11)	55	398	16	381	11.4%	3.29 [1.92 , 5.64]
Subtotal (95% CI)		**3122**		**1275**	**100.0%**	**2.61 [1.91 , 3.57]**
Total events:	961		96			
Heterogeneity: Tau² = 0.15; Chi² = 24.90, df = 12 (P = 0.02); I² = 52%						
Test for overall effect: Z = 6.02 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

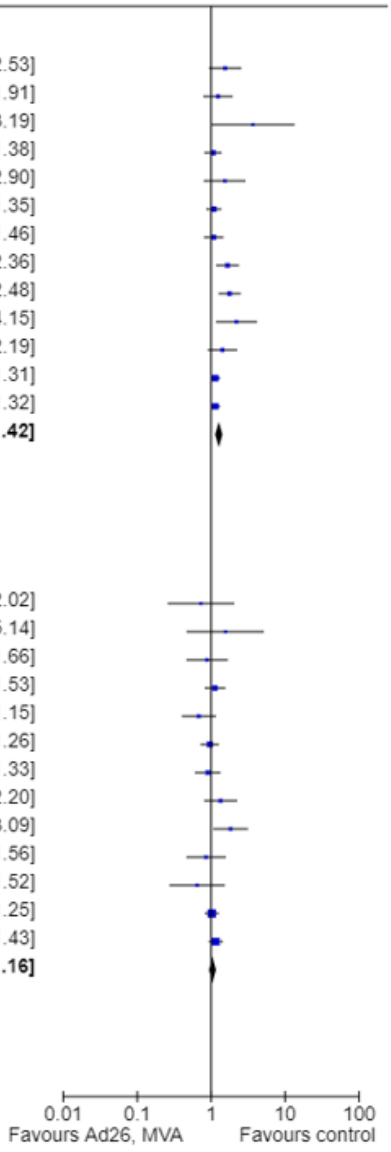


Footnotes

(1) follow-up: 7 days; Milligan 2016, Table 2
(2) follow-up: 7 days; https://clinicaltrials.gov/ct2/show/results/NCT02416453
(3) follow-up: 7 days; Barry 2021, table 2
(4) follow-up: 7 days; Anywaine 2022, supplement table A
(5) follow-up: 7 days; Ishola 2022, Table S1
(6) follow-up: 7 days; Afolabi 2022, Table S1, S2
(7) follow-up: 7 days; Bockstal 2021, Table 6
(8) follow-up: 7 days; combined batches; Bockstal 2021, Table 6
(9) follow-up: 7 days; pain proxy; Goldstein 2022, poster
(10) follow-up: 7 days; Bockstal 2022, Table 2
(11) follow-up: 7 days; PREVAC 2022, Table 2
(12) follow-up: 7 days; 2nd dose on day 29 or 57; Milligan 2016, Table 2

Figure A8. Systemic adverse events in Ad26.ZEBOV, MVA-BN-Filo RCTs

Study or Subgroup	Ad26.ZEBOV, MVA-BN-Filo Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI
2.4.1 After first dose						
EBL1001-UK (1)	27	30	7	12	4.4%	1.54 [0.94 , 2.53]
EBL2001-EU (2)	94	124	8	13	5.2%	1.23 [0.79 , 1.91]
EBL2002 adult HIV-AF (3)	36	59	2	12	0.8%	3.66 [1.02 , 13.19]
EBL2002 adult-AF (3)	140	224	26	44	10.2%	1.06 [0.81 , 1.38]
EBL2002 child-AF (4)	53	109	7	22	2.8%	1.53 [0.80 , 2.90]
EBL3001 adult-SL (5)	161	298	51	102	12.3%	1.08 [0.87 , 1.35]
EBL3001 child-SL (6)	133	431	41	144	9.0%	1.08 [0.81 , 1.46]
EBL3002-US (7)	83	150	25	75	7.2%	1.66 [1.17 , 2.36]
EBL3003-US (8)	212	282	20	47	7.6%	1.77 [1.26 , 2.48]
EBL3004-US (9)	315	862	8	48	2.8%	2.19 [1.16 , 4.15]
FLV1001-US (10)	12	15	13	23	5.2%	1.42 [0.91 , 2.19]
PREVAC 2022-AF adult (11)	198	396	182	412	16.4%	1.13 [0.98 , 1.31]
PREVAC 2022-AF child (11)	195	403	166	389	16.0%	1.13 [0.97 , 1.32]
Subtotal (95% CI)		**3383**		**1343**	**100.0%**	**1.27 [1.13 , 1.42]**
Total events:	1659		556			
Heterogeneity: Tau² = 0.02; Chi² = 20.45, df = 12 (P = 0.06); I² = 41%						
Test for overall effect: Z = 4.01 (P < 0.0001)						
2.4.2 After second dose						
EBL1001-UK (12)	7	29	4	12	1.1%	0.72 [0.26 , 2.02]
EBL2001-EU (2)	41	92	2	7	0.8%	1.56 [0.47 , 5.14]
EBL2002 adult HIV-AF (3)	26	59	6	12	2.8%	0.88 [0.47 , 1.66]
EBL2002 adult-AF (3)	121	200	21	39	11.1%	1.12 [0.82 , 1.53]
EBL2002 child-AF (4)	35	108	10	21	4.1%	0.68 [0.40 , 1.15]
EBL3001 adult-SL (5)	107	246	39	86	14.3%	0.96 [0.73 , 1.26]
EBL3001 child-SL (6)	76	428	28	142	7.3%	0.90 [0.61 , 1.33]
EBL3002-US (7)	43	145	16	72	4.5%	1.33 [0.81 , 2.20]
EBL3003-US (8)	120	270	11	45	4.0%	1.82 [1.07 , 3.09]
EBL3004-US (9)	135	756	9	43	3.2%	0.85 [0.47 , 1.56]
FLV1001-US (10)	4	11	13	23	1.6%	0.64 [0.27 , 1.52]
PREVAC 2022-AF adult (11)	124	382	127	398	23.8%	1.02 [0.83 , 1.25]
PREVAC 2022-AF child (11)	127	399	106	383	21.5%	1.15 [0.93 , 1.43]
Subtotal (95% CI)		**3125**		**1283**	**100.0%**	**1.04 [0.93 , 1.16]**
Total events:	966		392			
Heterogeneity: Tau² = 0.00; Chi² = 12.58, df = 12 (P = 0.40); I² = 5%						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Chi² = 5.94, df = 1 (P = 0.01), I² = 83.2%						



Footnotes

(1) follow-up: 7 days; Milligan 2016, Table 2
(2) follow-up: 7 days; https://clinicaltrials.gov/ct2/show/results/NCT02416453
(3) follow-up: 7 days; Barry 2021, table 2
(4) follow-up: 7 days; Anywaine 2022, supplement table A
(5) follow-up: 7 days; Ishola 2022, Table S2
(6) follow-up: 7 days; Afolabi 2022, Table S1, S2
(7) follow-up: 7 days; Bockstal 2021, Table 7
(8) follow-up: 7 days; combined batches; Bockstal 2021, Table 7
(9) follow-up: 7 days; headache proxy; Goldstein 2022, poster
(10) follow-up: 7 days; Bockstal 2022, Table 2
(11) follow-up: 7 days; PREVAC 2022, Table 2
(12) follow-up: 7 days; 2nd dose on day 29 or 57; Milligan 2016, Table 2

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Table A9. Local and systemic adverse events reported in Ad26.ZEBOV, MVA-BN-Filo studies.

