Cochrane Response

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

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Cochrane Response

1. Objective and Methods

In this report we report the results of a systematic review on the safety, efficacy, immunogenicity, and duration of protection of licensed Ebola virus vaccines in preventive vaccination and outbreak response settings.

We included studies of any design on the two licensed Ebola virus vaccines. The first Ebola virus vaccine Ervebo (rVSV-ZEBOV) was licensed in November 2019 by the European Medicines Agency and prequalified by WHO. In July 2020, the European Medicines Agency licensed a second new vaccine delivered in two doses called Zabdeno (Ad26.ZEBOV) and Mvabea (MVA-BN-Filo) for individuals one year and older.

We included studies on any populations or participants, irrespective of age, sex, or setting. We included studies from any country or setting, including preventive vaccination, outbreak response, and post-exposure prophylaxis.

The following populations are of special interest and are reported separately where data are available:

1. Contacts of Ebola virus disease cases.
2. Contacts of contacts of Ebola virus disease cases.
3. Probable contacts (all who request vaccination in a village with EVD cases).
4. Health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases.
5. Health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread.
6. Health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks.
7. General population in countries at risk of EVD outbreaks.
8. HCWs and FLWs in labs working with Ebola virus.
9. Contacts of survivors
10. Anyone else

Electronic searches ran on 30th January 2023 resulted in 2839 records after removing duplicates. After screening these records we included 47 published and unpublished studies from 144 reports of any design reporting on the efficacy, safety, or immunogenicity of a licensed Ebola vaccine.

In addition to the results presented below, the Appendix document that complements this review includes the review protocol, search strategy, a list of included studies, study characteristics and risk of bias assessments, and a list of studies “awaiting assessment” because results were not available. It also contains additional details on safety outcomes.

2. Efficacy of Ebola vaccines – rVSV-ZEBOV

We identified 9 published studies that reported on efficacy outcomes (i.e. confirmed Ebola virus disease (EVD)) following vaccination with rVSV-ZEBOV: one cluster randomised controlled trial (RCT) (Henao-Restrepo 2015 (1)), two individually randomised trials (Conteh 2018/STRIVE (2); Kennedy 2017 (3)), two cohort studies (Davis 2020 (4); Nsio 2023 (5)), one case series (Wong 2016 (6)), and three case reports (Cnops 2015 (7); Gunther 2011 (8); Mbala-Kingebeni 2021 (9)). Results are summarised below by population of interest.

In addition to these published studies, we also sought out reports on the use of rVSV-ZEBOV in ring vaccination to control Ebola outbreaks (10). Three published reports of ring vaccination were included in the review (Bolay 2019 (11); Gsell 2017 (12); WHO 2019 (13)), while the other examples are listed in Table 1.

2.1. Efficacy of rVSV-ZEBOV in contacts of Ebola virus disease cases

Data on efficacy of rVSV-ZEBOV in contacts of Ebola virus disease cases comes from one cluster RCT (Henao-Restrepo 2015 (1)), one cohort study (Davis 2020 (4)), a case series (Wong 2016 (6)), and two case reports (Cnops 2015 (7); Mbala-Kingebeni 2021 (9)). See Appendix Table A10 for characteristics of these studies.

The cluster RCT (Henao-Restrepo 2015 (1)) randomly assigned 4539 contacts of EVD cases and contacts of contacts in 51 clusters to immediate vaccination and 4557 contacts and contacts of contacts in 47 clusters to delayed vaccination (21 days later). No cases of EVD occurred 10 days or more after randomisation among contacts and contacts of contacts vaccinated in immediate clusters versus 16 cases (7 clusters affected) among eligible individuals in delayed clusters. Vaccine effectiveness was estimated to be 100% (95%CI 68.9% to 100%). There was high certainty evidence that immediate vaccination resulted in fewer cases of EVD than delayed vaccination; details are presented in Summary of Findings table 1.

Additional non-comparative studies reported on EVD cases following vaccination with rVSV-ZEBOV. One cohort study (Davis 2020 (4)) vaccinated 26 contacts of a healthcare worker with EVD. No cases of EVD were reported in any contact after 1 month or after 12 months.

A case series (Wong 2016 (6)) included 6 HCWs with occupational exposure to EVD. Five HCWs received rVSV-ZEBOV as post-exposure prophylaxis. None of these workers developed EVD.

One case report (Cnops 2015 (7)) was of a physician working for Médecins Sans Frontières (MSF) who was evacuated from Monrovia, Liberia, after a needlestick injury that had been in contact with the skin of a patient confirmed with EVD. The physician survived and did not develop EVD.

Another case report (Mbala-Kingebeni 2021 (9)) was of a 25-year-old man from DRC who received the rVSV-ZEBOV vaccine but tested positive for EVD six months later. Testing revealed that the patient had had a relapse of acute EVD that led to a transmission chain resulting in 91 cases across six health zones over four months.

2.1.1. Summary of Findings table 1. Efficacy of Ebola vaccine (rVSV-ZEBOV) for preventing Ebola virus disease in contacts of EVD cases and contacts of contacts

In the cluster RCT (Henao-Restrepo 2015 (1, 14) Ebola ça Suffit!) from Guinea, four results are presented comparing the randomised groups. These four results are considered important for policy decisions on the use of the vaccine as they focus on both vaccine effectiveness and vaccine efficacy. These are presented in separate rows in the summary of findings table below, where the GRADE ratings assess the certainty of each result. The risk of bias assessment can be seen in Appendix Table A11.

Outcomes	Illustrative comparative risks		Vaccine effectiveness (95% CI)†	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Delayed vaccination	Immediate vaccination				
Ebola virus disease* with onset 10 days or more from randomisation Follow-up 84 days	16/3075 (0.5%)	0/2108 (0.0%)	100% (68.9 to 100.0)	5183 1 cluster RCT (1)	⊕⊕⊕⊕ HIGH [a, b]	Analysis: All vaccinated in immediate *vs* all eligible in delayed Primary analysis of the trial, per-protocol analysis
Ebola virus disease* with onset 10 days or more from randomisation Follow-up 84 days	10/1429 (0.7%)	0/2108 (0.0%)	100% (63.5 to 100.0)	3537 1 cluster RCT (1)	⊕⊕⊕⊕ HIGH [a, b]	Analysis: All vaccinated *vs* all eligible and consented on day 0 Per-protocol analysis
Ebola virus disease* with onset 10 days or more from randomisation Follow-up 84 days	16/3075 (0.5%)	7/3212 (0.2%)	64.6% (-46.5 to 91.4)	6287 1 cluster RCT (1)	⊕⊕◯◯ LOW [c]	Analysis: All eligible *vs* all eligible Intention-to-treat analysis
Ebola virus disease* with onset 10 days or more from randomisation Follow-up 84 days	22/4529 (0.49%)	10/4513 (0.2%)	64.6% (-44.2 to 91.3)	9042 1 cluster RCT (1)	⊕⊕◯◯ LOW [c]	Analysis: All in immediate *vs* all in delayed Intention-to-treat analysis

Footnotes

[a] Not downgraded for imprecision: despite few events the effect estimate is clearly in favour of the intervention.

[b] Not downgraded for inconsistency: the findings of additional observational and ring vaccination studies were consistent with the effect seen in the RCT.

[c] Downgraded two levels for serious imprecision: few events and a 95% confidence interval that includes no effect, a potential benefit, and a potential harm

2.1.2. Ring vaccination with rVSV-ZEBOV

In addition to the above studies, the ring vaccination of over 360,000 vaccinated people provide data on the effectiveness of rVSV-ZEBOV as part of an outbreak response (see Table 1; Nsio 2023 (5); Bolay 2019 (11); Gsell 2017 (12); WHO 2019 (13)). Published details on the number of vaccinations, populations, and outcomes are lacking for many ring vaccination campaigns.

rVSV-ZEBOV has been used in an Expanded Access/Compassionate Use protocol during outbreaks in the form of ring vaccination campaigns (Table 1; Nsio 2023 (5); Bolay 2019 (11); Gsell 2017 (12); WHO 2019 (13)). These trials involve vaccinating "rings" of contacts and contacts of contacts around people with EVD. From the published reports, one trial from Guinea (Gsell 2017 (12)) reported no cases of EVD occurring 10 days or more following vaccination in 1510 vaccinees. One trial in Liberia (Bolay 2019 (11)) vaccinated 210 contacts and contacts of close contacts with no cases of EVD reported after 1 or 6 months. The third trial (WHO 2019 (13)) was performed during an outbreak in the Democratic Republic of the Congo (DRC) where 202,251 eligible contacts and contacts of contacts were vaccinated. 354 Ebola cases occurred among vaccinated individuals, with 26 cases having onset of symptoms 10 days or more days post- vaccination (this is the time after which vaccinees are assumed to be protected) and 320 cases had onset of symptoms 0-9 days post vaccination (it is assumed that during this period the vaccinees are not protected or partially protected).

In addition to these reports, one retrospective cohort study from the 2018-2020 outbreak in DRC (Nsio 2023 (5)) included 24,666 contacts with possible EVD infection. Of these, 3032 had received a recombinant vesicular stomatitis vaccine. Confirmed EVD diagnosis was much lower in those who had been vaccinated for 10 days or more (6.2%) than in those who had only recently received a vaccine (i.e. within <10 days of illness onset; 27.9%, p<0.0001).

Data from the MSD Global Safety Database reported cumulative breakthrough cases (EVD cases occurring >10 days post vaccination) occurring through to July 2021. More than 360,000 individuals were vaccinated in DRC and neighbouring countries with 92 breakthrough cases of EVD, of which 14 had a fatal outcome.

Table 1. Description of ring vaccination campaigns with rVSV-ZEBOV

Location	Characteristics	Health care workers (HCW)/front line workers (FLW)
Democratic Republic of the Congo (North Kivu & Ituri)	Year: 2018-2020 Total N vaccinated = 364,002	Number of HCW/FLW inside rings N = 39,074 Number of HCW/FLW outside rings N = 21,518
Uganda (Kasese District)	Year: 2019 Total N vaccinated = 1394	Number of HCW/FLW inside rings N = 28 Number of HCW/FLW outside rings N = 544
Democratic Republic of the Congo (Equateur)	Year: 2020 Total N vaccinated = 54,650	Number of HCW/FLW inside rings N = 2213 Number of HCW/FLW outside rings N = 7859
Guinea (N'Zerekore)	Year: 2021 Total N vaccinated = 13,775	Number of HCW/FLW inside rings N = 692 Number of HCW/FLW outside rings N = 2190
Democratic Republic of the Congo (North Kivu)	Year: 2021 Total N vaccinated = 2103	Number of HCW/FLW inside rings N = 81 Number of HCW/FLW outside rings N = 1370
Democratic Republic of the Congo (North Kivu)	Year: 2021 Total N vaccinated = 2464	Number of HCW/FLW inside rings N = 367 Number of HCW/FLW outside rings N = 199
Cote d'Ivoire (Abidjan)	Year: 2021 Total N vaccinated = NR	
Democratic Republic of the Congo (Equateur)	Year: 2022 Total N vaccinated = 2630	Number of HCW/FLW inside rings N = 752

South Sudan	Total N vaccinated = 2928	All were HCW/FLW in bordering areas at high-risk of spread
Uganda	Total N vaccinated = 6665	All were HCW/FLW in bordering areas at high-risk of spread
Rwanda	Total N vaccinated = 2627	All were HCW/FLW in bordering areas at high-risk of spread
Burundi	Total N vaccinated = 4069	All were HCW/FLW in bordering areas at high-risk of spread

2.2. Efficacy of rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases

Data on efficacy of rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases comes from one cluster RCT (Henao-Restrepo 2015 (1)) and the ring vaccination campaigns as part of an outbreak response. Contacts of contacts of Ebola virus disease cases are included in the estimates in Summary of Findings Table 1 as data is not reported separately for this population.

2.3. Efficacy of rVSV-ZEBOV in probable contacts (all who request vaccination in a village with EVD cases)

Data on efficacy of rVSV-ZEBOV in probable contacts of Ebola virus disease cases (all who request vaccination in a village with EVD cases) comes from one cluster RCT (Henao-Restrepo 2015 (1)) and the ring vaccination campaigns as part of an outbreak response. Probable contacts of Ebola virus disease cases are included in the estimates in Summary of Findings Table 1 as data is not reported separately for this population.

2.4. Efficacy of rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases

Data on efficacy of rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases comes from one cluster RCT (Henao-Restrepo 2015 (1)) and the ring vaccination campaigns as part of an outbreak response. HCW and FLW are included in the estimates in Summary of Findings Table 1 as data is not reported separately for this population.

2.5. Efficacy of rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread

Data on efficacy of rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread comes from one individually randomised trial in Sierra Leone (Conteh 2018/STRIVE (2)) which randomised HCW and FLW to immediate vaccination or deferred (18–24 weeks later) vaccination. Of 7998 workers vaccinated, no participants developed EVD.

2.6. Efficacy of rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks

No studies on efficacy of rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks were identified.

2.7. Efficacy of rVSV-ZEBOV in general population in countries at risk of EVD outbreaks

Data on efficacy of rVSV-ZEBOV in the general population in countries at risk of EVD outbreaks is limited to one RCT (Kennedy 2017 (3)) in Liberia which compared two types of Ebola vaccine (ChAd3-EBO-Z or rVSV-ZEBOV) with placebo. 500 healthy volunteers were vaccinated with rVSV-ZEBOV and no cases of EVD were identified in any group in 12 months follow-up.

2.8. Efficacy of rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus

Data on efficacy of rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus comes from one case report (Gunther 2011 (8)) where the vaccine was used as post-exposure prophylaxis. The report (Gunther 2011 (8)) was of PEP after needlestick injury during an animal experiment in the biosafety level 4 laboratory in Hamburg, Germany, in March 2009. The case survived and did not develop EVD.

2.9. Efficacy of rVSV-ZEBOV in contacts of survivors

No studies on efficacy of rVSV-ZEBOV in contacts of survivors were identified.

2.10. Efficacy of rVSV-ZEBOV in anyone else

No studies on efficacy of rVSV-ZEBOV in anyone else were identified.

3. Efficacy of Ebola vaccines – Ad26.ZEBOV, MVA-BN-Filo regimen

No studies were identified that reported on the efficacy of Ad26.ZEBOV, MVA-BN-Filo vaccination in humans.

The Ad26.ZEBOV, MVA-BN-Filo vaccine regimen has been authorised by the European Medicines Agency (EMA) under exceptional circumstances. This is because it has not been possible to obtain complete information about human efficacy of Ad26.ZEBOV, MVA-BN-Filo for scientific and ethical reasons (15).

Immunobridging studies have demonstrated that Ad26.ZEBOV, MVA-BN-Filo triggers an immune response that can provide protection against Ebola virus disease (16, 17). Although the level and duration of protection against the virus have not yet been determined, the EMA considered that the vaccine's benefits could be of great importance to help control an outbreak and prevent death.

Examples of the use of Ad26.ZEBOV, MVA-BN-Filo in field studies in areas where an outbreak has been reported ad where Ebola is likely to spread are shown in Table 2.

