Annexes to the recommendations for use of the Ebola vaccines

Evidence to decision tables

Date: 04 June 2024

World Health Organization

Background

A systematic review was conducted by Cochrane Response to assess safety, efficacy, immunogenicity, and duration of protection of licensed Ebola virus vaccines. The systematic review contains the summary of findings and GRADE certainty assessments. Annexes 1–3 below contain the SAGE evidence-to-decision framework tables (ETD tables). The ETD tables are based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel) (www.decide-collaboration.eu/, accessed 4 June 2024).

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Annex 1: DURING OUTBREAKS - INSIDE RINGS: Administration of rVSVΔG-ZEBOV-GP vaccine using ring vaccination strategy in areas with Ebola virus disease (EVD) cases

Question: Should rVSVΔG-ZEBOV-GP vaccine be administered to EVD contacts and contacts of contacts to prevent Ebola virus disease (EVD) in an area with EVD cases as part of ring vaccination?

Population: Contacts of EVD cases and contacts of contacts. This includes health care workers (HCWs) and front line workers (FLWs) that fulfill one of these three definitions of a contact.
Intervention: One dose of Ebola virus vaccine (rVSVΔG-ZEBOV-GP)
Comparison(s): No vaccine/ placebo
Outcome: Efficacy, effectiveness, immunogenicity and safety

Background:
Ebola virus disease (EVD) is a rare but severe illness in humans, with a high mortality. There are six species in the genus *Ebolavirus*, three of which (O*rthoebolavirus zairense (EBOV), Orthoebolavirus bundibugyoense, Orthoebolavirus sudanense*) have previously caused large outbreaks. Since 1976 when it was first identified, there have been 25 outbreaks of Ebolavirus with local transmission, of which 17 (71%) of these were caused by *Orthoebolavirus zairense*. The largest epidemic of Ebola since its discovery occurred from 2014-2016 in West Africa, wherein an estimated 28,600 persons were infected and 11,325 died.

During an outbreak response, rapid high levels of protection and a good safety profile are important vaccine characteristics. Therefore, a single-dose regimen with rapid onset of immunity (within 10 days) is highly preferred. The ring vaccination approach has been used since the first Ebola vaccine was available. Approximately 350,000 contacts and contacts of contacts have been promptly vaccinated with rVSVΔG-ZEBOV-GP during the Ebola Zaire outbreaks since 2016. The ring vaccination strategy has proven highly effective in contributing to stop EVD outbreaks.
In the Democratic Republic of the Congo (DRC) 2018-20 outbreak, no ring could be formed around only 145/ 3,323 (4.3%) of the total confirmed EVD cases because of security issues (24 cases) or community reticence (121 cases). Of the 3,481 cases of EVD reported (3,323 lab-confirmed) during the entire outbreak, 3,317/3,323 (95.7%) were either one of the cases around which the rings were formed, or EVD cases among contacts or contacts of contacts who were previously vaccinated as part of rings for other cases (e.g. in the same chain of transmission of another case). Of these 3,317 cases covered by rings, about 90/3317 (3%) had before ring formation already died from probable EVD.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Ebola Zaire virus has been the cause of approximately 71% (17/24) of Ebola virus outbreaks since its discovery. Mortality rates are very high, ranging from 60-80%. The risk of Ebola virus infection varies by type of contact with the EVD case. The rVSVΔG-ZEBOV-GP has been successfully implemented during outbreaks using the ring vaccination strategy in all outbreaks since 2016. In the DRC 2018-20 outbreak, of the 3,323 confirmed EVD cases during the entire outbreak 3,317/3,323 (95.7%) have their contacts and contacts of contacts enumerated in the vaccination rings. The majority were the index cases around which the rings were formed, or some were already vaccinated individuals (i.e., in the same chain of transmission of another case, probably already infected and incubating at the time of vaccination). (1) This detailed individual data collection permitted the evaluation of the EVD risk of infection per 1,000 within 0-9 days following ring definition and vaccination when the vaccine is expected to have little or no effect. The risks were: 6.2% per 1,000 among contacts of cases (incl. HCWs/FLWs who were contacts whose risk was 3.7%); 0.2% per 1,000 among contacts of contacts (incl, 0.6% among HCWs/FLWs who were contacts of contacts); and none among 3rd level contacts. (1,2) Male contacts of an index case have lower risk compared to females (risk ratio 0.62 (95% CI 0.50-0.77)) in the 9 days post-	