Study Country	Population	Follow-up	Local AEs/number included participants		Systemic AEs/number included participants	
			Ad26, MVA	control	Ad26, MVA	control
EBL1001-UK (25)	Healthy adults aged 18–50 years	7 days after first dose	26/30	2/12	27/30	7/12
		7 days after second dose	17/29	2/12	7/29	4/12
EBL1003-KEN (44)	Healthy adults 18-50 years in country at risk of EVD outbreak	7 days after any dose Ad26	38/59 doses	11/24 doses	44/59 doses	14/24 doses
		7 days after any dose MVA	48/60 doses	11/24 doses	41/60 doses	14/24 doses
EBL2001-EU (26) France, UK	Healthy adults aged 18–65 years	7 days after first dose	71/124	2/13	94/124	8/13
		7 days after second dose	54/92	0/7	41/92	2/7
EBL2002 adult-AF (27) Kenya, Burkina Faso, Cote d'Ivoire, Uganda	Healthy adults 18-70 years old	7 days after first dose	121/224	20/44	140/224	26/44
		7 days after second dose	113/200	16/39	121/200	21/39
	HIV-infected adults 18-50 years	7 days after first dose	35/59	2/12	36/59	2/12
		7 days after second dose	25/59	2/12	26/59	6/12
EBL2002 child-AF (28) Kenya, Burkina Faso, Cote d'Ivoire, Uganda	Healthy adolescents 12-17 years old	7 days after first dose	30/55	5/10	30/55	5/10
		7 days after second dose	20/54	3/10	25/54	6/10
	Healthy children 4-11 years old	7 days after first dose	29/54	5/12	23/54	2/12
		7 days after second dose	22/54	2/11	10/54	4/11
EBL2011 child boost-SL (30)	Children 1-3 years in countries at risk of EVD outbreak	7 days after booster	8/27	No control group	12/27	No control group
	Children 4-11 years in countries at risk of EVD outbreak	7 days after booster	10/23	No control group	4/23	No control group
EBL3001 adult-SL (31)	Adults in country at risk of EVD outbreak	7 days after first dose	51/298	17/102	161/298	51/102
		7 days after second dose	58/246	8/86	107/246	39/86
EBL3001 child-SL (32)	Adolescents in country at risk of EVD outbreak	7 days after first dose	14/143	3/48	52/143	14/48
		7 days after second dose	21/142	1/46	26/142	6/46

	Children 4-11 years in country at risk of EVD outbreak	7 days after first dose	30/144	2/48	45/144	15/48
		7 days after second dose	22/143	5/48	27/143	8/48
	Children 1-3 years in country at risk of EVD outbreak	7 days after first dose	21/144	5/48	36/144	12/48
		7 days after second dose	7/143	0/48	23/143	14/48
EBL3002-US (33)	Healthy adults, mean age 34 years	7 days after first dose	78/150	5/75	83/150	25/75
		7 days after second dose	61/145	5/72	43/145	16/72
EBL3003-US (33)	Healthy adults aged 18–50 years (combined batches)	7 days after first dose	167/282	12/47	212/282	20/47
		7 days after second dose	137/270	2/45	120/270	11/45
EBL3004-US (34)	Healthy adults aged 18–50 years (pain proxy)	7 days after first dose	499/862	10/48	315/862	8/48
		7 days after second dose	295/756	10/43	135/756	9/43
FLV1001-US (52)	Healthy adults aged 18–50 years	7 days after first dose	13/15	4/23	12/15	13/23
		7 days after second dose	5/11	4/23	4/11	13/23
PREVAC 2022-AF (21) Guinea, Liberia, Sierra Leone, Mali	Adults ≥18 years in countries at risk of EVD outbreaks	7 days after first dose	36/396	21/412	198/396	182/412
		7 days after second dose	49/380	20/392	124/382	127/398
	Children 1-17 years in countries at risk of EVD outbreaks	7 days after first dose	59/403	19/389	195/403	166/389
		7 days after second dose	55/398	16/381	127/399	106/383

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Table A10. Characteristics of included studies

Study name, identifiers, location, funding	Study design, dates	Vaccine (dose, type, strategy	Participants (N, age, sex, description)	Comparator	Outcomes extracted
rVSV-ZEBOV (28 studies)					
Agnandji 2017 (8, 53, 54, 55, 56) V920-007 PACTR201411000919191 Gabon, Lambaréné Funding: Wellcome Trust, Bill & Melinda Gates Foundation, Bundesministerium fűr Gesundheit (BMG), German Center for Infection Research (DZIF), Land Baden-Wűrttemberg	Cohort November 2014 to July 2015 Follow-up: 1 year	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	56 6-50 years Female and male Healthy, consenting volunteers resident in the study area, which had no history of an Ebola outbreak *General population in countries at risk of EVD outbreaks*	No comparator	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events
Bolay 2018 (9) PREVAIL I NCT02344407 Liberia Funding: NIAID; NIH; Liberian Ministry of Health	Cohort November 2015 to December 2015 Follow-up: 6 months	rVSV ZEBOV Once IM Standard licensed dose Ring vaccination	210 18–70 years Female and male Close contacts including people living in the same households, households around the family with EVD, HCWs and patients being cared for at a facility visited by cases *Contacts of EVD cases; Contacts of contacts of EVD cases; Probable contacts; HCWs/FLWs in areas with cases who are not contacts*	No comparator	Efficacy: Ebola virus disease Immunogenicity: antibody titres Safety: serious adverse events; systemic adverse events
Carnino 2021 (10) Switzerland, Geneva Funding: Geneva Centre for Emerging Viral Diseases, Division of Humanitarian and Tropical Medicine of the Geneva University Hospitals, Merck Sharp & Dohme	Cohort August 2019 to June 2020 Follow-up: 21 days	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	124 25–70 years Female and male Adult expatriate FLWs to be deployed to an EBOV zone *HCWs/FLWs in countries at risk of EVD outbreaks*	No comparator	Safety: serious adverse events, total adverse events, local adverse events, systemic adverse events

Cnops 2015 (46) Belgium, Brussels Funding: not reported	Case report December 2014 Follow-up: 2 days	rVSV ZEBOV Once IM Dose: ≥1 × 10^8 pfu/mL Post-exposure prophylaxis	1 Age NR Female A physician working for Médecins Sans Frontières, evacuated from Monrovia, Liberia, who, 2 days earlier, had pricked herself with an unused needle that had been in contact with the skin of a patient with confirmed EVD *Contacts of EVD cases*	No comparator	Efficacy: Ebola virus disease Safety: systemic adverse events
Dahlke 2017 (11, 53) V920-006 NCT02283099 Germany, Hamburg Funding: Wellcome Trust, German Center for Infection Research, German National Department for Education and Research (BMBF), Bundesministerium für Gesundheit (BMG)	Non-randomised November 2014 to May 2015 Follow-up: 6 months	rVSV ZEBOV once IM 1) 3 × 10^5 pfu 2) 3 × 10^6 pfu 3) Standard licensed dose Preventive vaccination	30 23-54 years Female and male Healthy adults *Anyone else*	Dose comparison	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events
Davis 2020 (47) UK, Glasgow Glasgow Ebola Vaccine Follow-up Study (GEVS) Funding: US FDA, German Research Foundation, Medical Research Council, Wellcome Trust	Case series October 2015 to October 2016 Follow-up: 12 months	rVSV ZEBOV Once IM Standard licensed dose Post-exposure prophylaxis	26 24–67 years Female and male People who came into direct contact with a HCW presenting with a late reactivation of EVD, who had possible direct skin contact with contaminated bodily fluids and elected to receive vaccination. *Contacts of EVD cases*	No comparator	Efficacy: Ebola virus disease Immunogenicity: seropositivity/conversion Safety: serious adverse events, local adverse events, systemic adverse events