Table 2. Description of ring vaccination campaigns with Ad26.ZEBOV, MVA-BN-Filo

Location	Characteristics	Health care workers (HCW)/front line workers (FLW)
Guinea	Year: 2021 First dose: other high risk exposure groups vaccinated N = 3929 Second dose: other high risk exposure groups N=3350	First dose: HCW vaccinated N = 2217 Second dose: HCW vaccinated N = 2036
Sierra Leone	Year: 2021 First dose: other high risk exposure groups vaccinated N = 4805	First dose: HCW vaccinated N = 5912

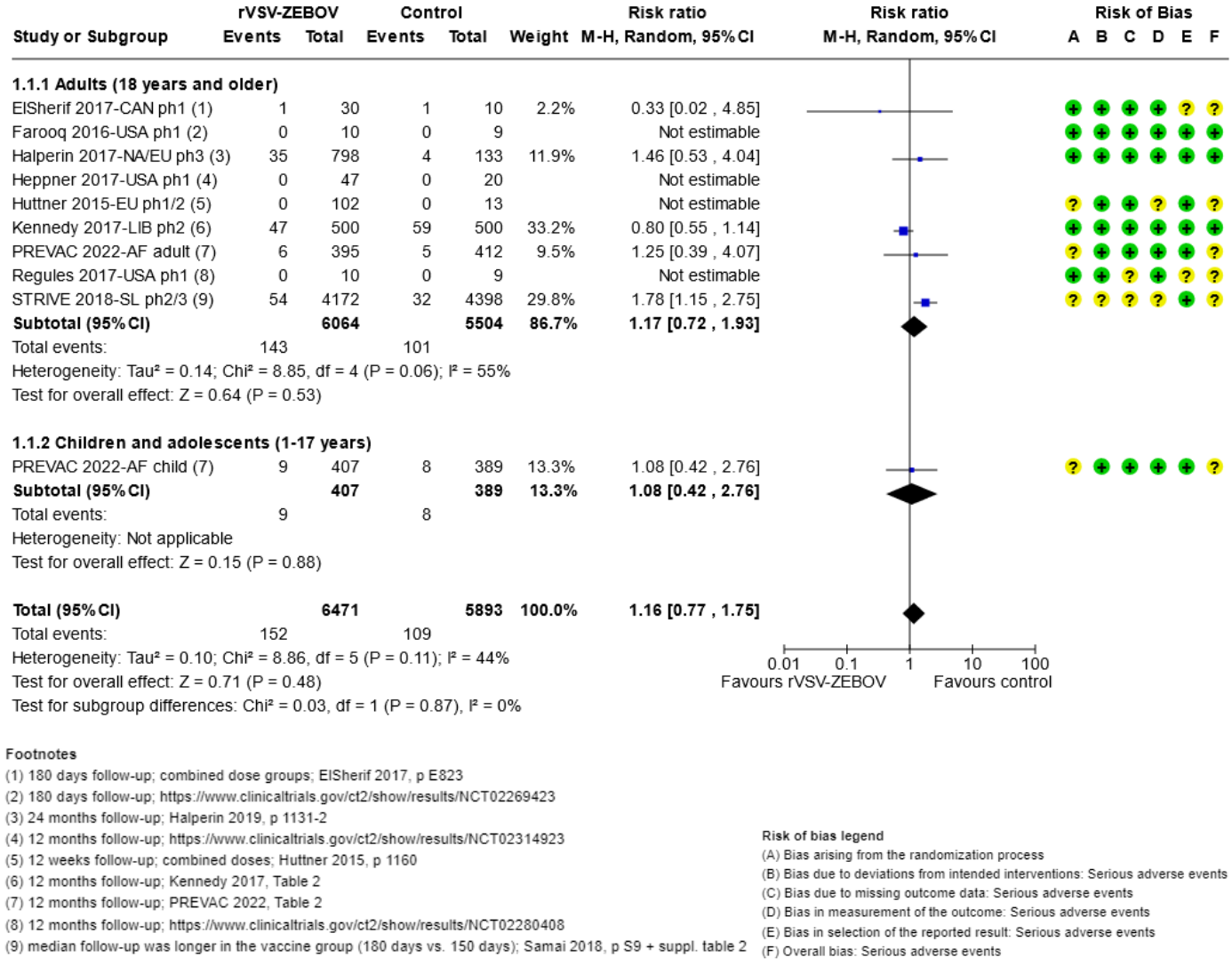
	Second dose: other high risk exposure groups vaccinated N = 3682	Second dose: HCW vaccinated N = 4591
Democratic Republic of the Congo (Goma)	Year: 2022 N vaccinated = 20,423	
Rwanda	Year: 2019-2020 General population (age 2-18+ years) in sectors bordering DRC - Rubavu and Rusizi Districts. N vaccinated = 216,114 with one dose, 203,309 with both doses	

4. Safety of Ebola vaccines – rVSV-ZEBOV

4.1. Serious adverse events

Seventeen studies reported on serious adverse events following rVSV-ZEBOV vaccination. Nine of these were RCTs comparing rVSV-ZEBOV with placebo (ElSherif 2017 (18); Farooq 2016 (19, 20); Halperin 2017 (21); Heppner 2017 (22, 23); Huttner 2015 (24); Kennedy 2017 (3); PREVAC 2022-AF (25); Regules 2017 (26, 27)) or with no intervention (STRIVE 2018 (28)). In the RCTs, serious adverse events were collected from 12 weeks to 24 months following vaccination.

Pooled results showed little to no difference between rVSV-ZEBOV and control (moderate certainty evidence; risk difference [RD] 3 more per 1000, 95% CI 4 fewer to 14 more; 9 trials, 12,364 participants; Figure 1; Summary of findings table A1). See Table A2 for details of the serious adverse events per study arm.



Footnotes
(1) 180 days follow-up; combined dose groups; ElSherif 2017, p E823
(2) 180 days follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02269423
(3) 24 months follow-up; Halperin 2019, p 1131-2
(4) 12 months follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02314923
(5) 12 weeks follow-up; combined doses; Huttner 2015, p 1160
(6) 12 months follow-up; Kennedy 2017, Table 2
(7) 12 months follow-up; PREVAC 2022, Table 2
(8) 12 months follow-up; https://www.clinicaltrials.gov/ct2/show/results/NCT02280408
(9) median follow-up was longer in the vaccine group (180 days vs. 150 days); Samai 2018, p S9 + suppl. table 2

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Serious adverse events
(C) Bias due to missing outcome data: Serious adverse events
(D) Bias in measurement of the outcome: Serious adverse events
(E) Bias in selection of the reported result: Serious adverse events
(F) Overall bias: Serious adverse events

Figure 1. Serious adverse events in RCTs comparing rVSV-ZEBOV with control (placebo or no intervention) at up to 24 months follow-up.

One of the RCTs (PREVAC 2022-AF (25)) included both adults and children. Analysis of only the children and adolescents showed little to no difference between rVSV-ZEBOV and placebo at 12 months follow-up (RD 2 more per 1000, 95% CI 12 fewer to 36 more; RR 1.08, 95% CI 0.42 to 2.76, 796 participants; Figure 1).

Serious adverse event data from the ring vaccination campaign in the Democratic Republic of the Congo (North Kivu & Ituri) in 2018-2020 was also available. From 303,171 vaccinated contacts of people with EVD and contacts of contacts, 886 (0.3%) serious adverse events were reported. Of these, 65 (0.02%) deaths were reported, 21 of which were due to EVD. Most serious adverse events (87.7%) were deemed to be unrelated to the vaccine.

Eight additional studies reported serious adverse events in vaccine groups only (Agnandji 2017 (29); Bolay 2019 (11); Carnino 2021 (30); Dahlke 2017 (31); Gsell 2017 (12); Henao-Restrepo 2015 (1, 14, 32); Juan-Giner 2019 (33); Proches 2023 (34)), details of these events are in Table A2.

4.2. Pregnancy and neonatal outcomes

Clinical trials did not include pregnant women, consequently, there are few data on pregnancy outcomes, see Figure A1 and Table A4 in the Appendix.

One study (PREVAC 2022-AF (25)) reported on **any pregnancy-related SAE**. Due to few events the estimate was imprecise with wide 95% CIs (2/802 vs 0/801; RR 3.00, 95% CI 0.31 to 28.74, 1603 participants).

Three studies (Kennedy 2017 (3); Halperin 2017 (35); STRIVE (36)) reported on **pregnancy loss** (spontaneous abortion and/or still birth). Due to few events the estimate was imprecise with wide 95% CIs (15/5283 vs 12/4739; RR 1.15, 95% CI 0.55 to 2.43, 10,022 participants).

Kennedy 2017 (3) reported on **foetal death** (RR 5.00, 95% CI 0.24 to 103.88, 1000 participants), **post-partum haemorrhage** (RR 3.00, 95% CI 0.12 to 73.47, 1000 participants) and **incomplete abortion** (RR 0.33, 95% CI 0.01 to 8.16, 1000 participants). STRIVE (36) reported on **preterm delivery** (RR 5.14, 95% CI 0.25 to 107.06, 8099 participants. Again, the estimates were imprecise with wide 95% CIs due to few events.

From 303,171 vaccinated contacts in the ring vaccination campaign in the Democratic Republic of the Congo (North Kivu & Ituri) in 2018-2020, 1663 pregnancies during the outbreak were reported of which 5 (0.3%) resulted in spontaneous abortion, 3 (0.2%) resulted in stillbirth, and there was 1 (0.1%) maternal death.

Juan-Giner 2019 (33) and Henao-Restrepo 2015 (32) reported on several pregnancy and neonatal outcomes in one group only, see Table A4. Data on pregnancy outcomes from four ring-vaccination campaigns in DRC and Guinea are also presented in Table A4.

4.3. Other safety outcomes

Four RCTs (Farooq 2016 (19); Heppner 2017 (23); Regules 2017 (27); STRIVE 2018 (37)) reported on **unsolicited adverse events** irrespective of severity comparing rVSV-ZEBOV with placebo. Unsolicited adverse events were followed up to 14 or 28 days and pooled results found 114 more events per 1000 participants (95% CI 82 fewer to 546 more per 1000) in the rVSV-ZEBOV group compared with placebo (RR 1.47, 95% CI 0.66 to 3.26, 4 trials, 986 participants, I^2=94%; Figure A3). In addition, the cluster randomised trial (Henao-Restrepo 2015 (1, 14, 32)) and a prospective cohort study in contacts of EVD survivors (Proches 2023 (34)) reported unsolicited adverse events in vaccine groups only (Table A6).

Nineteen studies reported on **solicited local adverse events** with rVSV-ZEBOV. Eight of these were RCTs comparing rVSV-ZEBOV with placebo (ElSherif 2017 (18); Farooq 2016 (19); Halperin 2017 (35); Heppner 2017 (23); Huttner 2015 (24); Kennedy 2017 (3); PREVAC 2022-AF (25); Regules 2017 (27)). In these RCTs local adverse events were followed up to 7-, 14-, or 42-days post-vaccination. Pooled results found 246 more cases per 1000 participants in the rVSV-ZEBOV group compared with placebo (95% CI 190 to 316 more per 1000; RR 4.51, 95% CI 3.70 to 5.50, 8 trials, 4252 participants, I^2= 7%; Figure A5). One of the RCTs (PREVAC 2022-AF (25)) included both adults and children. Analysis of only the children showed 158 more events per 1000 participants in the rVSV-ZEBOV group compared with placebo (95% CI 81 to 281 more per 1000; RR 4.24, 95% CI 2.66 to 6.75, 998 participants; Figure A5). Eleven studies reported local adverse events in vaccine groups only (Agnandji 2017 (29); Carnino 2021 (30); Dahlke 2017 (31); Davis 2019 (4); Ficko 2022 (38); Gunther 2011 (8); Henao-Restrepo 2015 (1, 14, 32); Juan-Giner 2019 (33); Proches 2023 (34); STRIVE 2018 (28); Wong 2016 (6)) (Table A8).

Nineteen studies reported on **solicited systemic adverse events** with rVSV-ZEBOV. Nine of these were RCTs comparing rVSV-ZEBOV with placebo (ElSherif 2017 (18); Farooq 2016 (19); Halperin 2017 (39); Heppner 2017 (23); Huttner 2015 (24); Kennedy 2017 (3); PREVAC 2022-AF (25); Regules 2017 (27)) or with no intervention (STRIVE 2018 (28)). In the RCTs systemic adverse events were followed up to 7-, 14-, or 42 days post-vaccination. Pooled results found 289 more events per 1000 participants in the rVSV-ZEBOV group compared with placebo (95% CI 183 to 409 more per 1000; RR 1.74, 95% CI 1.47 to 2.05, 9 trials, 4689 participants, I^2= 76%; Figure A6). One of the RCTs (PREVAC 2022-AF (25)) included both adults and children. Analysis of only the children found 171 more cases per 1000 participants in the rVSV-ZEBOV group compared with placebo (95% CI 94 to 252 more per 1000; RR 1.40, 95% CI 1.22 to 1.59, 998 participants; Figure A6). Ten studies reported systemic adverse events in vaccine groups only (Agnandji 2017 (29); Bolay 2018 (11); Carnino 2021 (30); Cnops 2015 (7); Davis 2019 (4); Ficko 2022 (38); Gunther 2011 (8); Henao-Restrepo 2015 (1, 14, 32); Proches 2023 (34); Wong 2016 (6)) (Table A8).

5. Safety of Ebola vaccines – Ad26.ZEBOV, MVA-BN-Filo regimen

5.1. Serious adverse events

Fifteen studies reported on serious adverse events with Ad26.ZEBOV, MVA-BN-Filo (Table A3). Twelve of these were RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with placebo (EBL1001 ph1-UK (40); EBL2001 ph2-EU (41, 42); EBL2002 adult ph2-AF (43); EBL2005 infant-AF (44, 45); EBL2002 child ph2-AF (46); EBL3002 ph3-US (47); EBL3003 ph3-US (47); EBL3004 ph3-US (48); EBL3010 pregnant-RWA (44, 49); PREVAC 2022-AF (25)) or with a non-Ebola control vaccine (EBL3001 adult ph3-SL (50) and EBL3001 child ph3-SL (51)).

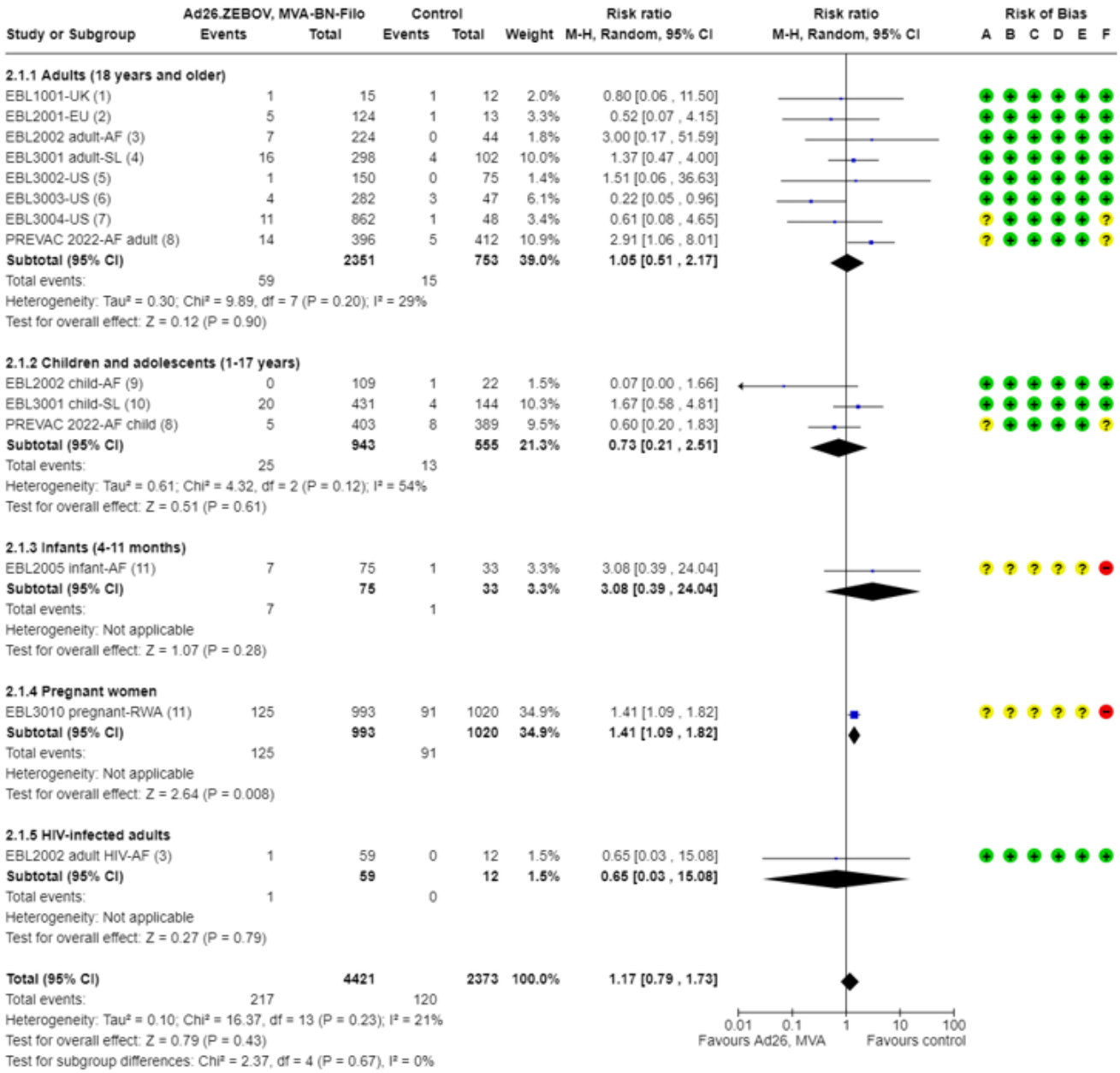
In the RCTs serious adverse events were followed up for 6 to 24 months post-vaccination and pooled results showed little to no difference between Ad26.ZEBOV, MVA-BN-Filo and control (moderate certainty evidence; RD 9 more per 1000, 95% CI 11 fewer to 37 more; RR 1.17, 95% CI 0.79 to 1.73; 10 trials, 6794 participants; Figure 2; Summary of findings table A1). See Table A3 for details of the serious adverse events per study arm.