			vaccination. The risk of EVD among pregnant and lactating women (11.7/1,000) was lower than that of other females aged 14-49 (15.8/1,000), but greater than men aged 14-49 (8.4/1,000). (3) The HCWs/FLWs vaccinated within rings had 30-day EVD risks of 1.9 per 1000, similar to the 30-day risks of 2.0 per 1000 among other ring members who were not HCWs/FLWs.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	One-dose vaccine efficacy for prevention of EVD: Estimated to be 100% (95% CI: 68.9 to 100.0) among those vaccinated immediately. (4,5) The observational data from the DRC 2018-2020 outbreak suggests 94% (CI 88-97%) vaccine efficacy against EVD onset. (3) Isolation of cases, other EVD control measures, and ring vaccination with single-dose live rVSVΔG-ZEBOV-GP vaccine can substantially alter the course of outbreaks of the Zaire species of Ebola virus. About 6 days after intervention with isolation of any recent cases and ring vaccination the incidence of EVD started to decrease substantially, and after another six days few further cases arose. The sooner after index case onset this intervention occurred the sooner the incidence of EVD in case-contacts decreased. Initial response after vaccination ranges from 80-100% of vaccinees demonstrating seroresponse ≥4-fold increase from baseline. Studies with slightly lower seroresponse rates (80-95%) showed slight decline over the 6-month to 1-year study periods, with no declines greater than 10%, where as those with high initial responses (>95%) maintained this level of seropositivity at the Year 2 follow up time point. (4)	

			Available studies suggest high and sustained levels specific antibodies and neutralizing antibodies in adults at 3- and 5-year time points following primary series vaccination (GP-ELISA GMT month 6: 713.8 [661.4, 770.3]; GMT month 60: 785.9 [722.3, 855.2]; with 85.8% [81.9, 89.1] with GP-ELISA ≥2-fold increase over baseline and ≥200 EU/mL at month 60). (4,6) Multiple studies have shown high seroresponse (≥4-fold increase from baseline) to Ebola specific antibodies over time after rVSVΔG-ZEBOV-GP vaccination. Case-fatality rates also decline following vaccination. In the DRC 2018-2020 outbreak, of the 462 cases among vaccinated individuals (contacts or, contacts of contacts), case-fatality rate was 26%, 14%, and 5% if the case was vaccinated 0-9, 10-29 days, or 30+ days pre-symptom onset, respectively. (3) Risk of transmission was also reduced among those vaccinated compared to those not vaccinated. Contacts of a recently-vaccinated index case had lower EVD infection rate of 3.4/1,000, compared to contacts of a never vaccinated index case at 6.9/1,000. (3) Modeling using the DRC outbreak data reported that the ring vaccination strategy may have resulted in a reduction of about 60% of EVD cases during the outbreak, and that it is three times more efficient (in terms of doses and resources used) compared to targeted or mass vaccination strategies. (7)	
	Harms of the intervention Are the undesirable	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Seventeen studies reported on **serious adverse events** following rVSVΔG-ZEBOV-GP vaccination. Nine of these were randomized controlled trials (RCTs) comparing rVSVΔG-ZEBOV-GP with placebo or with no intervention. In the RCTs, serious adverse events were collected from 12 weeks to 24 months following vaccination.	

	anticipated effects small?		Pooled results showed little to no difference between rVSVΔG-ZEBOV-GP and control (moderate certainty evidence; risk difference [RD] 3 more per 1000, 95% CI 4 fewer to 14 more; 9 trials, 12,364 participants). (4) Pooled results found 246 more cases of **solicited local adverse events** per 1000 participants in the rVSVΔG-ZEBOV-GP 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, I2= 7%). (4) Pooled results found 289 more cases of **solicited systemic adverse events** per 1000 participants in the rVSVΔG-ZEBOV-GP 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, I2= 76%). (4) Children were vaccinated throughout the outbreak in DRC 2018-2020. I latter part of the study included infants more than 6 months old, lactating women and pregnant women after the first trimester. Although the study did not involve a placebo-controlled comparison, no serious side-effects were apparent and the safety profile was similar to that of (non-pregnant) adults. (3)	
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	This is a single-dose vaccine with a good safety profile and very high efficacy. When implemented in ring vaccination approach it has demonstrated the ability to rapidly protect people at very high and high risk of EVD (i.e. Contacts and contacts of contacts) from a disease with a very high case-fatality rate. Vaccination has also been shown to reduce case fatality rates among those vaccinated, even if vaccinated a short time before infection, and reduce risk of secondary transmission to next-level contacts.	