ElSherif 2017 (12) V920-003 NCT02374385 Canada, Halifax Funding: Public Health Agency of Canada; Canadian Institutes of Health Research, US Department of Defense Joint Program Executive Office for Chemical and Biological Defense Medical Countermeasure Systems' Joint Vaccine Acquisition Program (MCS-JVAP)	RCT, phase 1 November 2014 to December 2014 Follow-up: 6 months	rVSV ZEBOV once IM 1) 1×10^5 pfu 2) 5×10^5 pfu 3) 3×10^6 pfu Preventive vaccination	40 18-62 years Female and male Healthy adult volunteers in Canada, without prior infection with a filovirus or VSV or risk of exposure to either, or not a health care worker *Anyone else*	Placebo, once IM	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events
Farooq 2016 (13, 57, 58) V920-001 NCT02269423 USA, Walter Reed Army Institute of Research Funding: Intramural Research Programs of NIAID, NIH; the National Cancer Institute, NIH; the Defense Threat Reduction Agency; and the Joint Vaccine Acquisition Program	RCT, phase 1 October 2014 to January 2015 Follow-up: 180 days	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	19 18-50 years Female and male Healthy adults, male or non-pregnant, non-lactating females *Anyone else*	Placebo, once	Immunogenicity: antibody titres Safety: serious adverse events, total adverse events, local adverse events, systemic adverse events, unsolicited adverse events
Ficko 2022 (48) DRC Funding: None	Cohort December 2018 to December 2020 Follow-up: 90 days	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	246 Mean age 39 years (SD 10) Female and male Humanitarian HWs deployed to the DRC *HCWs/FLWs in areas where the outbreak is likely to spread*	No comparator	Safety: local adverse events; systemic adverse events; unsolicited adverse events

Gsell 2017 (14) Guinea, Guinée Forestière Funding: WHO, Gavi, World Food Programme	Single-arm March 2016 to April 2016 Follow-up: 21 days	rVSV ZEBOV Once IM Dose NR Post-exposure prophylaxis Ring vaccination	1659 Mean age 21 to 44 years Female and male Individuals who visited or were visited by the index case after symptoms onset, had lived in the same household, or were in close physical contact with patients' body, bodily fluids, clothes or linen within the last 21 days; neighbours, family, or extended family members who lived within the nearest geographical boundary of all contacts, and the household members of high-risk contacts *Contacts of EVD cases; Contacts of contacts of EVD cases; Probable contacts; HCWs/FLWs in areas with cases who are not contacts*	No comparator	Efficacy: ebola virus disease Safety: serious adverse events, total adverse events
Gunther 2011 (49) Germany, Hamburg Funding: not reported	Case report March 2009 to April 2009 Follow-up: 21 days	rVSV ZEBOV Once IM Standard licensed dose Post-exposure prophylaxis	1 Age NR Female A virologist working in the BSL-4 laboratory who pricked herself in the finger during a mouse experiment *HCWs/FLWs in labs working with virus*	No comparator	Efficacy: Ebola virus disease Safety: local adverse events, systemic adverse events
Halperin 2017 (15, 37, 50) V920-012 NCT02503202 USA, Spain, Canada Funding: Merck & Co, Biomedical Advanced Research and Development Authority (BARDA, US Department of Health and Human Services)	RCT August 2015 to September 2017 Follow-up: 24 months	rVSV ZEBOV Once IM 1) Standard licensed dose 2) High-dose (1×10^8 pfu) Preventive vaccination	1197 18-65 years Female and male Healthy individuals *Anyone else*	Placebo, once	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, total adverse events, local adverse events, systemic adverse events

Henao-Restrepo 2015 (16, 38, 59) Ebola ça Suffit! V920-010 PACTR201503001057193 Guinea, Basse-Guinée Funding: World Health Organization, Wellcome Trust, Research Council of Norway, Médecins sans frontières, Public Health Agency of Canada	Cluster RCT April 2015 to January 2016 Follow-up: 84 days	rVSV ZEBOV Immediate vaccination Once IM Standard licensed dose Ring vaccination	4690 Age NR Female and male All contacts and contacts of contacts including absent residents *Contacts of EVD cases; Contacts of contacts of EVD cases; Probable contacts; HCWs/FLWs in areas with cases who are not contacts*	rVSV ZEBOV Delayed vaccination	Efficacy: Ebola virus disease Safety: serious adverse events, total adverse events
Heppner 2017 (17, 42) V920-004 USA Funding: Biomedical Advanced Research and Development Authority, US Department of Health and Human Services	RCT, phase 1b December 2014 to June 2015 Follow-up: 360 days	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	141 18-61 years Female and male Healthy adults *Anyone else*	Placebo, once IM	Immunogenicity: seropositivity/conversion, antibody titres Safety: local adverse events, systemic adverse events
Hoff 2022 (60) DRC, North Kivu Funding: Bill and Melinda Gates Foundation, US FDA Medical Countermeasures Initiative, NIAID	Cohort August 2018 to September 2018 Follow-up: 6 months	rVSV ZEBOV once IM Standard licensed dose Ring vaccination	608 12-82 years Female and male EVD-exposed and potentially exposed populations in North Kivu Province, including contacts and contacts of contacts of confirmed cases, and health care/frontline workers in EVD-affected or potentially affected areas *Contacts of EVD cases; Contacts of contacts of EVD cases; Probable contacts; HCWs/FLWs in areas with cases who are not contacts; HCWs/FLWs in areas where the outbreak is likely to spread; HCWs/FLWs in countries at risk of EVD outbreaks*	No comparator	Immunogenicity: antibody titres

Huttner 2015 (18, 53, 54, 55) V920-005 NCT02287480 Switzerland, Geneva Funding: Wellcome Trust	RCT, phase 1/2 January 2015 Follow-up: 12 weeks	rVSV ZEBOV Once IM 1) 1×10^7 pfu 2) 5×10^7 pfu 3) 3×10^7 pfu Preventive vaccination	115 20-63 years Female and male Non-pregnant, immunocompetent, healthy adults *Anyone else*	Placebo, once	Immunogenicity: antibody titres Safety: serious adverse events, total adverse events
Juan-Giner 2019 (19, 61, 62, 63) V920-018 PACTR201503001057193 Guinea, Conakry Funding: Médecins Sans Frontières	Non-randomised March 2015 to July 2016 Follow-up: 6 months	rVSV ZEBOV Once IM Standard licensed dose Ring vaccination	2016 18-75 years Female and male Personnel working in health services, including Ebola treatment centre, Ebola outreach and non-Ebola related health services. *HCWs/FLWs in areas with cases who are not contacts of EVD cases;* *HCWs/FLWs in areas where the outbreak is likely to spread;* *HCWs/FLWs in countries at risk of EVD outbreaks*	No vaccine	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, total adverse events, local adverse events,

Kasereka 2019 (64) DRC, Mangina, Butembo, North Kivu Funding: Association for Health Innovation in Africa	Cross-sectional September 2018	rVSV-ZEBOV Once IM Dose NR Ring vaccination	186 >18 years Sex NR Convenience sample of vaccine recipients among health workers, contacts, and contacts of contacts infected with Ebola, and unvaccinated community members, selected from the rural commune of Mangina, where the epidemic began, and the urban centre of Butembo 80km away, where there is current ongoing transmission. *Contacts of EVD cases; Contacts of contacts of EVD cases; Probable contacts (all who request vaccination in a village with EVD cases); HCWs/FLWs in areas with cases who are not contacts of EVD cases; HCWs/FLWs in areas where the outbreak is likely to spread*	No vaccine	Safety: total adverse events
Kennedy 2017 (20, 62, 63, 65) PREVAIL I V920-009 NCT02344407 Liberia, Monrovia Funding: NIAID, Liberian Ministry of Health	RCT February 2015 to April 2015 Follow-up: 12 months	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	1500 ≥18 years Female and male Volunteers *General population in countries at risk of EVD outbreaks*	Placebo, once	Efficacy: Ebola virus disease Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events