Two studies (EBL2005 infant-AF (44, 45); EBL3010 pregnant-RWA (44, 49)) were assessed at high risk of overall bias due to unpublished preliminary results. Removing these studies from the analysis 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, 8 trials, 4673 participants; analysis not shown).

Analysis of children and adolescents showed little to no difference in SAEs between Ad26.ZEBOV, MVA-BN-Filo and control at 12 months follow-up (RD 6 fewer per 1000, 95% CI 19 fewer to 35 more; RR 0.73, 95% CI 0.21 to 2.51, 3 trials, 1498 participants, Figure 2).

Preliminary unpublished data of infants (EBL2005 infant-AF (44, 45)) aged 4 to 11 months showed 7/75 (9.3%) SAEs in the vaccine group and 1/33 (3%) SAEs in the control group (Figure 2). Preliminary unpublished data of pregnant women (EBL3010 pregnant-RWA (44, 49)) showed 125/993 (12.6%) SAEs in the vaccine group and 91/1020 (8.9%) in the control group (Figure 2). Analysis of HIV-infected adults showed little to no difference between Ad26.ZEBOV, MVA-BN-Filo and control at 12 months follow-up (RR 0.65, 95% CI 0.03 to 15.08, 1 trial, 71 participants, Figure 2).

Three studies (EBL2011 child boost-SL (52) (assessing Ad26.ZEBOV booster dose); EBL3008-DRC (53, 54); EBL4002 UMURINZI-RWA (55)) reported serious adverse events in vaccine groups only (Table A3). One study (EBL3008-DRC (53, 54) reported < 1% (50/19187) of children and adults (who did not report a pregnancy during the study) experienced a SAE at any time after the first dose. There were 43 SAEs after dose 1 and 7 SAEs after dose 2.



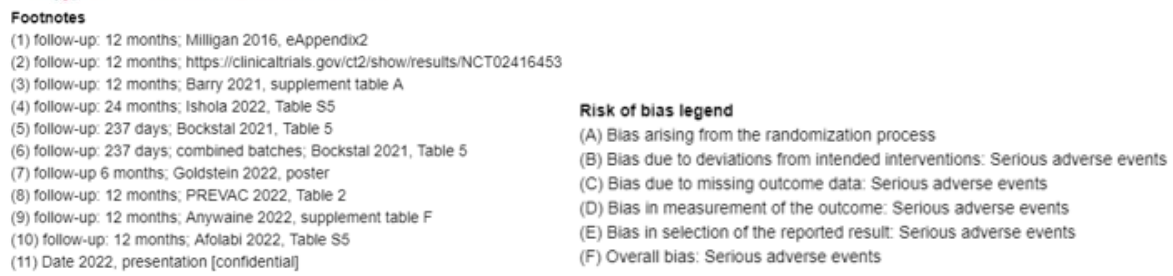


Figure 2. Serious adverse events in RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with control (placebo or non-Ebola control vaccine) at up to 24 months follow-up.

5.2. Pregnancy and neonatal outcomes

Most clinical trials did not include pregnant women, consequently, there are few data on pregnancy and neonatal outcomes, see Figure A2 and Table A5 in the appendix.

Preliminary, unpublished data (EBL3010 pregnant ph3-RWA (44, 49) showed 265/993 **SAEs in neonates** in the vaccine group compared with 185/1020 in the control group (delayed vaccination) (Figure A2).

Five studies (PREVAC 2022-AF (25); EBL3001 adult ph3-SL (50); EBL2001 ph2-EU (42); EBL3003 ph3-US (47); EBL3004 ph3-US (48)) reported on **any pregnancy-related SAE**. Due to few events the estimate was imprecise with wide 95% CIs (5/1952 in the vaccine groups vs 0/622 in the control groups; RR 0.63, 95% CI 0.15 to 2.62, 2574 participants).

Two studies (EBL2001 ph2-EU (42); EBL3003 ph3-US (47)) reported on **spontaneous abortion**. Again, due to few events the estimate was imprecise with wide 95% CIs (2/396 in the vaccine groups vs 0/60 in the control groups; RR 0.43, 95% CI 0.05 to 4.05, 456 participants).

One study (EBL3001 adult ph3-SL (50)) reported one event in the vaccine group for **preterm labour**, **haemorrhage in pregnancy**, **threatened abortion,** and **placenta praevia** (1/298 in the vaccine group vs 0/102 in the control group, RR 1.03, 95% CI 0.04 to 25.17, 400 participants).

EBL4002 UMURINZI-RWA (55) and EBL3008 ph3-DRC (53) reported on several pregnancy and neonatal outcomes in one group only, see Table A5. EBL3008 ph3-DRC (53) reported that in 1169 pregnancies with a known birth outcome, 1100 babies were born alive. Preterm births were in 21% (188/891) of babies with known gestational age, low birth weight in 8% (79/1032) of babies with known gestational age and birth weight. Early neonatal death (up to 7 days) occurred in 1% (11/1100) of babies born alive. Congenital abnormalities occurred in 0.5% (5/1100) of babies born alive (1 inguinal hernia, 1 umbilical hernia, 1 congenital anomaly of the tongue, 1 cleft lip and 1 exomphalos).

5.3. Other safety outcomes

Thirteen studies reported on **unsolicited adverse events** irrespective of severity with Ad26.ZEBOV, MVA-BN-Filo. Nine of these were RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with placebo (EBL1003 ph1-KEN (56); EBL2001 ph2-EU (41); EBL2002 adult ph2-AF (43); EBL2002 child ph2-AF (46); EBL3002 ph3-US (47); EBL3003 ph3-US (47); EBL3004 ph3-US (48); FLV1001 ph1-US (57)) or a non-Ebola control vaccine (EBL3001 adult ph3-SL (50); EBL3001 child ph3-SL (51)). In the RCTs, unsolicited adverse events were followed up for 1 to 4 months and pooled results after the first Ad26.ZEBOV dose (RR 0.97, 95% CI 0.84 to 1.12, 2025 participants, 7 trials, Figure A4), second MVA-

BN-Filo dose (RR 1.02, 95% CI 0.89 to 1.17, 1907 participants, 7 trials, Figure A4), and after any dose (RR 1.16, 95% CI 0.48 to 2.80, 1047 participants, 2 trials, Figure A4) found little to no difference between Ad26.ZEBOV, MVA-BN-Filo and control. EBL1003 ph1-KEN compared different schedules and reported on events after any Ad26.ZEBOV or MVA-BN-Filo dose, whether it was the first or second dose, and were not pooled with the other RCTs. Three studies (EBL1001 ph1-UK (40); EBL2011 child boost-SL (assessing an Ad26.ZEBOV booster dose) (52); EBL4002 UMURINZI-RWA (55)) reported unsolicited adverse events in vaccine groups only (Table A7).

Thirteen studies reported on **solicited local adverse events** with Ad26.ZEBOV, MVA-BN-Filo. Twelve of these were RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with placebo (EBL1001-UK (40); EBL1003-KEN (56); EBL2001-EU (41); EBL2002 adult-AF (43); EBL2002 child-AF (46); EBL3002-US (47); EBL3003-US (47); EBL3004-US (48); FLV1001-US (58); PREVAC 2022-AF (25)) or with a non-Ebola control vaccine (EBL3001 adult-SL (50); EBL3001 child-SL (51)). In the RCTs local adverse events were evaluated for up to 7 days post-vaccination and pooled results found more events per 1000 participants in the Ad26.ZEBOV, MVA-BN-Filo group compared with control after the first Ad26.ZEBOV dose (RR 2.33, 95% CI 1.67 to 3.26, 12 trials, 4726 participants; Figure A7) and after the second MVA-BN-Filo dose (RR 2.61, 95% CI 1.91 to 3.57, 11 trials, 4397 participants; Figure A7). One of the RCTs (EBL1003-KEN (56)) reported on events per number of doses and were not analysed with the other RCTs. One study (EBL2011 child boost-SL (52), assessing Ad26.ZEBOV booster dose) reported local adverse events in the vaccine group only (Table A9).

Thirteen studies reported on **solicited systemic adverse events** with Ad26.ZEBOV, MVA-BN-Filo. Twelve of these were RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with placebo (EBL1001 ph1-UK (40); EBL1003 ph1-KEN (56); EBL2001 ph2-EU (41); EBL2002 adult ph2-AF (43); EBL2002 child ph2-AF (46); EBL3002 ph3-US (47); EBL3003 ph3-US (47); EBL3004 ph3-US (48); FLV1001 ph1-US (58); PREVAC 2022-AF (25)) or with a non-Ebola control vaccine (EBL3001 adult ph3-SL (50); EBL3001 child ph3-SL (51)). In the RCTs systemic adverse events were evaluated for up to 7 days post-vaccination and pooled results found more events in the Ad26.ZEBOV, MVA-BN-Filo group compared with control after the first Ad26.ZEBOV dose (RR 1.27, 95% CI 1.13 to 1.42, 11 trials, 4726 participants; Figure A8) but little to no difference after the second MVA-BN-Filo dose (RR 1.04, 95% CI 0.93 to 1.16, 11 trials, 4408 participants; Figure A8). One of the RCTs (EBL1003 ph1-KEN (56)) reported on events per number of doses and one study (EBL2011 child boost-SL (52), assessing Ad26.ZEBOV booster dose) reported local and systemic adverse events in vaccine group only (Table A9).

6. Immunogenicity of Ebola vaccines - rVSV-ZEBOV

Immune monitoring for responses to rVSV-ZEBOV vaccine was commonly assessed by measuring glycoprotein (GP)-specific antibodies or neutralizing antibodies. The focus of this review is the duration of immune responses over time following vaccination, categorised by population subgroup.

Immune responses to rVSV-ZEBOV vaccine were evaluated by 2 types of assays in the program, GP-ELISA and virus neutralization assays (Pseudovirion neutralization assay [PsVNA] and Plaque Reduction Neutralization Test [PRNT]).

6.1. Specific antibodies (GP-ELISA)

6.1.1. Specific antibodies after rVSV-ZEBOV in contacts of Ebola virus disease cases

Two studies (Bolay 2019 (11); Hoff 2022 (59)) reported on specific antibodies following vaccination by rVSV-ZEBOV in contacts of EVD cases. Both were single-arm cohort studies which were carried out during ring vaccination campaigns in Liberia (Bolay 2019 (11); n = 96) and DRC (Hoff 2022 (59); n = 608). The studies indicated a rapid increase in antibodies during the first month following vaccination, with one study (Hoff 2019 (59)) showing continued levels of antibodies for 6 months (Figure 3).

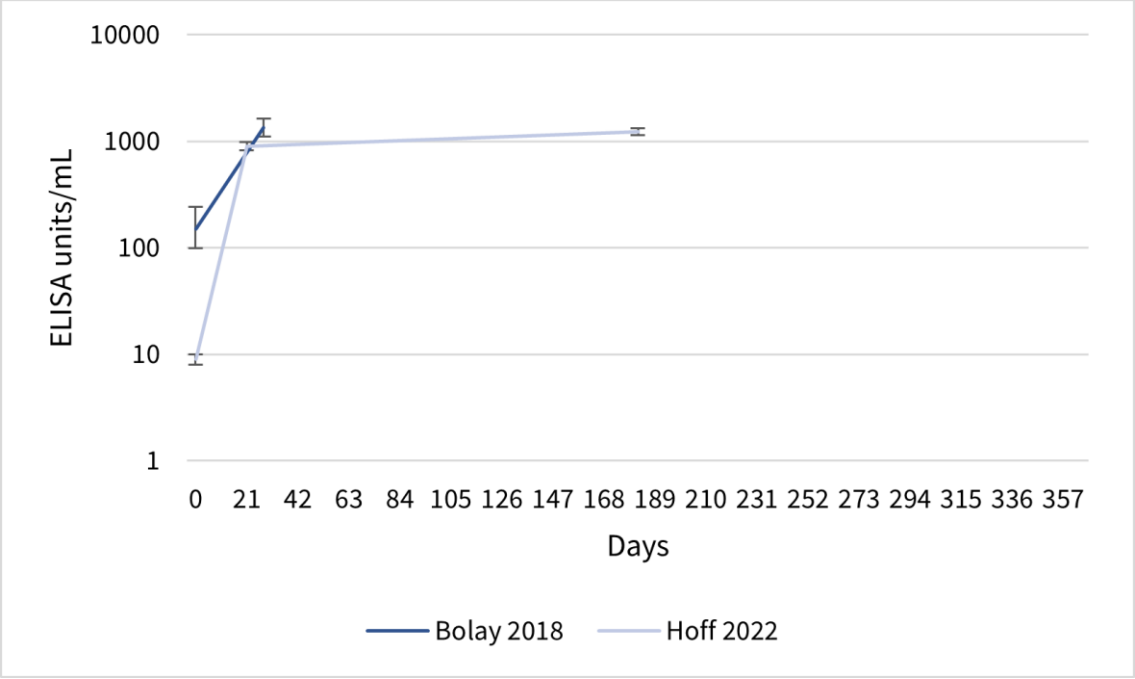


Figure 3. Specific antibodies after rVSV-ZEBOV in contacts of Ebola virus disease cases

6.1.2. Specific antibodies after rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases

Two studies (Bolay 2019 (11); n = 96) and DRC (Hoff 2022 (59); n = 608) reported on specific antibodies following vaccination by rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases. The data for these studies is shown in Figure 3.

6.1.3. Specific antibodies after rVSV-ZEBOV in probable contacts (all who request vaccination in a village with EVD cases)

One study (Hoff 2022 (59); n = 608) reported on specific antibodies following vaccination by rVSV-ZEBOV in probable contacts of Ebola virus disease cases. The data for this study is shown in Figure 3.

6.1.4. Specific antibodies after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases

Two studies (Hoff 2022 (59); n = 608; Juan-Giner 2019 (60); n = 1018) were included that reported on specific antibodies following vaccination by rVSV-ZEBOV in HCWs and FLWs in areas with cases who are not contacts of EVD cases.

One study was a non-randomised trial of HCW and FLW in Guinea (Juan-Giner 2019 (60)) where FLWs who refused vaccination were offered to participate as the control group. 1018 participants received one dose of vaccine and were followed-up for 84 days, among them 79 participants were followed-up for 180 days. The other study (Hoff 2022 (59)) was carried out in DRC and included HCW and FLW in a ring vaccination trial. Data for this group was not reported separately to that of the contacts and contacts of contacts (Figure 4).