	What is the overall quality of this evidence for the critical outcomes?	Efficacy of the intervention ☐ No included studies ☐ Very low ☐ Low ☐ Moderate ☒ High Safety of the intervention ☐ No included studies ☐ Very low ☐ Low ☒ Moderate ☐ High	Efficacy and effectiveness: GRADE HIGH (4) The available evidence indicates the rVSVΔG-ZEBOV-GP can provide durable protection for at least 3 – 5 years, and potentially longer, based on the sustained antibody responses observed in clinical trials. Moderate certainty evidence for the serious adverse events. (4) For further details, please see the Cochrane review.	Safety: Acceptable safety profile. Most adverse events (AE) are mild and resolve within days without sequelae. Refer to GACVS December 2019 review (8)
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☒ Probably no important uncertainty or variability ☐ No important uncertainty or variability ☐ No known undesirable outcomes	While there is no research evidence, it is assumed that there is no important uncertainty or variability in how the target populations values the disease outcomes.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies	The desirable effects of the intervention largely outweigh the undesirable effects. The high risk of EVD infection for <u>contacts</u> and the case fatality rate of EVD versus the safety profile inform this statement. Following previous recommendations for vaccinating at-risk HCWs during outbreaks, 7approx. 107,000 HCWs/FLWs have been vaccinated since 2016 in Guinea, DRC, Rwanda, Burundi, Uganda, Sierra Leone, Cote d'Ivoire, and South Sudan, another approximately 194,000 in DRC, Guinea Bissau, and Uganda have	Given high efficacy and suggested durability of protection of the vaccine among people at high risk and high case fatality rate, the

			been vaccinated preventively using repurposed doses with short shelf-life from the stockpile. (17)	desirable outcome (protection from EVD) is likely to be important compared to the undesirable outcomes (primarily short-lasting mild AEFIs).
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	The locations where outbreaks occur (often with access and security concerns), the clear differences in risk of EVD infection by various population groups, the effectiveness of the ring vaccination strategy and the market availability and high price of Ebola vaccines makes access to these vaccines focused to those with very high and high risk of EVD infection. The Gavi Alliance has supported countries at risk of Ebola and the establishment and funding of a global vaccine stockpile managed by the International Coordinating Group on Vaccine Provision (ICG), which supports manufacturing and rapid availability of vaccines during outbreaks. The Ebola vaccine stockpile has been included in the Gavi Vaccine Investment Strategy. rVSVΔG-ZEBOV-GP is currently offered to Gavi for procurement for the Ebola vaccine stockpile at approximately USD $99/dose including the service component of managing, storing, maintaining, and replenishing of Ebola vaccine stockpile. (10) Operational costs for delivery are also required, including preparation of the vaccination, planning, implementing, and monitoring. Vaccine storage and transport costs are also required given the cold chain specific requirements of the vaccine. Countries with confirmed outbreak can access the stockpile submitting a request to the ICG. Operational costs and vaccines	

			are supported by GAVI in Gavi eligible countries (that include most at risk-countries[1]).	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Observational data from outbreaks since 2016 and results of mathematical models has demonstrated that ring vaccination is the most effective, operationally efficient, resource and dose-sparing strategy while substantially reducing individual risk of infection, disease transmission, and disease mortality. (7)	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ *Varies* ☐	The at-risk countries (countries with history of EVDoutbreaks) are primarily low-income countries. Access to Ebola vaccine during outbreaks reduces health inequities for individuals at high-risk and very high risk of infection independent of the income of the country.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunizatio n Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Ministries of Health have supported rapid deployment of Ebola vaccines to support outbreak response since such vaccines were available and interim recommendations from SAGE guided their use. Vaccines have been administered to over 400,000 individuals at risk since 2016 in areas with outbreaks and to HCWs/FLWs in areas at risk of the outbreak spreading.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Individual-level demand for Ebola vaccines during outbreaks in areas with cases and in areas where the outbreak is expected to spread is anticipated to continue to be high. Regarding HCWs/FLWs in a trial, those who opted to participate and be vaccinated were motivated by a desire to save and protect themselves and others, contribute to scientific progress, or lead by example. Non-participants expressed concerns around the fear of unknown side effects following vaccination, and distrust or fear of stigmatization. (9)	