Mbala-Kingebeni 2021 (66) DRC, Mangina Funding: Bill and Melinda Gates Foundation, National Science Foundation Graduate Research Fellowship Program, Pew Biomedical Scholarships, National Institutes of Health, National Cancer Institute	Case report December 2018 to December 2019 Follow-up: 12 months	rVSV ZEBOV Once IM Dose NR Post-exposure prophylaxis Ring vaccination	1 25 years Male A man who presented to the Ebola treatment unit with a 2-day history of fever, nausea, vomiting, asthenia, anorexia, myalgia, and chest pain, who had received the rVSV-ZEBOV vaccine 6 months previously because he was a contact of a person with confirmed EVD *Contacts of EVD cases*	No comparator	Efficacy: Ebola virus disease
Nsio 2023 (67) DRC, North-Kivu and Ituri provinces Funding: Médecins Sans Frontières and its research affiliate Epicentre	Cohort August 2018 to August 2019 Follow-up: not reported	rVSV ZEBOV Dose not reported Ring vaccination	24,666 <5 to >26 years Female and male Individuals with possible EVD, registered by response authorities according to the WHO case definition, admitted to 30 Ebola facilities (treatment or transit centres, or isolation units in health centres) *Contacts of EVD cases; Contacts of contacts of EVD cases; Probable contacts; HCWs/FLWs in areas with cases who are not contacts*	No comparator	Efficacy: Ebola virus disease
Proches 2023 (22) Guinea, Basse-Guinée Funding: the UN Foundation; the WHO	Cohort May to September 2016 Follow-up: 28 days	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	2115 ≥6 years Female and male *Contacts of EVD survivors*	No comparator	Immunogenicity; Safety

Raabe 2021 (68) PREPARE V920-013 NCT02788227 USA Funding: NIAID	Cohort October 2016 to December 2023 (estimated) Follow-up: 6 months	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	32 24-67 years Female and male Healthy adults at risk of exposure to Ebola virus at work through lab or clinical contact *HCWs/FLWs in labs working with virus*	No comparator	Immunogenicity: seropositivity/conversion
Regules 2017 (23, 58) V920-002 NCT02280408 USA, NIH Clinical Center, Bethesda, Maryland Funding: Intramural Research Programs of the NIAID, NIH, National Cancer Institute, Defense Threat Reduction Agency, Joint Vaccine Acquisition Program	RCT, phase 1 October 2014 to January 2015 Follow-up: 1 year	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	19 18-65 years Female and male Healthy adults from the Washington, D.C.–Baltimore metropolitan area *Anyone else*	Placebo, once	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, total adverse events, local adverse events, systemic adverse events, unsolicited adverse events
STRIVE (24, 39, 43, 62, 63, 69, 70, 71) V920-011 NCT02378753 PACTR201502001037220 Sierra Leone Funding: CDC; NIH	RCT, phase 2/3 April 2015 to August 2015 Follow-up: 6 months	rVSV ZEBOV Once IM Standard licensed dose Preventive vaccination	8651 18– 79.5 years Female and male HCWs and FLWs after aggressive Ebola control efforts were implemented and after the epidemic peaked. *HCWs/FLWs in areas where the outbreak is likely to spread*	Delayed vaccination	Efficacy: Ebola virus disease Safety: serious adverse events, local adverse events, systemic adverse events
V920-008 ph1 (53, 54, 72, 73) NCT02296983 Kenya, Kilifi Funding: Wellcome Trust, Public Health Agency of Canada	Non-randomised December 2014 to January 2015 Follow-up: 12 months	rVSV ZEBOV Once IM 1) $3x10^6$ pfu 2) Standard licensed dose Preventive vaccination	40 22-52 years Female and male Healthy adult volunteers *General population in countries at risk of EVD outbreaks*	Dose comparison	Immunogenicity: seropositivity/conversion, antibody titres

WHO Ebola Virus Outbreak Response Team 2019 (74, 75) DRC, North Kivu and Ituri provinces Funding: Wellcome Trust, UK Government through the Department of International Development, Gavi, World Bank	Cohort August 2018 to December 2019 Follow-up: 16 months	rVSV ZEBOV Once IM Standard licensed dose Ring vaccination	292,251 All ages Female and male *Contacts of EVD cases; Contacts of contacts of EVD cases; Probable contacts; HCWs/FLWs in areas with cases who are not contacts*	No comparator	Efficacy: Ebola virus disease
Wong 2016 (51, 76) USA, Sierra Leone Funding: CDC	Case series September 2014 to April 2015 Follow-up: 21 days	rVSV ZEBOV Once IM Standard licensed dose Post-exposure prophylaxis	6 36-45 years Female and male Persons who had occupational exposures to Zaire ebolavirus in Sierra Leone (ETU patient care areas, and outside a nearby ETU), monitored initially in US healthcare facilities. *Contacts of EVD cases*	No comparator	Efficacy: Ebola virus disease Safety: local adverse events, systemic adverse events
Ad26.ZEBOV, MVA-BN-Filo and rVSV-ZEBOV (1 study)					
PREVAC 2022 (21, 77, 78) Guinea, Liberia, Sierra Leone, Mali Funding: National Institutes of Health, INSERM, London School of Hygiene and Tropical Medicine, Janssen, Merck Sharp and Dohme, European Union, Innovative Medicines Initiative 2 Joint Undertaking, EU Horizon 2020 Research and Innovation Program, European Federation of Pharmaceutical Industries and Associations, National Cancer Institute	RCT April 2018 to December 2018 Follow-up: 1 year	1) Ad26.ZEBOV I dose IM + MVA-BN-Filo I dose IM, 56 days apart 2) rVSV ZEBOV 1 dose IM + Placebo, 56 days apart Standard licensed doses Preventive vaccination	2810 Median age adults 27 years (IQR 20–38); children 8 years (IQR 4–13) Female and male Adults ≥18 years of age and children aged 1 to 17 years, without a history of EVD, who were not pregnant or breastfeeding. *General population in countries at risk of EVD outbreaks*	Placebo 2 doses, 56 days apart rVSV ZEBOV 2 doses, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events

Ad26.ZEBOV, MVA-BN-Filo (18 studies)					
EBL1001-UK (25, 79, 80, 81, 82) NCT02313077 UK, Oxford Funding: EU Innovative Medicines Initiative (receives support from the European Union Horizon 2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations, Crucell Holland	RCT, phase 1 December 2014 to February 2015 Follow-up: 1 year	Ad26 + MVA: 2) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on Day 29 4) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on Day 57 5) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on Day 15 Standard licensed doses Preventive vaccination	87 18-50 years Female and male Healthy adults *Anyone else*	Placebo, 2 doses IM, 56 days apart 1) MVA-BN-Filo 1 dose IM + Ad26.ZEBOV 1 dose IM on Day 29 3) MVA-BN-Filo 1 dose IM + Ad26.ZEBOV 1 dose IM on Day 57	Immunogenicity: antibody titres Safety: serious adverse events, local adverse events, systemic adverse events
EBL1003-KEN (44, 79) NCT02376426 Kenya, Nairobi Funding: Innovative Medicines Initiative 2 Joint Undertaking, Janssen Ebola Vaccine Program, Janssen Vaccines and Prevention, EU Horizon 2020 Research and Innovation Programme, European Federation of Pharmaceutical Industries and Association, National Institute of Allergy and Infectious Diseases, National Institutes of Health	RCT, phase I March 2015 to September 2016 Follow-up: 360 days	Ad26 + MVA: 1) 2 doses IM, 28 days apart 2) 2 doses IM, 56 days apart MVA + Ad26: 1) 2 doses IM, 28 days apart 2) 2 doses IM, 56 days apart Standard licensed dose Preventive vaccination	72 18-45 years Female and male Healthy volunteers living in Kenya and local to the study centre. *Anyone else*	Placebo, 2 doses IM, 28 or 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: local adverse events, systemic adverse events, unsolicited adverse events