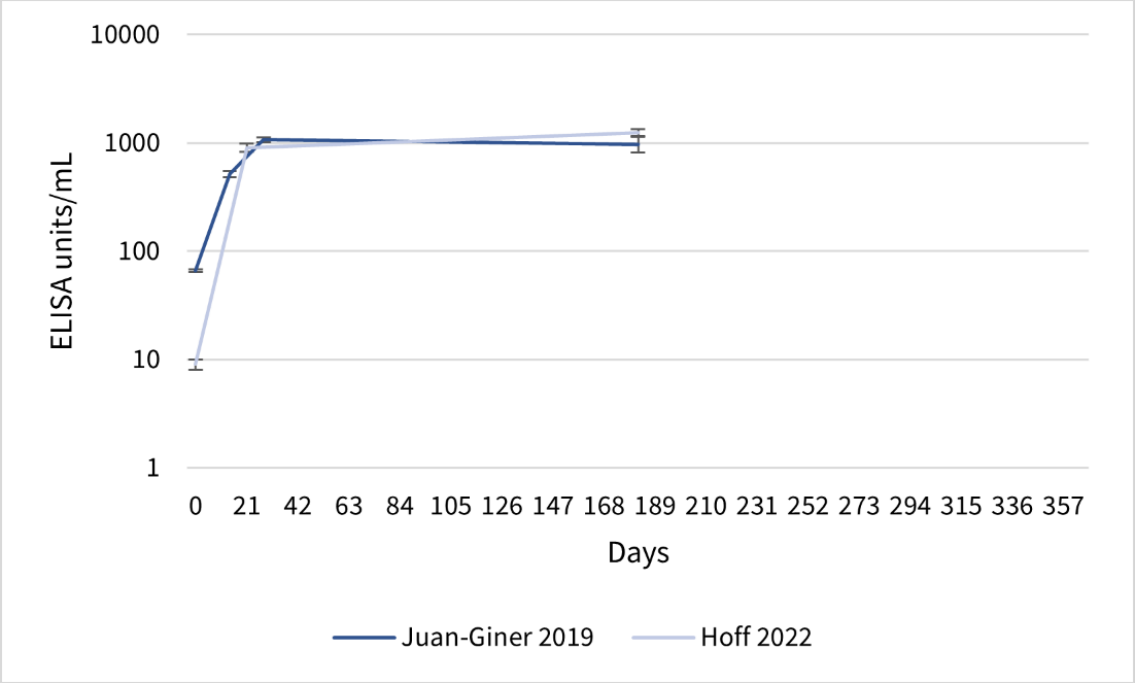


Figure 4. Specific antibodies after rVSV-ZEBOV in HCWs and FLWs in areas with cases who are not contacts of EVD cases

6.1.5. Specific antibodies after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread

Three studies (Conteh 2018/STRIVE (2); Hoff 2022 (59); Juan-Giner 2019 (60)) were included that reported on specific antibodies following vaccination by rVSV-ZEBOV in HCWs and FLWs in areas where the outbreak is likely to spread.

One study was a non-randomised trial of HCWs and FLWs in Guinea (Juan-Giner 2019 (60)) where FLWs who refused vaccination were offered to participate as the control group. 1108 participants received one dose of vaccine and were followed-up for 84 days, among them 79 participants were followed-up for 180 days. No data on immunogenicity of the control group was reported. The second study (Hoff 2022 (59)) was carried out in DRC and included HCW and FLW in a ring vaccination trial. Data for this group was not reported separately to that of the contacts and contacts of contacts. The third study (Conteh 2018/STRIVE (2); n = 503) was an individually randomised trial where healthcare and frontline Ebola response workers were individually randomized to either immediate vaccination or deferred (18–24 weeks later) vaccination. All vaccinated participants were included in the immunogenicity assessment (Figure 5).

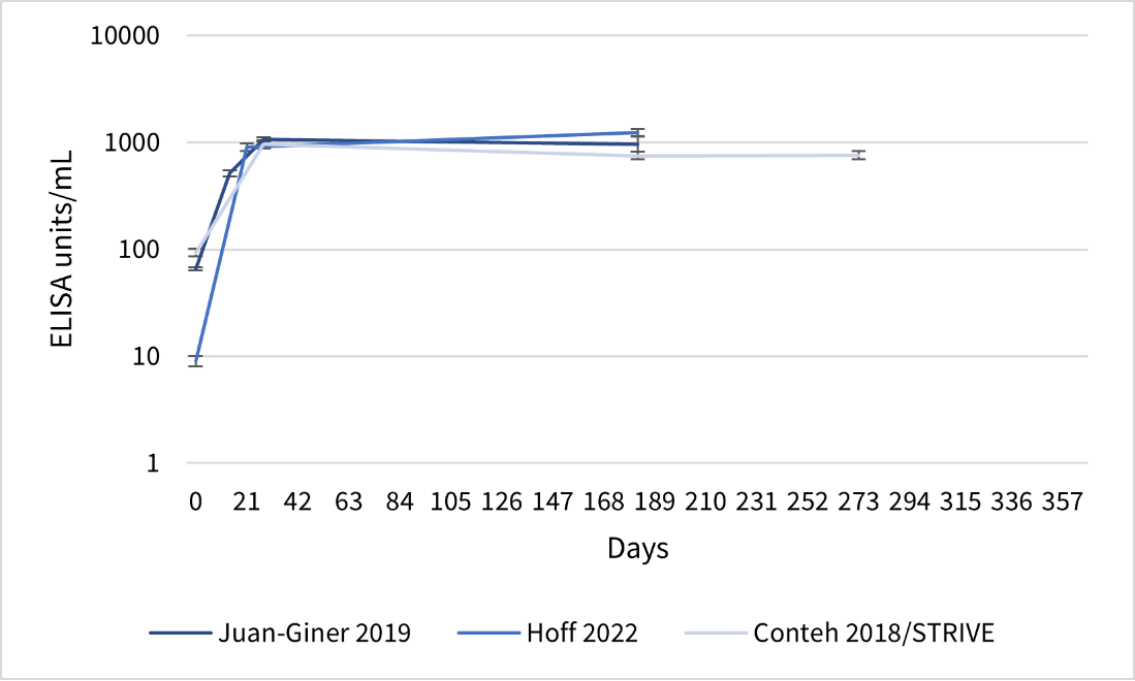


Figure 5. Specific antibodies after rVSV-ZEBOV in HCWs and FLWs in areas where the outbreak is likely to spread

6.1.6. Specific antibodies after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks

Two studies (Hoff 2022 (59); Juan-Giner 2019 (33)) were included that reported on specific antibodies following vaccination by rVSV-ZEBOV in HCWs and FLWs in countries at risk of EVD outbreaks. The data for these studies is shown in Figure 4.

6.1.7. Specific antibodies after rVSV-ZEBOV in general population in countries at risk of EVD outbreaks

Four studies (Agnandji 2017 (29); PREVAC 2022-AF (25); Kennedy 2017 (3); V920-008 ph1-KEN (61)) were included that reported on specific antibodies following vaccination by rVSV-ZEBOV in the general population in countries at risk of EVD outbreaks.

One study (PREVAC 2022-AF (25)) reported on 2801 adults and children comparing the rVSV-ZEBOV vaccine to placebo, and the Ad26.ZEBOV, MVA-BN-Filo vaccine regimen to placebo. A second randomised trial in Liberia (Kennedy 2017 (3)) compared two types of Ebola vaccine (ChAd3-EBO-Z or rVSV-ZEBOV) with placebo. The geometric mean ratios (GMR) between the rVSV-ZEBOV groups and the placebo groups are shown in Figure 6 below. The third study (Agnandji 2017 (29)) was a phase 1 trial in adults (n = 16) and children (n = 35) in Lambarene, Gabon and the fourth (V920-008 ph1-KEN (61); n = 85) was a phase 1 trial in Kilifi, Kenya (Figure 7).

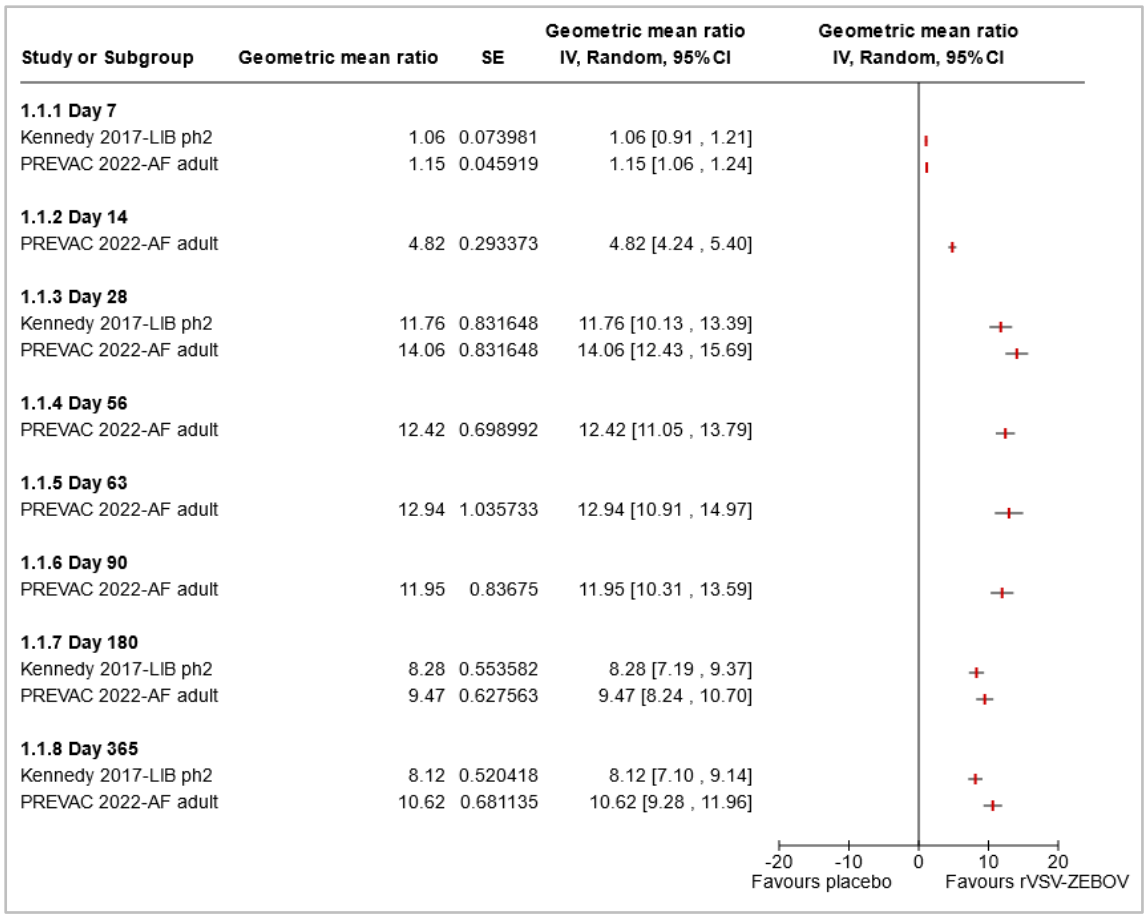


Figure 6. Geometric mean ratios between rVSV-ZEBOV and placebo groups in adults.

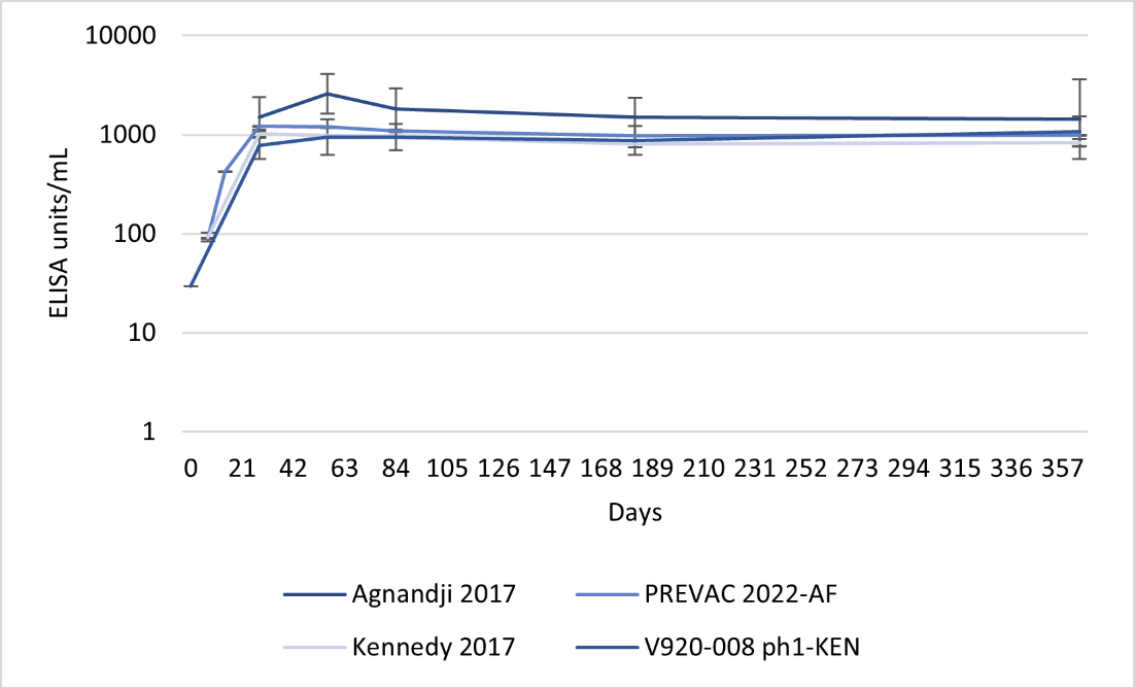


Figure 7. Specific antibodies after rVSV-ZEBOV in general population in countries at risk of EVD outbreaks

Two studies (Agnandji 2017 (29); PREVAC 2022-AF (25)) also reported on specific antibodies in children and adolescents. One study (n = 61) reported the GMR compared with placebo (Figure 8) and the other reported GMT over time in children and adolescents (n = 35) separately (Figure 9).

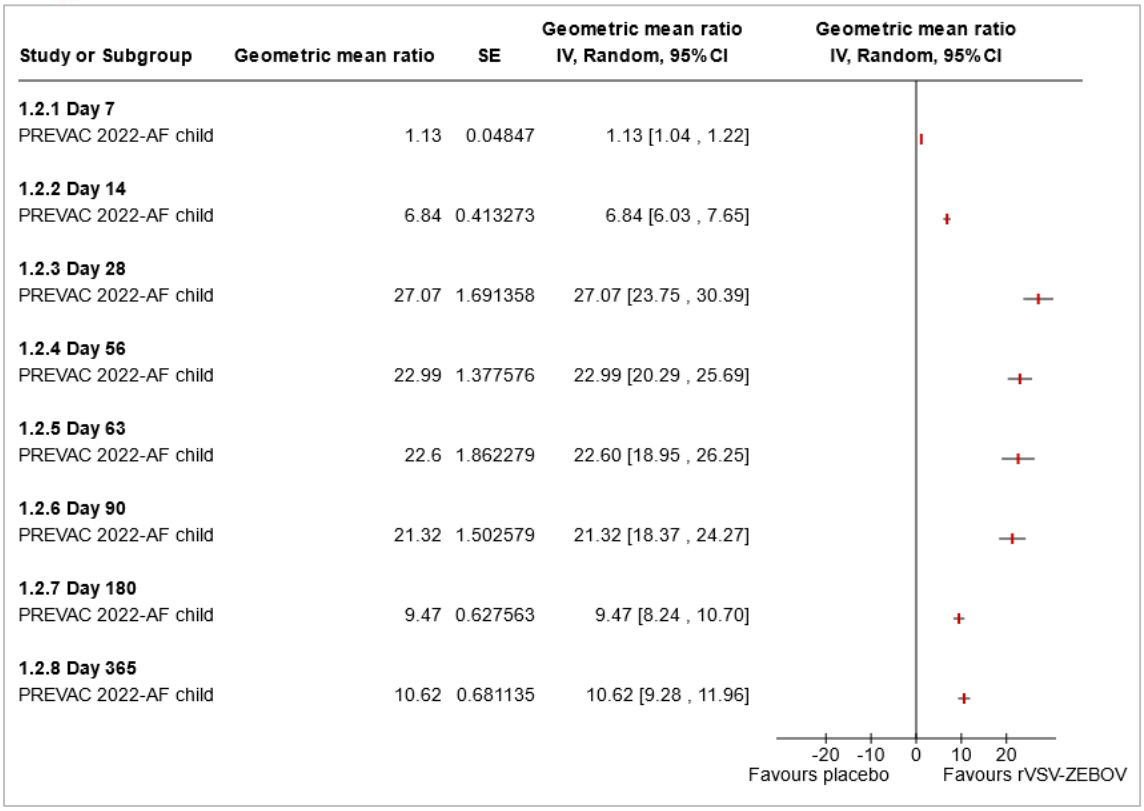


Figure 8. Geometric mean ratios between rVSV-ZEBOV and placebo groups in children and adolescents.

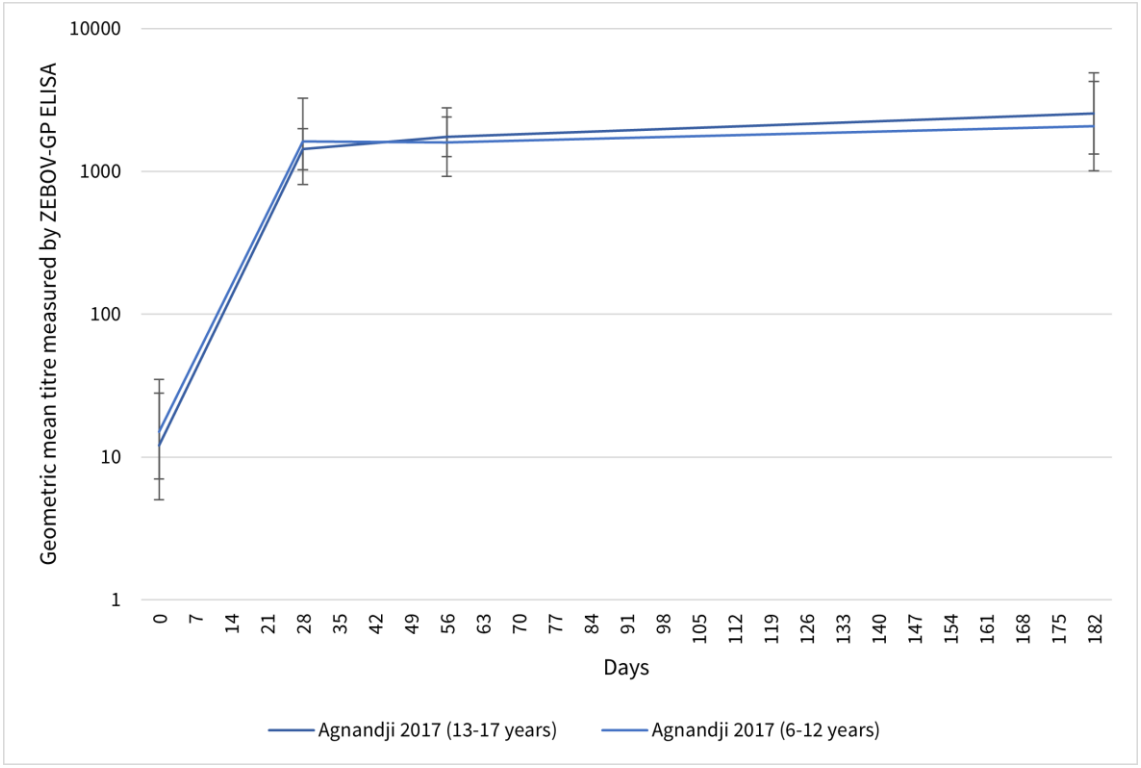


Figure 9. Specific antibodies after rVSV-ZEBOV in children and adolescents in countries at risk of EVD outbreaks

6.1.8. Specific antibodies after rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus

No studies were identified that reported on specific antibodies after rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus.

6.1.9. Specific antibodies after rVSV-ZEBOV in contacts of survivors

One study (Proches 2023 (34)) was identified that reported on specific antibodies after rVSV-ZEBOV in 1403 contacts of survivors. Results were stratified by seropositivity at baseline (seropositive/seronegative) and age (children/adults). Of those seronegative at baseline, children gave rise to a higher day 28 GMT of 0.17 (95%CI 0.15 to 0.19) compared with adults who had a GMT of 0.09 (95%CI 0.08 to 0.10, p<0.0001). With regards to those seropositive at baseline, children attained higher day 28 titres (GMT 0.34 (95%CI 0.27 to 0.43) than adults (GMT 0.21, 95%CI 0.19 to 0.24, p=0.003).

6.1.10. Specific antibodies after rVSV-ZEBOV in anyone else

Seven studies (Halperin 2017 (21); Dahlke 2017 (31); ElSherif 2017 (18); Farooq 2016 (20); Heppner 2017 (23); Huttner 2015 (24); Regules 2017 (26)) were identified that reported on specific antibodies in anyone else (mostly high-income countries).

Six studies (Halperin 2017 (21), n = 696; Farooq 2016 (20), n = 10; Heppner 2017 (23), n = 45; Regules 2017 (26), n = 10; ElSherif 2017 (18), n = 10; Huttner 2015 (24), n = 51) were placebo controlled randomised trials. All studies reported higher antibody levels at all time points following vaccination compared with placebo. One study (Dahlke 2017 (31); n = 10) was a non-randomised single arm study. Data on the antibody levels over time are presented in Figure 10.

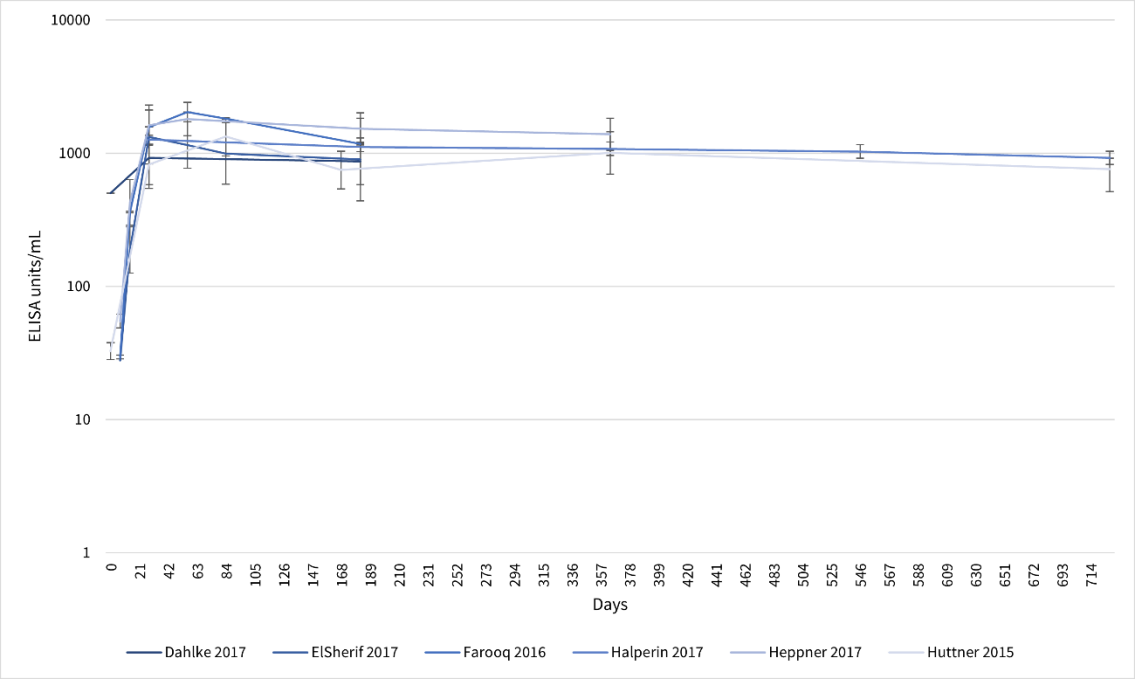


Figure 10. Specific antibodies after rVSV-ZEBOV in anyone else

6.2. Neutralising antibodies

6.2.1. Neutralising antibodies after rVSV-ZEBOV in contacts of Ebola virus disease cases

No studies were identified that reported on neutralising antibodies after rVSV-ZEBOV in contacts of Ebola virus disease cases.

6.2.2. Neutralising antibodies after rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases

No studies were identified that reported on neutralising antibodies after rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases.

6.2.3. Neutralising antibodies after rVSV-ZEBOV in probable contacts (all who request vaccination in a village with EVD cases)

No studies were identified that reported on neutralising antibodies after rVSV-ZEBOV in probable contacts of Ebola virus disease cases.

6.2.4. Neutralising antibodies after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases

One study (Juan-Giner 2019 (60), n = 1108) was identified that reported on neutralising antibodies using plaque reduction neutralization assay against ZEBOV-GP following rVSV-ZEBOV vaccination. This was a non-randomised trial of HCW and FLW in Guinea where FLWs who refused vaccination were offered to participate as the control group. All participants were included in the immunogenicity assessment (Figure 11).

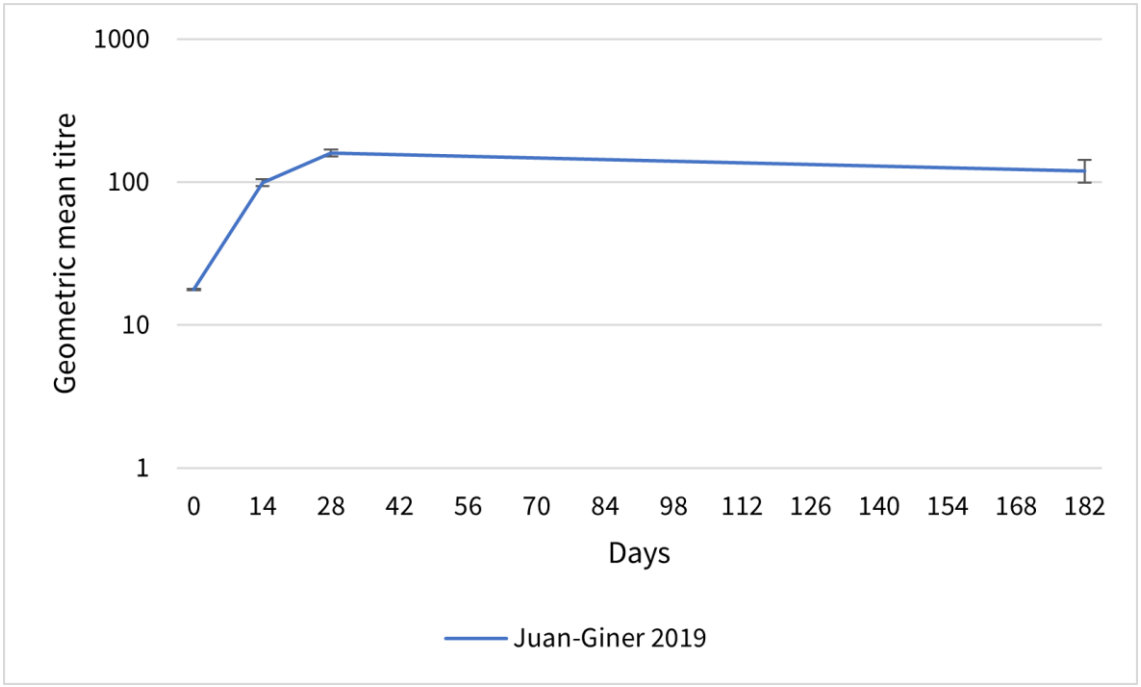


Figure 11. Neutralising antibodies after rVSV-ZEBOV in HCWs and FLWs in areas with cases who are not contacts of EVD cases

6.2.5. Neutralising antibodies after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread

Two studies (Conteh 2018/STRIVE (2); Juan-Giner 2019 (60)) were included that reported on neutralising antibodies using plaque reduction neutralization assay following vaccination by rVSV-ZEBOV in HCWs and FLWs in areas where the outbreak is likely to spread.

One individually randomised trial in Sierra Leone (Conteh 2018/STRIVE (2), n = 438) randomised HCW and FLW to immediate vaccination or deferred (18–24 weeks later) vaccination. The other study (Juan Giner 2019 (60), n = 1108) was a non-randomised trial of HCW and FLW in Guinea where FLWs who refused vaccination were offered to participate as the control group. All participants for both studies were included in the immunogenicity assessment (Figure 12).

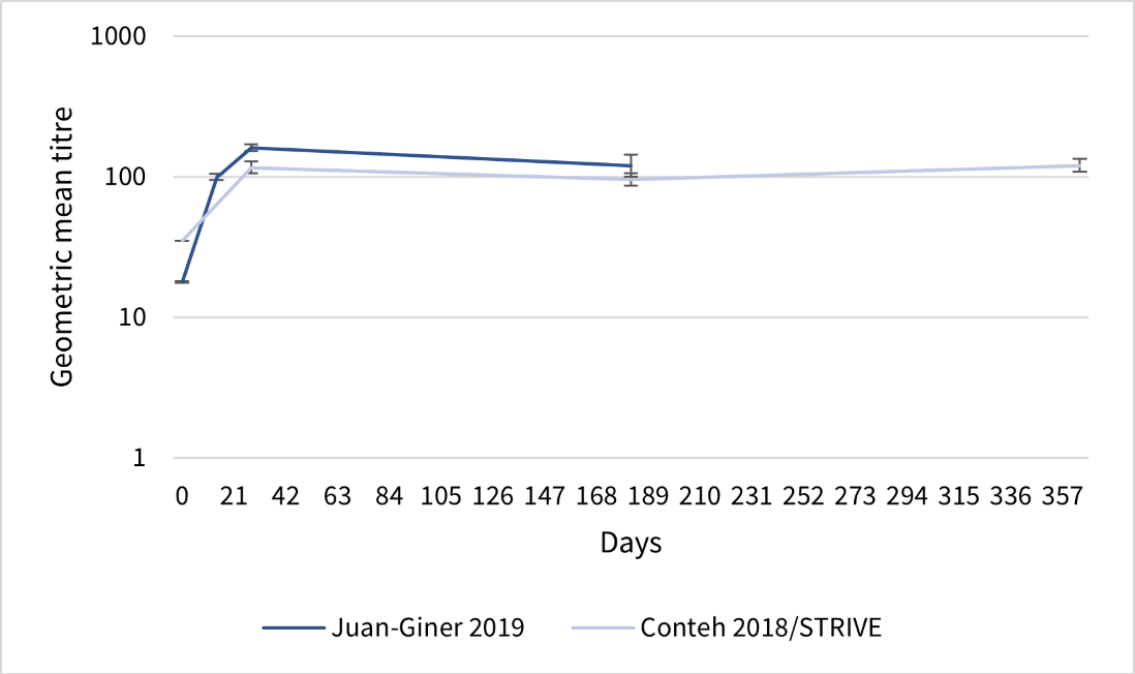


Figure 12. Neutralising antibodies after rVSV-ZEBOV in HCWs and FLWs in areas where the outbreak is likely to spread

6.2.6. Neutralising antibodies after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks

One study (Juan-Giner 2019 (60)) was included that reported on neutralising antibodies following vaccination by rVSV-ZEBOV in HCWs and FLWs in countries at risk of EVD outbreaks. The data for this study is shown in Figure 11.

6.2.7. Neutralising antibodies after rVSV-ZEBOV in general population in countries at risk of EVD outbreaks

Two studies (Agnandji 2017 (29), n = 16; V920-008 ph1-KEN (61), n = 20) were identified that reported on neutralising antibodies using PsVNA50 neutralisation titres following vaccination by rVSV-ZEBOV in the general population in countries at risk of EVD outbreaks. Both were phase 1 trials in Gabon and Kenya (Figure 13). One study (Agnandji 2017 (29)) also reported separately on level of neutralising antibodies in children and adolescents (Table 3).

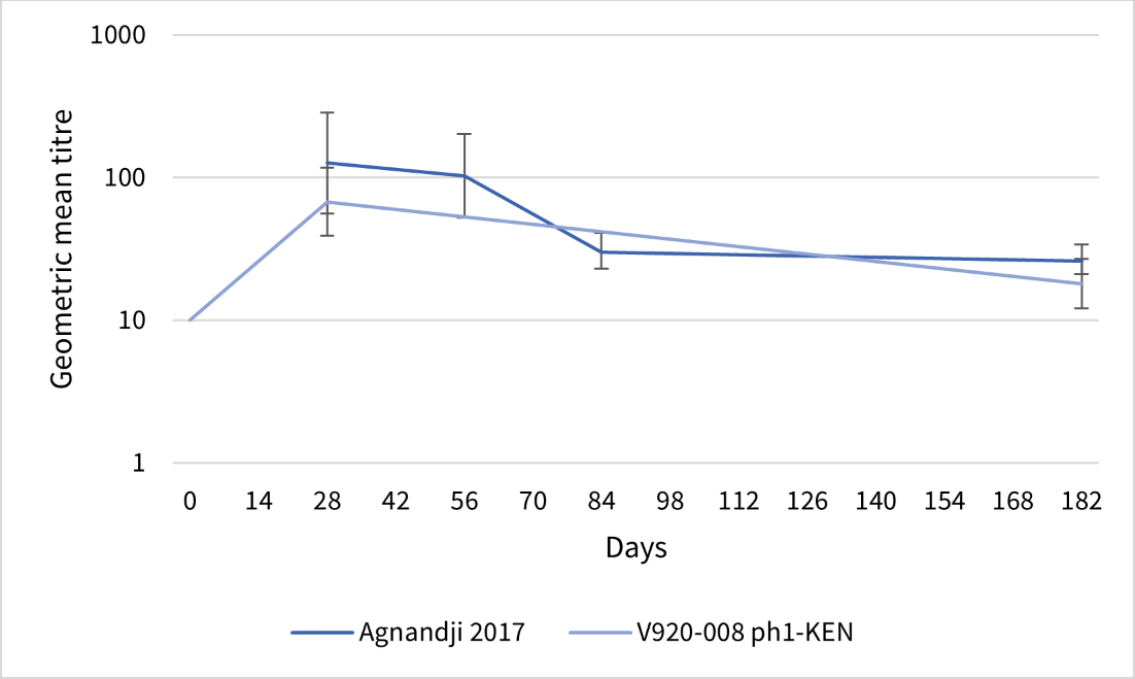


Figure 13. Neutralising antibodies after rVSV-ZEBOV in the general population in countries at risk of EVD outbreaks

Table 3. Neutralizing antibodies in children and adolescents measured by Pseudovirion Neutralization Assay following rVSV ZEBOV vaccination.