EBL1004-AF (79, 83) NCT02376400 Tanzania (Mwanza), Uganda (Masaka) Funding: Innovative Medicines Initiative 2 Joint Undertaking, Janssen Vaccines and Prevention, EU Horizon 2020 Research and Innovation Programme, European Federation of Pharmaceutical Industries and Association, NIAID	RCT, phase 1 February 2015 to September 2016 Follow-up: 12 months	Ad26 + MVA: Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM, 56 days apart Standard licensed Preventive vaccination	72 19-43 years Female and male Healthy adult volunteers recruited from two malaria-endemic areas. *General population in countries at risk of EVD outbreaks*	Placebo, 2 doses IM, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres
EBL2001-EU (26, 41, 45) EBOVAC2 NCT02416453 France, UK Funding: Innovative Medicines Initiative, Janssen Vaccines & Prevention B.V.	RCT, phase 2 June 2015 to April 2016 Follow-up: 12 months	Ad26 + MVA: Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM, 56 days apart Standard licensed dose Preventive vaccination	423 18-65 years Female and male Healthy adults with no history of Ebola vaccination *Anyone else*	Placebo, 2 doses IM, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events
EBL2002 adult-AF (27) NCT02564523 PACTR202002606736841 Kenya, Burkina Faso, Cote d'Ivoire, Uganda Funding: Janssen Vaccines and Prevention B.V., European Commission IMI2 programme, Innovative Medicines Initiative Ebola+ Program, National Institute for Health Research, Oxford Biomedical Research Centre	RCT, phase 2 November 2015 to February 2019 Follow-up: 729 days	Ad26 + MVA: 1) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on day 29 2) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on day 57 3) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on day 85 Preventive vaccination	1073 18-69 years Female and male Healthy adults, HIV-infected adults (aged 18 to 50 years *General population in countries at risk of EVD outbreaks*	Placebo: 1) 2 doses, 28 days apart 2) 2 doses, 56 days apart 3) 2 doses, 84 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events

EBL2002 child-AF (28) NCT02564523 PACTR202002606736841 Kenya, Burkina Faso, Cote d'Ivoire, Uganda Funding: Janssen Vaccines and Prevention B.V., European Commission IMI2 programme, Innovative Medicines Initiative Ebola+ Program, National Institute for Health Research, Oxford Biomedical Research Centre	RCT, phase 2 November 2015 to February 2019 Follow-up: 729 days	Ad26 + MVA: 1) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on day 29 2) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on day 57 3) Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on day 85 Preventive vaccination	1073 4-17 years Female and male Adolescents aged 12-17; Children aged 4-11 *General population in countries at risk of EVD outbreaks*	Placebo: 1) 2 doses, 28 days apart 2) 2 doses, 56 days apart 3) 2 doses, 84 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events
EBL2005 infant-AF (29, 84) NCT03929757 Guinea, Sierra Leone Funding: Janssen Vaccines & Prevention B.V.	RCT, phase 2 August 2019 and ongoing Follow-up: 6 months	Ad26 + MVA 2 doses IM on days 0 and 57 + 1 dose MenACWY at 6 months follow-up visit	108 4-11 months Infants (female and male) *General population in countries at risk of EVD outbreaks*	MenACWY, 3 doses day 0, 57, and at 6 months	Safety; Immunogenicity NB: data collected from confidential presentation
EBL2010 HIV boost-AF (77, 85) PACTR202102747294430 Kenya, Uganda Funding: London School of Hygiene and Tropical Medicine	Cohort March 2021 and ongoing Follow-up: not reported	Ad26.ZEBOV booster Standard licensed dose Preventive vaccination	26 HIV infected adults vaccinated with Ad26.ZEBOV 1 dose IM + MVA 1 dose IM four years earlier (EBL2002) *General population in countries at risk of EVD outbreaks*	No control group	Immunogenicity NB: data collected from confidential presentation

EBL2011 child boost-SL (30) NCT04711356 PACTR202102484171450 Sierra Leone, Kambia Town Funding: Innovative Medicines Initiative 2 Joint Undertaking, Janssen Vaccines and Prevention, EU Horizon 2020 research and innovation programme, European Federation of Pharmaceutical Industries and Associations	Cohort July 2021 to August 2021 Follow-up: 1 month	Ad26.ZEBOV booster One dose IM Standard licensed dose Preventive vaccination	50 4-15 years Female and male Healthy children who had received Ad26.ZEBOV, MVA-BN-Filo regimen at least 2 years earlier in the EBOVAC Salone trial. *General population in countries at risk of EVD outbreaks*	No comparator	Immunogenicity: antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events
EBL3001 adult-SL (31) NCT02509494 PACTR201506001147964 Sierra Leone, Kambia district Funding: Innovative Medicines Initiative 2 Joint Undertaking, Janssen Vaccines & Prevention B.V.	Single-arm (stage 1) and RCT (stage 2) September 2015 to October 2016 Follow-up: Single-arm 3 years: RCT 2 years	Ad26 + MVA: Stage 1: 2 doses IM, 56 days apart; Ad26.ZEBOV booster 1 dose IM Stage 2: 2 doses IM, 56 days apart Standard licensed doses Preventive vaccination	Stage 1: 43 adults Stage 2: 400 adults Female and male Healthy adults aged ≥18 years, residing in or near Kambia district. *General population in countries at risk of EVD outbreaks*	MenACWY + placebo, 2 doses IM, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events,
EBL3001 child-SL NCT02509494 PACTR201506001147964 Sierra Leone, Kambia district Funding: Innovative Medicines Initiative 2 Joint Undertaking, Janssen Vaccines & Prevention B.V.	RCT April 2017 to July 2018 Follow-up: 2 years	Ad26 + MVA: 2 doses IM, 56 days apart Standard licensed doses Preventive vaccination	576 children Female and male Healthy children and adolescents aged 1–17 years, residing in or near Kambia district. *General population in countries at risk of EVD outbreaks*	MenACWY + placebo, 2 doses IM, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events,

EBL3002-US (33) NCT02543567 USA, Alabama, California, Florida, Illinois, Indiana, Maryland Funding: Janssen Vaccines & Prevention B.V., Biomedical Advanced Research and Development Authority (BARDA)	RCT, phase 3 July 2015 to November 2016 Follow-up: 7.8 months	Ad26 + MVA: Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM on day 56 Standard licensed doses Preventive vaccination	525 (225 in the relevant/extracted arms) Mean age 34 and 33 years per extracted arm Female and male Healthy individuals without prior exposure to Ebola virus *Anyone else*	Placebo, 2 doses IM, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events
EBL3003-US (33) NCT02543268 USA, Alabama, California, Florida, Illinois, Indiana, Maryland Funding: Janssen Vaccines & Prevention B.V., Biomedical Advanced Research and Development Authority (BARDA)	RCT, phase 3 September 2015 to January 2016 Follow-up: 237 days	Ad26 + MVA: Ad26.ZEBOV 1 dose IM + MVA-BN-Filo 1 dose IM, 56 days apart Preventive vaccination	329 18-50 years Female and male Adults in good health *Anyone else*	Placebo, 2 doses IM, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events
EBL3004-US (34) NCT04228783 USA Funding: Janssen Vaccines & Prevention B.V.	RCT, phase 3 February 2020 to April 2022 Follow-up: 6 months	Ad26 + MVA 2 doses IM, 56 days apart Preventive vaccination	910 18-50 years Female and male Healthy adults *Anyone else*	Placebo, 2 doses IM, 56 days apart	All-cause mortality Safety: serious adverse events, local adverse events, systemic adverse events, unsolicited adverse events
EBL3008-DRC (35, 86) DRC-EB-001 NCT04152486 DRC, Goma Funding: the Coalition for Epidemic Preparedness Innovations (CEPI); the Paul G. Allen Family Foundation; the UK Department for International Development (DFID); Wellcome; the European Union's Horizon 2020 research and innovation programme.	Cohort November 2019 and ongoing Follow-up: 2 years	Ad26 + MVA 2 doses IM, 56 days apart Preventive vaccination	20,408 (including 1221 pregnant women) Age from 1 year Female and male Adults, children, pregnant women *General population in countries at risk of EVD outbreaks*	No comparator	Safety; Pregnancy outcomes; Immunogenicity NB: data collected from confidential presentation

EBL3010 pregnant-RWA (29, 87) INGABO NCT04556526 Rwanda Funding: Janssen Vaccines & Prevention B.V.	RCT, phase 3 October 2020 and ongoing Follow-up: 1 year	Ad26 + MVA 2 doses IM, 56 days apart Preventive vaccination	4022 From 18 years Pregnant women *General population in countries at risk of EVD outbreaks*	Delayed vaccination (Ad26 + MVA 2 doses IM, 56 days apart)	Pregnancy and neonatal outcomes; serious adverse events NB: data collected from confidential presentation
EBL4002 UMURINZI-RWA (36) Rwanda, Rubavu district, Rusizi, Kigali Funding: Wellcome Trust/UK Foreign, Commonwealth and Development Office, J&J. Ebola Vaccine Deployment, Acceptance and Compliance Consortium (funded by the Innovative Medicines Initiative)	Cohort December 2019 to July 2021 Follow-up: 296 days	Ad26 + MVA 2 doses, 56 days apart Standard licensed dose Preventive vaccination	216,113 2 to ≥18 years Female and male Rwandan residents in bordering regions most at risk of Ebola spread from the DRC. *General population in countries at risk of EVD outbreaks*	No comparator	Safety: serious adverse events, unsolicited adverse events
FLV1001-US (52) NCT02860650 USA Funding: NIAID; Janssen Vaccines & Prevention B.V.	RCT, phase 1 September 2016 to January 2018 Follow-up: 12 months	Ad26 + MVA: Ad26.ZEBOV I dose IM + MVA I dose IM, 56 days later Standard licensed dose Preventive vaccination	72 19-50 years Female and male Healthy adults, no prior filovirus vaccine candidate vaccination, no known previous exposure to MARV, EBOV, SUDV, or Taï Forest Ebolavirus *Anyone else*	Placebo 2 doses IM, 56 days apart	Immunogenicity: seropositivity/conversion, antibody titres Safety: local adverse events, systemic adverse events, unsolicited adverse events

CDC= Centers for Disease Control and Prevention; DRC= Democratic Republic of Congo; EVD= Ebola virus disease; MenACWY= Meningococcal bacteria type A, C, W, and Y vaccine; NIAID= National Institute of Allergy and Infectious Diseases; NIH= National Institutes of Health

Table A11. Risk of bias in RCTs reporting on efficacy

Study	Domain	Judgement	Support for judgement
Henao-Restrepo 2015 (16, 59) Ebola ça Suffit! Guinea, Basse-Guinée	1. Bias arising from the randomization process	Low	Low risk of bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomization
	2. Bias due to deviations from intended interventions	Low	The SAP proposed analytical strategies for the primary and secondary objectives but did not explicitly define the ITT and PP comparison groups. However, the amendment to the SAP defined the ITT and PP analysis periods. An overview of all possible comparisons is reported.
	3. Bias due to missing outcome data	Low	Data were available for nearly all participants defined for this analysis: of 2119 vaccinated in the immediate group 99.5% (n=2108) were included in the analysis; of 1435 eligible and consenting in the delayed group 99.6% (n=1429) were included in the analysis.
	4. Bias in measurement of the outcome	Low	Confirmation of cases with Ebola virus disease was done independently of the study team as part of the national surveillance of Ebola virus disease, throughout and beyond the follow-up period of the trial. Confirmatory retesting of samples of index cases and endpoints augmented the independence of the process.
	5. Bias in selection of the reported result	Low	This is an additional analysis that was not included in the protocol. Reported to be included following interim analysis.
	Overall bias	Low	The study is judged to be of low risk of bias.

Table A12. Risk of bias in RCTs reporting on serious adverse events

Study	Domain	Judgement	Support for judgement
EBL1001-UK (25, 82)	1. Bias arising from the randomization process	Low	"Participants were centrally randomized, using an interactive web response system."; allocation sequence probably random, allocation concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomization process.
	2. Bias due to deviations from intended interventions	Low	"Masking: Triple (Participant, Investigator, Outcomes Assessor)."Blinded study (participants and personnel). ITT and available case analysis, no participants excluded from analysis due to protocol violation.
	3. Bias due to missing outcome data	Low	Data available for all participants.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The prospective trial registry record and protocol were available. Outcomes analysed as pre-specified.
	Overall bias	Low	
EBL2001-EU (26, 41) France, UK	1. Bias arising from the randomization process	Low	Computer-generated randomisation codes using interactive web response system; sequence random, allocation concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.

	2. Bias due to deviations from intended interventions	Low	Partially blinded study for safety outcomes: Cohort I (10/137; 7% participants) was open-label. Other participants were blinded, personnel preparing vaccines were unblinded, all other personnel in Cohorts II & III were blinded. No participant cross-over; deviations did probably not arise because of the trial context. Appropriate analysis: all vaccinated participants were analysed.
	3. Bias due to missing outcome data	Low	Data available for all 137 participants randomised to these arms.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Partially unblinded study (10/137; 7% participants); however, given the severity of this outcome and the small percentage of the sample involved, this was probably not affected by knowledge of intervention assignment.
	5. Bias in selection of the reported result	Low	The prospective protocol, trial registry record, and statistical analysis plan were available. Outcome analysed as pre-specified.
	Overall bias	Low	
EBL2002 adult-AF (27) Kenya, Burkina Faso, Cote d'Ivoire, Uganda	1. Bias arising from the randomization process	Low	Interactive web response system used for randomization; sequence random; allocation concealed; minor imbalances in baseline characteristics do not suggest problems with the randomization process.
	2. Bias due to deviations from intended interventions	Low	Blinded study (participants and personnel); Appropriate analysis: all vaccinated participants were analysed for safety.
	3. Bias due to missing outcome data	Low	Data available for all 1073 randomised participants for safety.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The protocol prospective trial registry record was available. Outcome analysed as pre-specified.
	Overall bias	Low	
EBL3001 adult-SL (31)	1. Bias arising from the randomization process	Low	Central computer-generated block randomisation; sequence random, allocation concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	Partially blinded study: participants were blinded, personnel preparing vaccines unblinded; No participant cross-over; deviations did probably not arise because of the trial context; Appropriate safety analysis, total vaccinated cohort.
	3. Bias due to missing outcome data	Low	Data available for nearly all [400/402] participants randomised.