Study	Subgroup	Day 28 (GMT, 95% CI)	Day 56 (GMT, 95% CI)
Agnandji 2017 (29)	Children aged 6-12 years	118.2 (56.2 to 248.6)	-
Agnandji 2017 (29)	Adolescents aged 13-17 years	76.5 (36.9 to 158.5)	95.7 (50.5 to 181.6)

6.2.8. Neutralising antibodies after rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus

No studies were identified that reported on neutralising antibodies after rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus.

6.2.9. Neutralising antibodies after rVSV-ZEBOV in contacts of survivors

No studies were identified that reported on neutralising antibodies after rVSV-ZEBOV in contacts of survivors.

6.2.10. Neutralising antibodies after rVSV-ZEBOV in anyone else

Six studies (Halperin 2017 (21); Dahlke 2017 (31); Farooq 2016 (20); Heppner 2017 (23); Huttner 2015 (24); Regules 2017 (26)) were identified that reported on neutralising antibodies using PRNT or PsVNA titres in anyone else (mostly high-income countries).

Five studies (Halperin 2017 (21), n = 696; Farooq 2016 (20), n = 10; Heppner 2017 (23), n = 46; Regules 2017 (26), n = 10; Huttner 2015 (24), n = 10) were placebo controlled randomised trials. All studies reported higher neutralising antibody levels at all time points following vaccination compared with placebo. One study (Dahlke 2017 (31), n = 10) was a non-randomised single arm study. Data on the neutralising antibodies over time are presented in Figure 14.

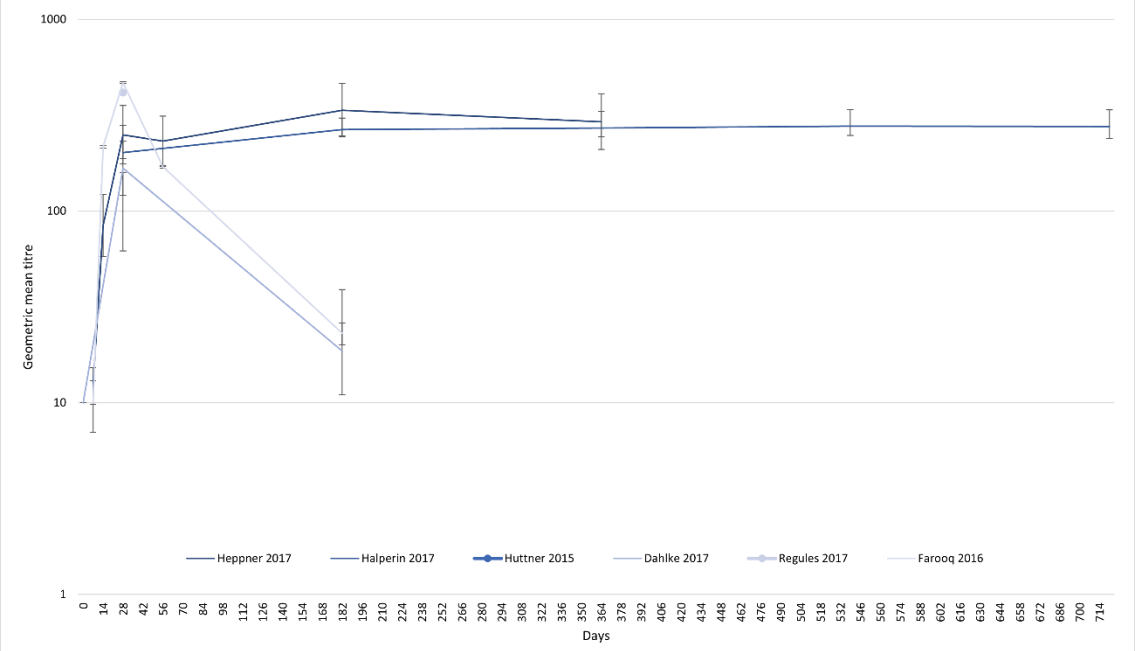


Figure 14. Neutralising antibodies after rVSV-ZEBOV in anyone else

6.3. Seroresponse

6.3.1. Seroresponse after rVSV-ZEBOV in contacts of Ebola virus disease cases

Two single arm studies (Davis 2020 (4), n = 18; Hoff 2022 (59), n = 548) were identified that reported on seroresponse after rVSV-ZEBOV in contacts of Ebola virus disease cases. At the six month follow up, one study (Davis 2020 (4)) reported 94% seroresponse and the other (Hoff 2022 (59)) reported 95.6% seroresponse (Figure 15).

6.3.2. Seroresponse after rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases

One single arm study (Hoff 2022 (59), n = 548) was identified that reported on seroresponse after rVSV-ZEBOV in contacts of contacts of Ebola virus disease cases (Figure 135).

6.3.3. Seroresponse after rVSV-ZEBOV in probable contacts (all who request vaccination in a village with EVD cases)

One single arm study (Hoff 2022 (59), n = 548) was identified that reported on seroresponse after rVSV-ZEBOV in probable contacts of Ebola virus disease cases (Figure 15).

6.3.4. Seroresponse after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases

Two studies (Hoff 2022 (59), n = 548; Juan-Giner 2019 (60), n = 1072) were identified that reported on seroresponse following vaccination by rVSV-ZEBOV in HCWs and FLWs in areas with cases who are not contacts of EVD cases (Figure 15).

6.3.5. Seroresponse after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread

Three studies (Hoff 2022 (59), n = 548; Conteh 2018/STRIVE (2), n = 441; Juan-Giner 2019 (60), n = 1072) were identified that reported on seroresponse following vaccination by rVSV-ZEBOV in HCWs and FLWs in areas where the outbreak is likely to spread (Figure 15).

6.3.6. Seroresponse after rVSV-ZEBOV in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks

Two studies (Hoff 2022 (59), n = 548; Juan-Giner 2019 (60), n = 1072) were identified that reported on seroresponse following vaccination by rVSV-ZEBOV in HCWs and FLWs in countries at risk of EVD outbreaks (Figure 15).

6.3.7. Seroresponse after rVSV-ZEBOV in general population in countries at risk of EVD outbreaks

Four studies (Agnandji 2017 (29), n = 16; PREVAC 2022-AF (25), n = 560; Kennedy 2017 (3), n = 495; V920-008 ph1-KEN (61), n = 20) were identified that reported on seroresponse following vaccination by rVSV-ZEBOV in the general population in countries at risk of EVD outbreaks (Figure 15).

Two of these studies (Agnandji 2017 (29); PREVAC 2022-AF (25)) reported data separately on seroresponse in children and adolescents (Table 4).

Table 4. Immune responders (defined as a ≥4-fold increase in GMT) in children and adolescents following rVSV ZEBOV vaccination.

Study	Subgroup	Day 28	Day 56	Day 180
Agnandji 2017 (29)	Children aged 6-12 years	19/20 (95%)	20/20 (100%)	18/20 (90%)
Agnandji 2017 (29)	Adolescents aged 13-17 years	15/15 (100%)	16/16 (100%)	17/17 (100%)
PREVAC 2022-AF (25)	Children aged 1-17 years	522/580 (90%)	531/584 (91%)	332/388 (86%)

6.3.8. Seroresponse after rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus

One study (Raabe 2021 (62), n = 21) was identified that reported on seroresponse following vaccination by rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus (Figure 15).

6.3.9. Seroresponse after rVSV-ZEBOV in contacts of survivors

One study (Proches 2023 (34)) was identified that reported on specific antibodies after rVSV-ZEBOV in 1403 contacts of survivors. Results were stratified by seropositivity at baseline (seropositive/seronegative) and age (children/adults). Of the 1175 baseline seronegative participants, 955 (81.3%) were seropositive by ELISA on day 28. Children showed 91.1% seroresponse rate (308 of 338, 95%CI: 87.6% to 93.7%) compared with adults who showed a 77.3% seroresponse rate by day 28 (647 of 837, 95%CI: 74.3% - 80.0%).

6.3.10. Seroresponse after rVSV-ZEBOV in anyone else

Six studies (Halperin 2017 (21), n = 696; Dahlke 2017 (31), n = 10; ElSherif 2017 (18), n = 10; Heppner 2017 (23), n = 46; Huttner 2015 (24), n = 35; Regules 2017 (26), n = 10) were identified that reported on seroresponse following vaccination by rVSV-ZEBOV in anyone else (high-income countries) (Figure 15).

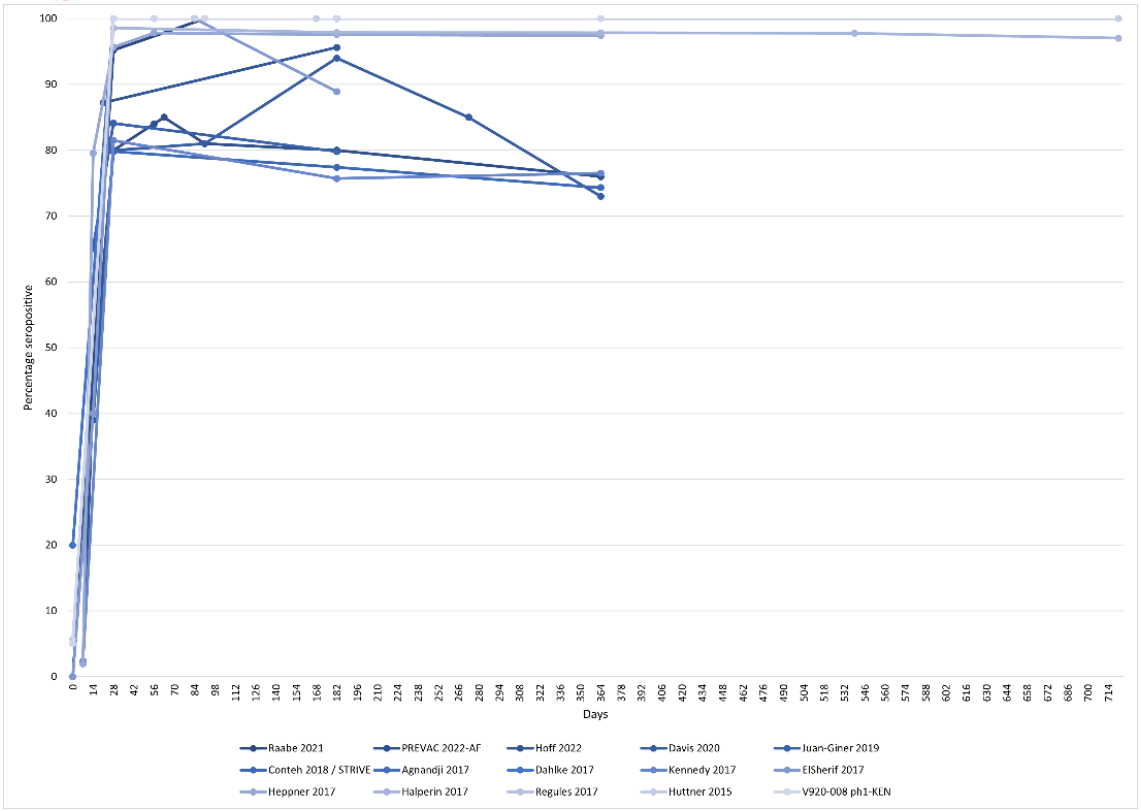


Figure 15. Seroresponse (≥4-fold increase from baseline) to Ebola specific antibodies over time after rVSV-ZEBOV vaccination

7. Immunogenicity of Ebola vaccines - Ad26.ZEBOV, MVA-BN-Filo regimen

Immune monitoring for responses to Ad26.ZEBOV, MVA-BN-Filo vaccine was commonly assessed by measuring glycoprotein (GP)-specific antibodies or neutralizing antibodies. The focus of this review is the duration of immune responses over time following vaccination. GP-specific antibodies were quantified using the homologous Zaire-Kikwit strain glycoprotein, approved as the Filovirus Animal Non-Clinical Group (FANG) assay. In addition, the Pseudovirion Neutralization Assay (PsVNA) was used.

7.1. Specific antibodies

7.1.1. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in contacts of Ebola virus disease cases

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of Ebola virus disease cases.

7.1.2. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in contacts of contacts of Ebola virus disease cases

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of contacts of Ebola virus disease cases.

7.1.3. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in probable contacts (all who request vaccination in a village with EVD cases)

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in probable contacts of Ebola virus disease cases.

7.1.4. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in areas with cases who are not contacts of Ebola virus disease cases.

7.1.5. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in areas where the outbreak is likely to spread.

7.1.6. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in countries at risk of EVD outbreaks.

7.1.7. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in general population in countries at risk of EVD outbreaks

Six studies (EBL1004-AF (63); EBL2002 adult-AF (43); PREVAC 2022-AF (25); EBL1003-KEN (56); EBL3001 adult-SL (50); EBL3008-DRC (53)) were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in the general population of countries at risk of EVD outbreaks. Two of these studies reported on specific antibodies following a booster dose in adults (EBL3001 adult-SL (50); EBL2002 adult-AF (43)).

Five studies (EBL3001 child-SL (51); EBL2002 child-AF (46); PREVAC 2022-AF (25); EBL2005 infant-AF (44); EBL3008-DRC (53)) reported on level of specific antibodies following Ad26.ZEBOV, MVA-BN-Filo vaccination in children and adolescents. One study reported on specific antibodies following a booster dose in children (EBL2011 child boost-SL (52)).

In addition, two studies (EBL2002 adult-AF (43); EBL2010 HIV boost-AF (64)) were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in people living with HIV. At day 21 following the first dose in EBL2002 adult-AF (43), a GMC of 5283 EU/mL (compared to 7501 EU/mL in healthy adults) was reported. The other study is unpublished (EBL2010 HIV boost-AF (64)) and followed a subset of 26 participants living with HIV in Kenya and Uganda who received a booster dose after prime vaccination from an earlier trial (EBL2002 adult-AF), reporting persistent antibody response up to 4.5 years post dose one.

Three of the studies in adults (EBL1004-AF (63), n = 15; EBL2002 adult-AF (43), n = 136; EBL3001 adult-SL (50), n = 188) were RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with placebo or a control vaccine. At all timepoints the antibody levels were higher in the vaccine groups than the placebo groups. One study (PREVAC 2022-AF (25)) reported on two RCTs of 2801 adults and children comparing the rVSV-ZEBOV to placebo, and Ad26.ZEBOV, MVA-BN-Filo to placebo. Data for these four studies is shown in Figure 16.

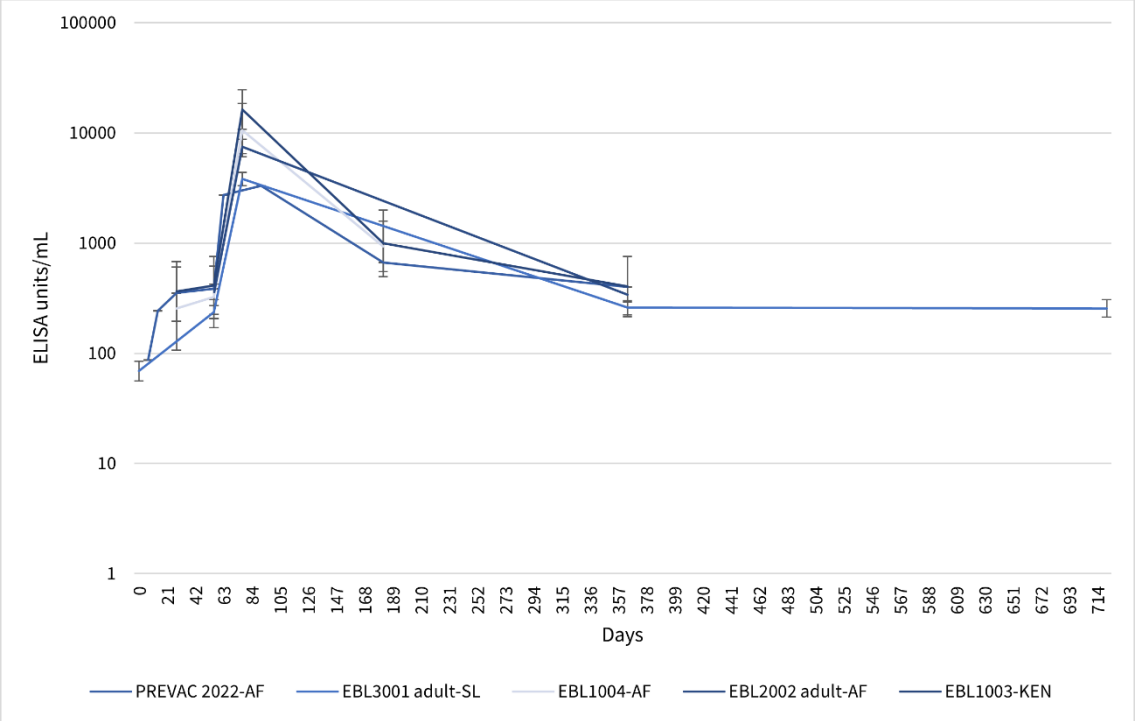


Figure 16. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in the general population in countries at risk of EVD outbreaks

Two studies (EBL2002 adult-AF (43), n = 136; EBL3001 adult-SL (50), n = 188) also reported on the level of specific antibodies following booster vaccination with Ad26.ZEBOV, MVA-BN-Filo at one year (EBL2002 adult-AF (43)) or two years (EBL3001 adult-SL (50)) from the first dose (Figure 17).

One additional unpublished cohort study (EBL3008-DRC (53)) reported that with an extended interval between doses (median 9 months), antibody responses remained high at 21 days post dose two for adults.

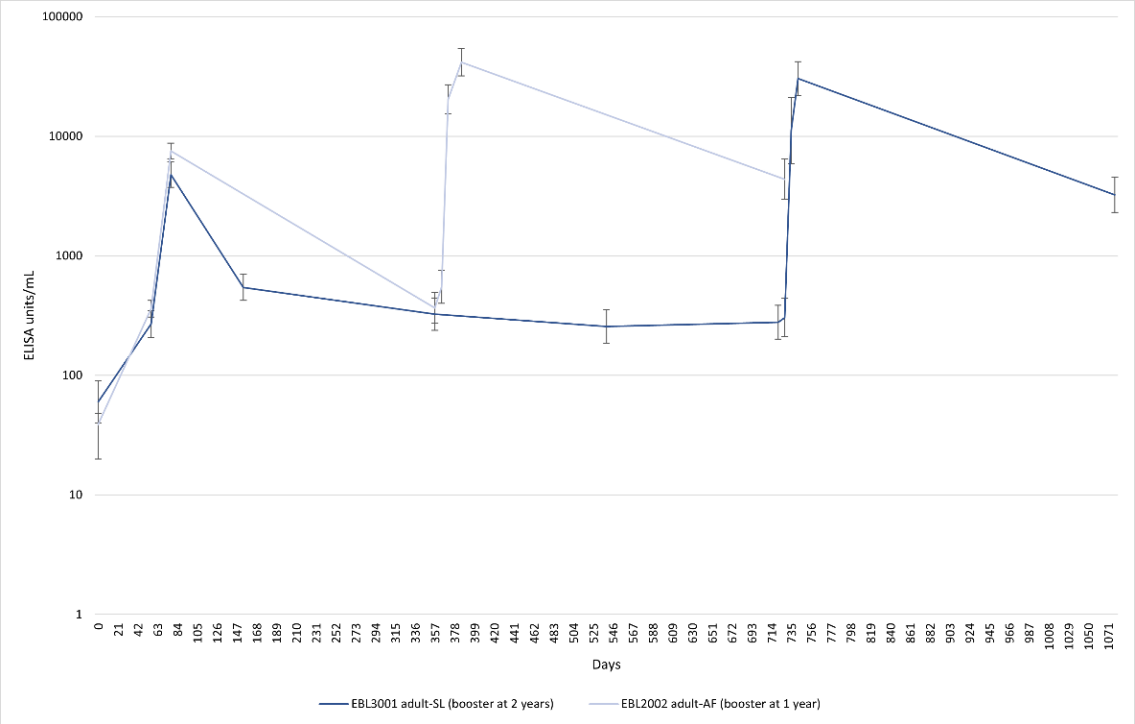


Figure 17. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo boosters in the general population in countries at risk of EVD outbreaks

Five studies (EBL3001 child-SL (51); EBL2002 child-AF (46); PREVAC 2022-AF (25); EBL2005 infant-AF (44); EBL3008-DRC (53)) reported on level of specific antibodies following Ad26.ZEBOV, MVA-BN-Filo vaccination in children and adolescents (Figure 18). Two of these are unpublished, with one (EBL2005 infant-AF (44)) reporting high antibody response at 21 days post dose two in infants aged 4-11 months. One unpublished cohort study (EBL3008-DRC (53)) reported that with an extended interval between doses (median 9 months), antibody responses remained high at 21 days post dose two for adolescents and children.

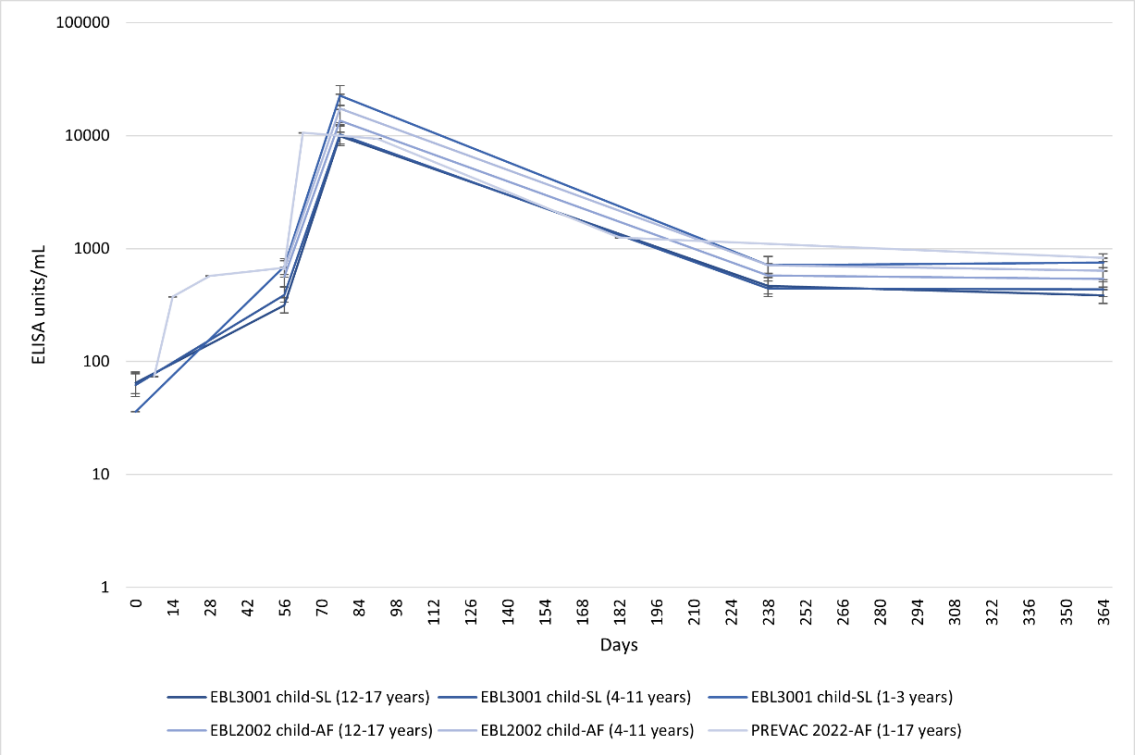


Figure 18. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo boosters in children and adolescents in countries at risk of EVD outbreaks

One study (EBL2011 child boost-SL (52)) was a single arm trial of a booster dose of Ad26.ZEBOV, MVA-BN-Filo after more than three years in children and adolescents in Sierra Leone. This study included 50 children and adolescents from the EBL3001 child-SL trial (51). Data on the specific antibodies is reported in Table 5.

When compared with the binding antibody GMC before their first vaccine dose, 40 of 46 participants (87%) still had a response at a median of 3.2 years from the first dose. In the 1–3 years cohort, 23 of 24 participants (96%) had a response at a median of 3.1 years from the first dose. In the 4–11 years cohort, 17 of 22 participants (77%) had a response at a median of 3.8 years from the first dose.

Table 5. GP-specific antibodies following booster dose at two years in children and adolescents following Ad26.ZEBOV, MVA-BN-Filo vaccination.

Study	Subgroup	Day 1 (pre-booster) (GMT, 95% CI)	Day 7 (GMT, 95% CI)	Day 21 (GMT, 95% CI)
EBL2011 child boost-SL (52)	1–3 years cohort	934 (568 to 1534)	30,463 (18,087 to 51,307)	71,143 (47,819 to 105,844)
EBL2011 child boost-SL (52)	4–11 years cohort	418 (287 to 608)	26,478 (16,512 to 42,461)	57,564 (36,375 to 91,095)

7.1.8. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in labs working with Ebola virus

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in labs working with Ebola virus.

7.1.9. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in contacts of survivors

No studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of survivors.

7.1.10. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in anyone else

Five studies (EBL3003-US (47); EBL3002-US (47); FLV1001-US (58); EBL1001-UK (40); EBL2001-EU (42)) were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in anyone else.

All five of these studies (EBL3003-US (47); EBL3002-US (47); FLV1001-US (58); EBL1001-UK (40); EBL2001-EU (42)) were RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with placebo. At all timepoints the antibody levels were higher in the vaccine groups than the placebo groups. Data for these studies is shown in Figure 19.

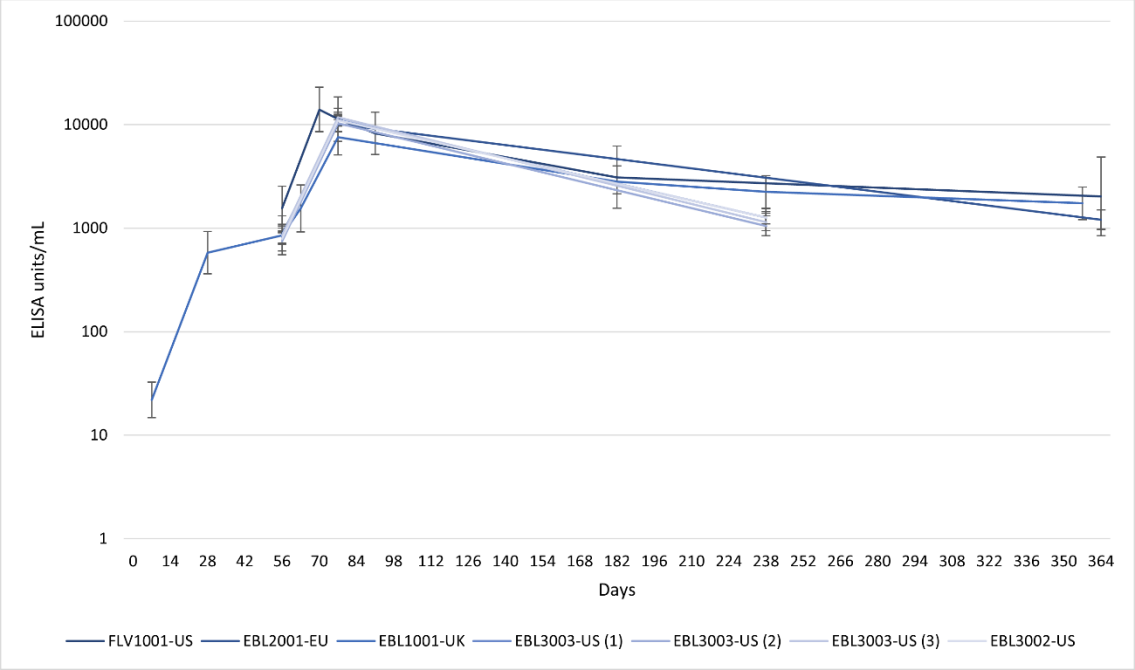


Figure 19. Specific antibodies after Ad26.ZEBOV, MVA-BN-Filo in anyone else

7.2. Neutralising antibodies

7.2.1. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in contacts of Ebola virus disease cases

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of Ebola virus disease cases.

7.2.2. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in contacts of contacts of Ebola virus disease cases

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of contacts of Ebola virus disease cases.

7.2.3. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in probable contacts (all who request vaccination in a village with EVD cases)

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in probable contacts of Ebola virus disease cases.

7.2.4. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in areas with cases who are not contacts of Ebola virus disease cases.

7.2.5. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in areas where the outbreak is likely to spread.

7.2.6. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in countries at risk of EVD outbreaks.

7.2.7. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in general population in countries at risk of EVD outbreaks

Four studies (EBL1004-AF (63), n = 15; EBL2002 adult-AF (43), n = 37; EBL3001 adult-SL (50), n = 55; EBL1003-KEN (56), n = 15) were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in the general population in countries at risk of EVD outbreaks. All four were RCTs comparing Ad26.ZEBOV, MVA-BN-Filo with placebo. At all timepoints the antibody levels were higher in the vaccine groups than the placebo groups (Figure 20).

Two studies (EBL3001 child-SL (51); EBL2002 child-AF (46)) were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in children and adolescents (Figure 21).

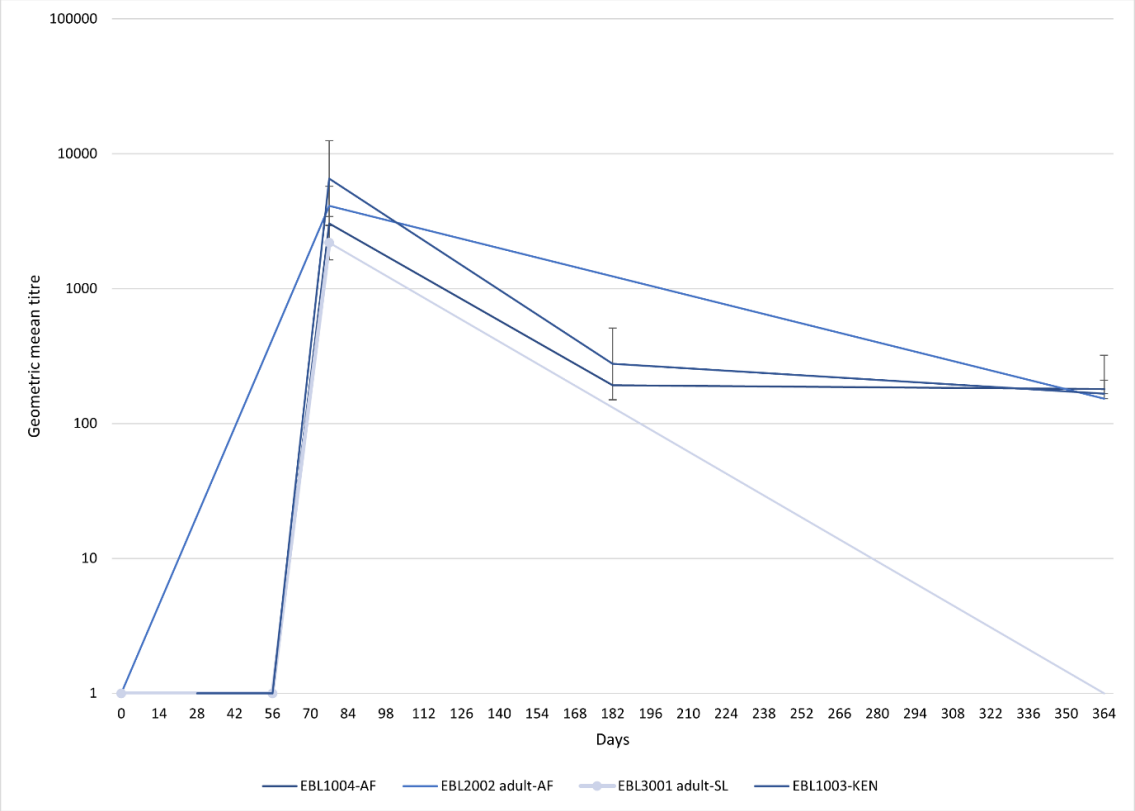


Figure 20. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in the general population in countries at risk of EVD outbreaks