	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups; Outcome assessors were unaware of intervention allocations
	5. Bias in selection of the reported result	Low	The prospective protocol/trial registry were available: Outcomes analysed as pre-specified
	Overall bias	Low	
EBL3002-US (33)	1. Bias arising from the randomization process	Low	Computer-generated schedule via an Interactive Web Response System provided by the sponsor, balanced using randomly permuted blocks, and stratified by site; sequence random, allocation concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	Partially blinded study: participants were blinded, personnel preparing vaccines were unblinded, all other personnel were blinded. Appropriate analysis: all vaccinated participants were analysed.
	3. Bias due to missing outcome data	Low	Data available for all 225 participants randomised to these arms.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The protocol prospective trial registry record was available. Outcome analysed as pre-specified.
	Overall bias	Low	
EBL3003-US (33)	1. Bias arising from the randomization process	Low	Computer-generated schedule via an Interactive Web Response System; allocation sequence random, allocation concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	Blinded study (participants and personnel). ITT and available case analysis performed for safety.
	3. Bias due to missing outcome data	Low	Data available for all participants for safety.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Double-blinded study. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The prospective protocol, trial registry record and statistical analysis plan were available. Outcomes analysed as pre-specified.
	Overall bias	Low	
EBL3004-US (34)	1. Bias arising from the randomization process	Some concerns	"Eligible participants in the United States (aged 18-50 years [inclusive]) were randomised in a 6:6:6:1 ratio to one of four groups"; allocation sequence probably random, no information on allocation concealment. Minor imbalances in baseline

			characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	Blinded study (participants and personnel). ITT analysis, no participants excluded from analysis due to protocol violation.
	3. Bias due to missing outcome data	Low	Data available for all (910) randomised participants.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The protocol prospective trial registry record was available. Outcome analysed as pre-specified.
	Overall bias	Some concerns	
ElSherif 2017 (12) Canada	1. Bias arising from the randomization process	Low	"A randomization list was computer generated with a block size of 8... Study pharmacists prepared allocated treatment; an unblinded nurse concealed and administered it. The pharmacists did not have any interaction with study participants or blinded study staff, and the unblinded nurse had no other role in the study." Sequence random, allocation probably concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	"Partially blinded study: participants were blinded, personnel preparing and administering vaccines were unblinded, all other personnel were blinded." Appropriate analysis: ITT, no participants excluded from analysis due to protocol violation.
	3. Bias due to missing outcome data	Low	Data available for all participants randomised (40/40).
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Some concerns	The trial registry record was retrospective. No information on whether the result was selected from multiple outcome measurements or analyses of the data.
	Overall bias	Some concerns	
Farooq 2016 (13, 57) USA	1. Bias arising from the randomization process	Low	Masking: Triple (Participant, Care Provider, Investigator) Allocation sequence probably random, allocation probably concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	"Masking: Triple (Participant, Care Provider, Investigator)" Blinded study (participants and personnel). Appropriate analysis: all available vaccinated participants were analysed.

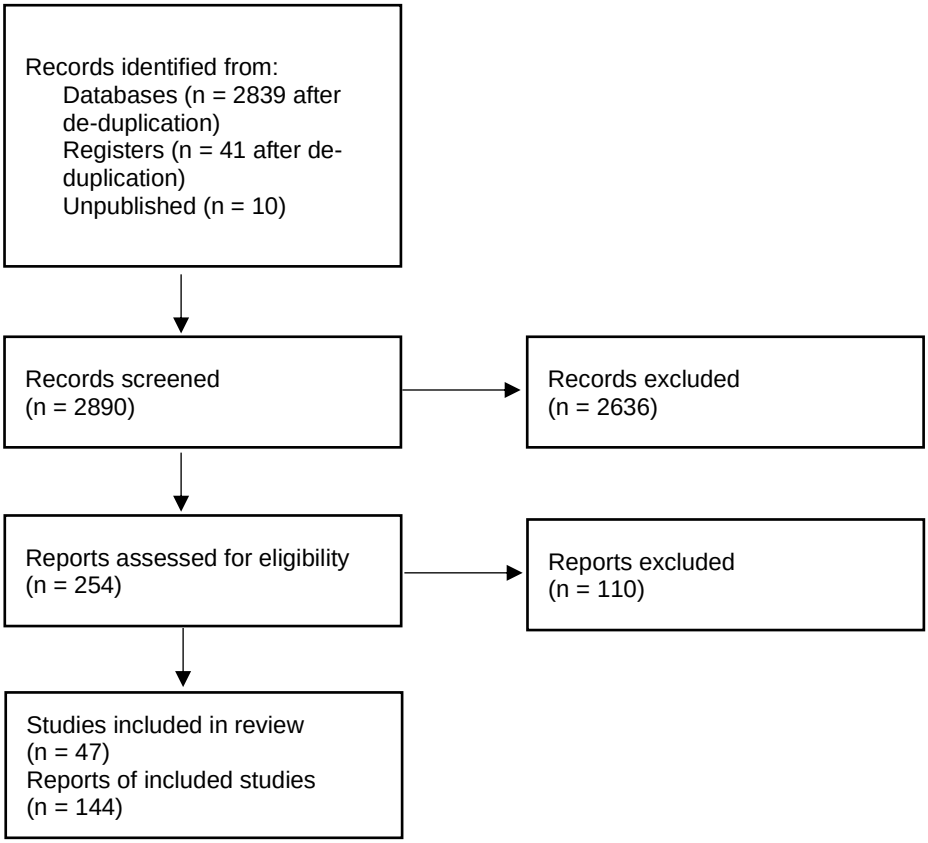
	3. Bias due to missing outcome data	Low	Data available for all participants for outcomes to day 28 and nearly all participants to day 180.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The protocol (prospective) and trial registry record (registered 2 weeks after trial start) record were available. Outcomes analysed as pre-specified.
	Overall bias	Low	
Halperin 2017 (15, 37, 50) USA, Spain, Canada	1. Bias arising from the randomization process	Low	Treatment allocation/randomization occurred centrally using an interactive voice response system using a computer-generated, site-balanced allocation schedule. Allocation sequence random, allocation concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	"A double-blind/masking technique was used. The rVSVΔG- ZEBOV-GP vaccine and placebo were prepared and dispensed by an unblinded pharmacist or qualified trial site personnel. The subject, the investigator, and personnel involved in the vaccine administration or clinical evaluation were blinded. All study assessments were conducted in a blinded manner; unblinding occurred after database lock." Blinded study (participants and personnel/carers). For safety at 6 months, all available cases were included in analyses. As we are assessing the effect of assignment to intervention, the analysis method performed on these outcomes was considered appropriate.
	3. Bias due to missing outcome data	Low	Comment: 1197 participants randomized; 1183 participants analysed for safety at 6 months. Data available for nearly all participants randomized for safety at 6 months.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The prospective protocol and registries were available. Outcomes were included in the registries and/or protocol and analysed as pre-specified.
	Overall bias	Low	
Huttner 2015 (18, 53, 54, 55, 88) Switzerland	1. Bias arising from the randomization process	Some concerns	Central randomization using investigator-blinded, randomly permuted blocks. Sequence random, allocation concealed. 19 participants were not randomized and all received the vaccine.
	2. Bias due to deviations from intended interventions	Low	Unblinded study (participants, personnel, and carers). No participant cross-over; deviations did probably not arise because of the trial context' Appropriate analysis: ITT.
	3. Bias due to missing outcome data	Low	Data available for 111/115 participants.

	4. Bias in measurement of the outcome	Some concerns	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Unblinded outcome assessment. Safety outcomes require clinical judgement and could be affected by knowledge of intervention assignment.
	5. Bias in selection of the reported result	Low	The prospective protocol and trial registry record plan were available. Outcome analysed as pre-specified.
	Overall bias	Some concerns	
Kennedy 2017 (20) Liberia	1. Bias arising from the randomization process	Low	Block randomization (block size of 12) with centrally prepared randomization schedule. Allocation sequence probably random, probably concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	Study volunteers, clinical staff following the participants for safety and efficacy outcomes and laboratory staff performing the analyses were fully blinded. Appropriate analysis: all available vaccinated participants were analysed.
	3. Bias due to missing outcome data	Low	Data available for nearly all participants (993/1000 to 1000/1000).
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The prospective trial registry records were available. Safety and efficacy outcomes analysed as pre-specified.
	Overall bias	Low	
PREVAC 2022 (21, 78) Guinea, Liberia, Sierra Leone, Mali	1. Bias arising from the randomization process	Some concerns	"Participants were randomly assigned." Allocation sequence probably random. No information on allocation concealment. Minor imbalances in baseline characteristics do not suggest problems with the randomization process.
	2. Bias due to deviations from intended interventions	Low	"Study participants and clinical and laboratory staff assessing the study participants for safety and laboratories carrying out safety and immunogenicity analyses were blinded to whether vaccine or matched placebo was given." Blinded study (participants and personnel). Appropriate analysis: available case analysis.
	3. Bias due to missing outcome data	Low	Safety assessed in the full analysis set, with data available for all or nearly all participants.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Low	The prospective protocol, trial registry record and statistical analysis plan were available. Outcomes analysed as pre-specified.
	Overall bias	Some concerns	