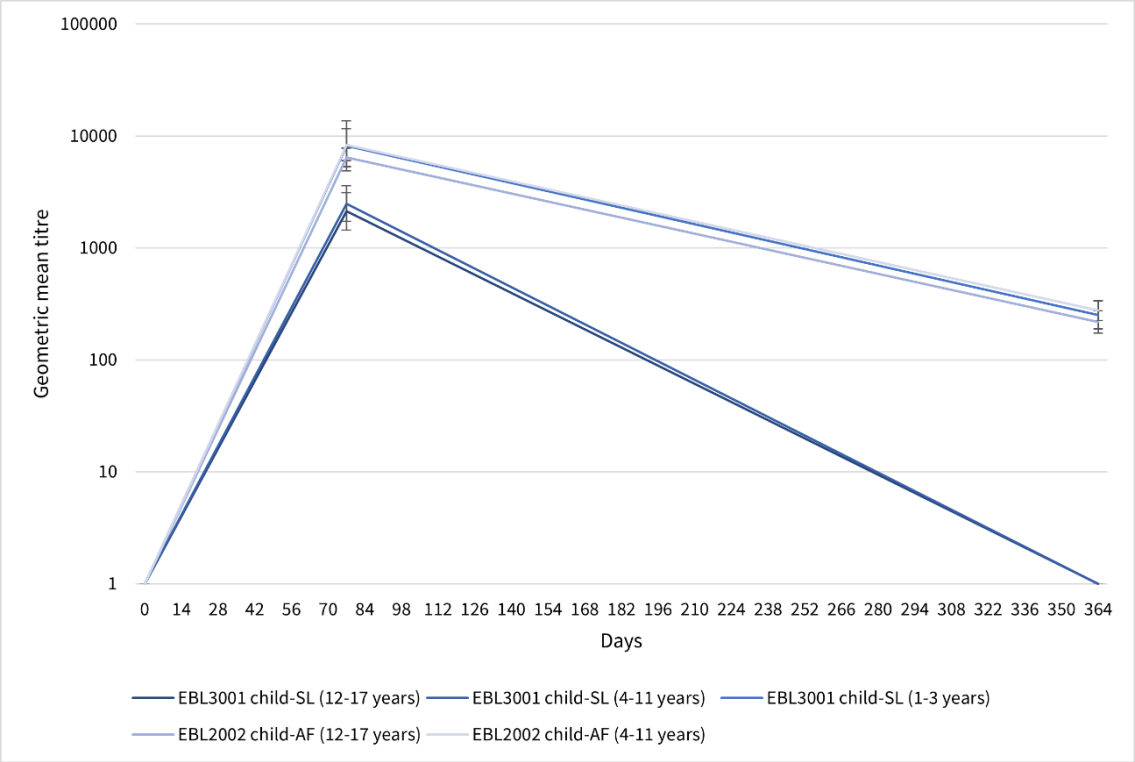


Figure 21. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in children and adolescents in countries at risk of EVD outbreaks

7.2.8. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in labs working with Ebola virus

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in labs working with Ebola virus.

7.2.9. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in contacts of survivors

No studies were identified that reported on neutralising antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of survivors.

7.2.10. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in anyone else

Four studies (EBL3003-US (47); EBL3002-US (47); FLV1001-US (58); EBL2001-EU (42)) were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV, MVA-BN-Filo in anyone else (Figure 22).

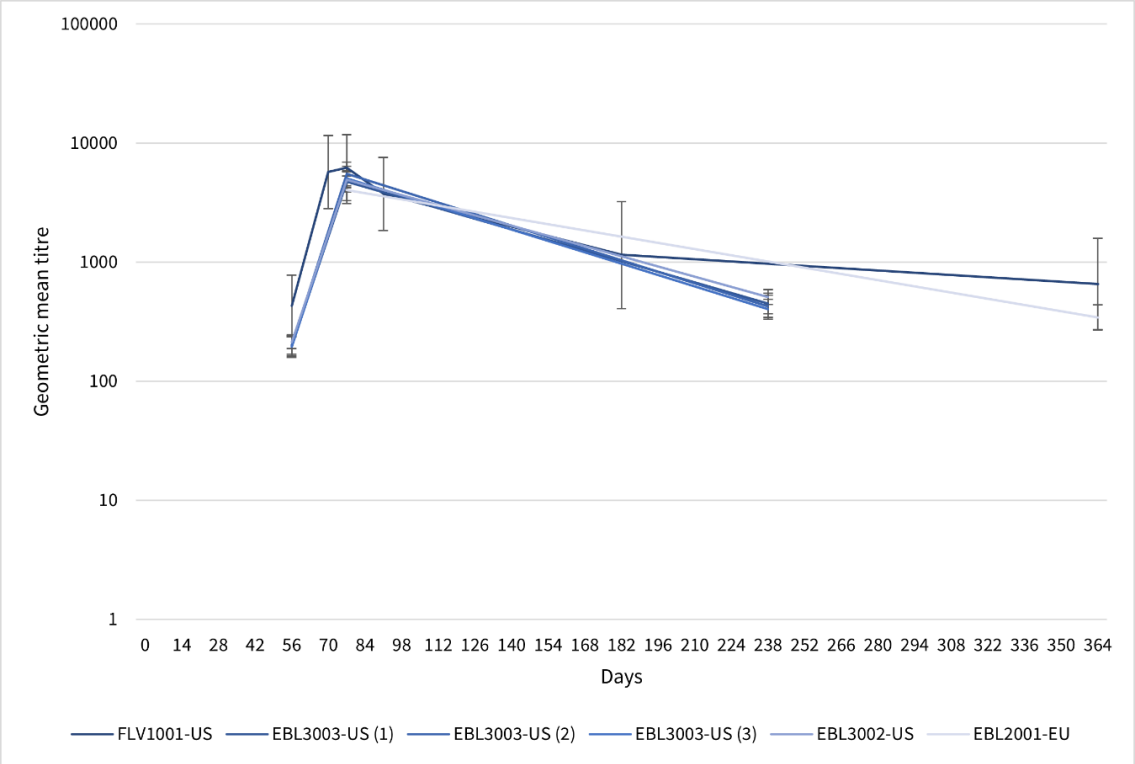


Figure 22. Neutralising antibodies after Ad26.ZEBOV, MVA-BN-Filo in anyone else

7.3. Seroresponse

7.3.1. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in contacts of Ebola virus disease cases

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of Ebola virus disease cases.

7.3.2. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in contacts of contacts of Ebola virus disease cases

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of contacts of Ebola virus disease cases.

7.3.3. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in probable contacts (all who request vaccination in a village with EVD cases)

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in probable contacts of Ebola virus disease cases.

7.3.4. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in areas with cases who are not contacts of EVD cases

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in areas with cases who are not contacts of Ebola virus disease cases.

7.3.5. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in areas where the outbreak is likely to spread

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in areas where the outbreak is likely to spread.

7.3.6. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in health care workers (HCWs) and front-line workers (FLWs) in countries at risk of EVD outbreaks

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in countries at risk of EVD outbreaks.

7.3.7. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in general population in countries at risk of EVD outbreaks

Five studies (EBL1004-AF (63); EBL2002 adult-AF (43); EBL1003-KEN (56); PREVAC 2022-AF (25); EBL3001 adult-SL (50)) were identified that reported on seroresponse following Ad26.ZEBOV, MVA-BN-Filo in the adult general population in countries at risk of EVD outbreaks (Figure 23).

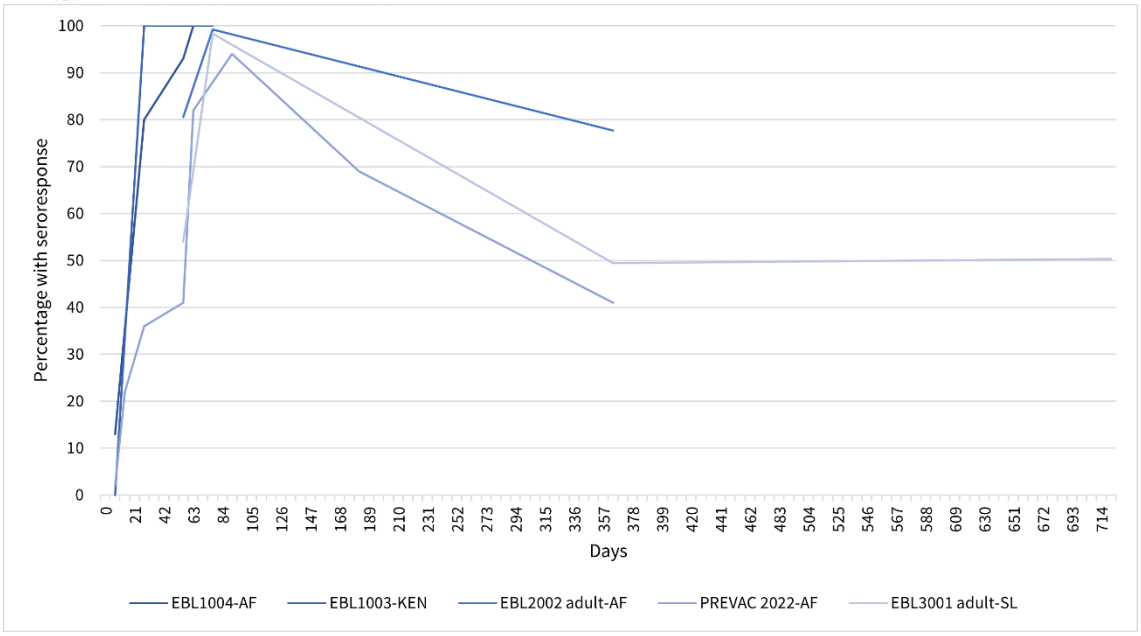


Figure 23. Seroresponse to Ebola specific antibodies over time after Ad26.ZEBOV, MVA-BN-Filo vaccination in the adult general population in countries at risk of EVD outbreaks

Three studies (EBL2002 child-AF (46); PREVAC 2022-AF (25); EBL3001 child-SL (51)) reported on seroresponse following Ad26.ZEBOV, MVA-BN-Filo in children and adolescents (Figure 24).

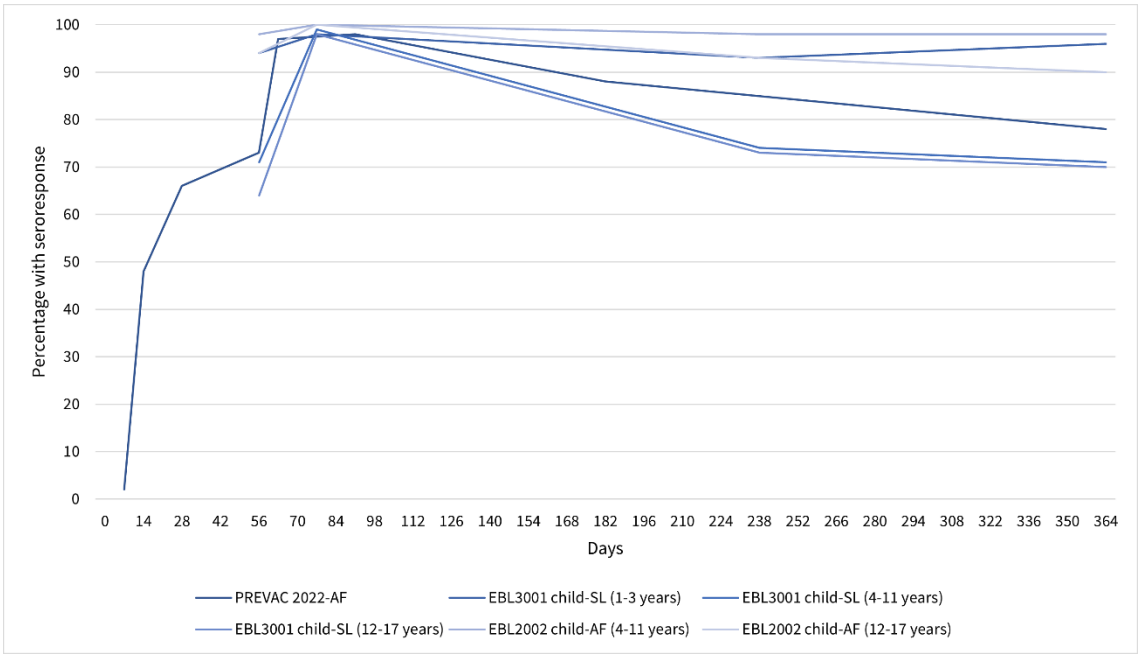


Figure 24. Seroresponse to Ebola specific antibodies over time after Ad26.ZEBOV, MVA-BN-Filo vaccination in children and adolescents in countries at risk of EVD outbreaks

7.3.8. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in labs working with Ebola virus

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in HCWs and FLWs in labs working with Ebola virus.

7.3.9. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in contacts of survivors

No studies were identified that reported on seroresponse following vaccination by Ad26.ZEBOV, MVA-BN-Filo in contacts of survivors.

7.3.10. Seroresponse after Ad26.ZEBOV, MVA-BN-Filo in anyone else

Five studies (EBL3003-US (47); EBL3002-US (47); FLV1001-US (58); EBL1001-UK (40); EBL2001-EU (42)) were identified that reported on seroresponse following Ad26.ZEBOV, MVA-BN-Filo in anyone else (Figure 25).

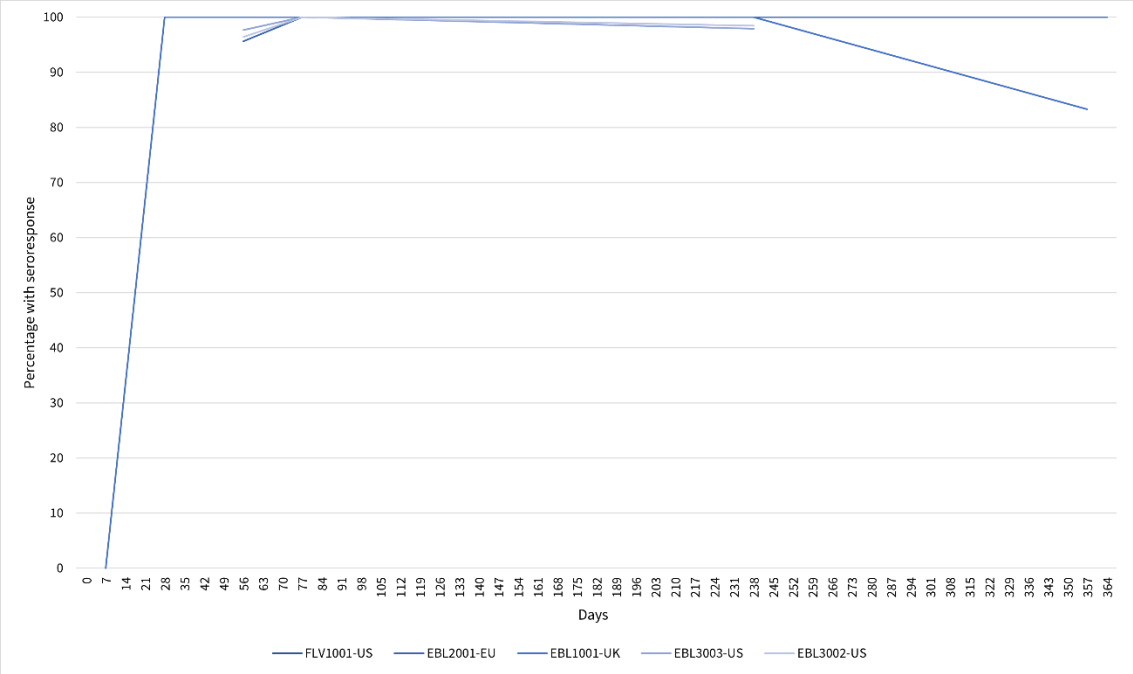


Figure 25. Seroresponse to Ebola specific antibodies over time after Ad26.ZEBOV, MVA-BN-Filo vaccination

8. References

Citations are provided in this list to indicate the source of data for each outcome. See Appendix list of included studies for complete list of study publications.

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