Regules 2017 (23, 58) USA	1. Bias arising from the randomization process	Low	"Randomly assigned in a blinded manner" Masking: Double (Participant, Investigator) Trial declared as randomised, but no additional information provided. Allocation sequence probably random. Allocation probably concealed. Minor imbalances in baseline characteristics do not suggest problems with the randomisation process.
	2. Bias due to deviations from intended interventions	Low	Masking: Double (Participant, Investigator). Appropriate analysis: all available vaccinated participants were analysed.
	3. Bias due to missing outcome data	Some concerns	Not all data available (17/19) for 1 year safety outcomes.
	4. Bias in measurement of the outcome	Low	Method of measuring outcome probably appropriate. Probable that measurement or ascertainment of outcome did not differ between groups. Outcome assessors were unaware of intervention allocations.
	5. Bias in selection of the reported result	Some concerns	The protocol (prospective) and trial registry (registered 3 weeks after trial start) record were available. 1-year outcomes not pre-specified. No information on whether the result was selected from multiple outcome measurements or analyses of the data.
	Overall bias	Some concerns	
STRIVE 2018 (24, 39, 62, 70) Sierra Leone	1. Bias arising from the randomization process	Some concerns	"We randomized participants separately in each of the 7 enrolment sites and minimized site-level imbalance using the Big Stick Design with a maximum imbalance of 3." Allocation sequence probably random. No information on allocation concealment. Minor imbalances in baseline characteristics do not suggest problems with the randomization process.
	2. Bias due to deviations from intended interventions	Some concerns	Unblinded study. Of 4139 randomized to immediate vaccination, 154 were not vaccinated and analysed in the untreated arm; of 4332 randomized to deferred vaccination, 12 were vaccinated in error and analysed in the vaccinated arm. This deviation could affect the outcome. Nevertheless, this domain was rated as some concern as it is impossible to distinguish deviation because of trial context and deviation because of intervention effect. As-treated analysis, not considered appropriate to assess effect of assignment to intervention.
	3. Bias due to missing outcome data	Some concerns	Of 8651 randomized, 8049 (93.0%) were analysed for Ebola virus disease, 8099 (93.6%) for serious adverse events; of 449 in the safety sub study, 436 (97.1%) were analysed for reactogenicity; of 508 enrolled in the immunogenicity sub-study, 326-503 (64-99%) were included in analyses. Data not available for all or nearly all participants randomized for EBV and SAE.

	4. Bias in measurement of the outcome	Some concerns	Follow-up time was longer in the vaccine group compared to the control group (median 180 vs. 150 days). Unblinded outcome assessment. This outcome requires clinical judgement and could be affected by knowledge of intervention assignment.
	5. Bias in selection of the reported result	Low risk	The prospective trial registry records were available. Safety and efficacy outcomes analysed as pre-specified.
	Overall bias	Some concerns	

Figure A9. PRISMA flow diagram



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Ring vaccination campaigns	Diallo A. Summary of the safety data of rVSV-ZEBOV-GP in pregnant women and in other age groups. Unpublished presentation to SAGE Ebola vaccine working group, June 2022 (Day 1_2 Abdhourahamane Diallo_safety)

Ongoing studies and completed studies awaiting assessment

Study ID Status	Sources	Design	Country	Population	Intervention
NCT05202288 ANRS 0064S IMOVA Ongoing	https://clinicaltrials.gov/ct2/show/NCT05202288	RCT, phase 2	Guinea	healthy volunteers, n=135	rVSV-ZEBOV with or without Inmazeb
NCT05130398 PACTR202005733552021 V920-014 EBOLAPED Ongoing	https://clinicaltrials.gov/ct2/show/NCT05130398	RCT, phase 1/2	Gabon	children + their contacts/relatives, n=120	rVSV-ZEBOV vs. chicken pox / varicella (Varilix) vaccine
NCT03031912 V920-015 ACHIV-Ebola Ongoing	https://clinicaltrials.gov/ct2/show/NCT03031912	RCT, phase 2	Burkina Faso, Canada, Senegal	HIV infected adults and adolescents, n=250	rVSV-ZEBOV vs. saline placebo
EBL1005 Unknown, awaiting assessment	listed as ongoing in EMA report: "Signal assessment report on Embolic and Thrombotic events (SMQ) with COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant])"	RCT, phase 1	not reported	healthy adults	Ad26.ZEBOV, MVA-BN-Filo
EBL1007 Completed, awaiting assessment	listed as ongoing in EMA report: "Signal assessment report on Embolic and Thrombotic events (SMQ) with COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant])"; confirmed as an existing study by Johnson & Johnson	RCT, phase 1	not reported	healthy adults	Ad26.ZEBOV, MVA-BN-Filo
NCT02891980 EBL1008 Completed, awaiting assessment	https://clinicaltrials.gov/ct2/show/NCT02891980	RCT, phase 1	USA	18-45 years, n=65	Ad26.ZEBOV, MVA-BN-Filo
EBL2006 Completed, awaiting assessment	listed as ongoing in EMA report: "Signal assessment report on Embolic and Thrombotic events (SMQ) with COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant])"; confirmed as an existing study by Johnson & Johnson	open-label, phase 2	not reported	participants who received investigational Ebola vaccines (ChAd3-EBO-Z, MVA-BN-Filo, MVA-EBO-Z, or Ad26.ZEBOV) administered in	Ad26.ZEBOV booster

				previous studies led by the Oxford Vaccine Center (EBL1001, EBL1004, and EBL1005)	
NCT04186000 EBL2007 EBOVAC3DRC Completed, awaiting assessment	Lariviere 2021 doi: 10.1136/bmjopen-2020-046835 Lemey 2021 doi: 10.1136/bmjgh-2021-005726	RCT, phase 2	DRC, Boende	HCWs ≥18 years, n=699	Ad26.ZEBOV, MVA-BN-Filo; randomized to booster 1 or 2 years later
EBL2008 Completed, awaiting assessment	listed as ongoing in EMA report: "Signal assessment report on Embolic and Thrombotic events (SMQ) with COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant])" ; confirmed as an existing study by Johnson & Johnson	open-label, phase 2	not reported	previously enrolled in the EBL2006 trial	Ad26.ZEBOV booster
EBL2009 Completed, awaiting assessment	listed as ongoing in EMA report: "Signal assessment report on Embolic and Thrombotic events (SMQ) with COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant])" ; confirmed as an existing study by Johnson & Johnson	non-randomized	not reported	HCWs, FLWs	Ad26.ZEBOV, MVA-BN-Filo
EBOVAC-Salone Extension NCT03820739 EBL3005 Completed follow-up, ongoing analysis, awaiting assessment	https://clinicaltrials.gov/ct2/show/NCT03820739?cond=NCT03820739&draw=2&rank=1	Observational long term follow-up study	Sierra Leone	Previously vaccinated adults and children	Ad26.ZEBOV, MVA-BN-Filo
EBL4005 Ongoing	listed as ongoing in unpublished presentation to SAGE 2002: "Day1_3_Marco Cavaleri_Summary of efficacy" ; confirmed as an existing study by Johnson & Johnson	not reported	Western Africa	not reported	Ad26.ZEBOV, MVA-BN-Filo

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