[1] Please see: https://www.who.int/groups/icg/ebola-virus-disease

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐		Ring vaccination outside of a clinical trial has demonstrated that the strategy can be rapidly and safely implemented. Vaccination was initiated within 7-14 days after outbreak declaration and the same pattern has been observed in every outbreak since 2016. Ring vaccination has been implemented rapidly and successfully in countries declaring outbreaks including DRC, Guinea, and Uganda. It is estimated that among 3,721 cases confirmed from 2016-2022, vaccination rings were formed around all but 195 of them (5%), and vaccination rates within the rings were very high (>90%). (12)		Speed of response is also a key factor in limiting outbreak spread. Availability and access to Ebola vaccines through a global emergency stockpile for outbreak response greatly improve timeliness of effective response to EVD outbreaks.
Balance of consequences		Undesirable consequences *clearly outweigh* desirable consequences in most settings ☐	Undesirable consequences *probably outweigh* desirable consequences in most settings ☐	The balance between desirable and undesirable consequences *is closely balanced or uncertain* ☐	Desirable consequences *probably outweigh* undesirable consequences in most settings ☐	Desirable consequences *clearly outweigh* undesirable consequences in most settings ☒

Type of recommendation	We recommend the intervention ☒	We suggest considering recommendation of the intervention ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	We recommend the comparison ☐	We recommend against the intervention and the comparison ☐
Recommendation (text)	**Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.**			
Implementation considerations	**Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.**			
Monitoring and evaluation	**Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.**			
Research priorities	**Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.**			

Annex 2a: DURING OUTBREAKS – OUTSIDE RINGS: Administration of Ad26.ZEBOV and MVA-BN-Filo vaccines outside the rings in areas with EVD cases AND in areas where an EVD outbreak is likely to spread

Question: During outbreaks and outside rings, should Ad26.ZEBOV and MVA-BN-Filo vaccines be administered to HCWs/FLWs in areas with confirmed cases AND in areas where outbreak is likely to spread?

Population: HCWs/FLWs in areas with confirmed cases and in areas where outbreak is likely to spread
Intervention: Two-dose regimen of Ad26.ZEBOV and MVA-BN-Filo vaccines, 56 days apart
Comparison(s): No vaccine/ placebo
Outcome: Immunogenicity**,** efficacy derived from immunobridging, duration of protection, safety

Background:

Ebola virus disease (EVD) is a rare but severe illness in humans, with a high mortality which varies with the EBOV species from 25% to 90% (average 50%). There are six species in the genus Ebolavirus, three of which (Bundibugyo, Sudan and Zaire) have previously caused large outbreaks. Since 1976 when it was first identified, there have been 25 outbreaks of Ebolavirus with local transmission, of which 17 (71%) of these were caused by *Orthoebolavirus zairense*. The largest epidemic of Ebola since its discovery occurred from 2014-2016 in West Africa, wherein an estimated 28,600 persons were infected and 11,325 died.

During an outbreak response and inside a ring, rapid high levels of protection and a good safety profile are important vaccine characteristics. Therefore, a single-dose regimen with rapid onset of immunity (within 10 days) is highly preferred in this setting. The ring vaccination approach has been used since the first Ebola vaccine was available. Approximately 350,000 contacts and contacts of contacts have been promptly vaccinated with rVSVΔG-ZEBOV-GP during the Ebola Zaire outbreaks since 2016. The ring vaccination strategy has proven highly effective in contributing to stop EVD outbreaks.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Zaire Ebola virus has been the cause of approximately 71% (17/24) of Ebola virus outbreaks since its discovery. Mortality rates are very high, ranging from 25-90%. In a review of EVD outbreaks from 2018 to 2023, a total of 3,716 cases were reported. Of these cases, 216 (6%) were healthcare workers. HCWs often comprise a greater proportion of all cases at the start of an outbreak compared to later stages of the outbreak when infection prevention and control measures are implemented. (14) During the EVD outbreak in West Africa, it appeared that HCWs/FLWs were between 21 and 32 times more likely to be infected with Ebola virus than the people in the general adult population, especially in the first months of the outbreak (13). However, these figures referred to proportion of cases and do not include denominators of people at risk that would allow adequate estimation of their risks and comparison to other population groups. The risk of EVD infection varies by proximity and contact with an EVD case. In the DRC 2018-20 outbreak of the 3,323 confirmed EVD cases during the entire outbreak 3,317/3,323 (95.7%) have their contacts and contacts of contacts enumerated in the vaccination rings. The majority were the index cases around which the rings were formed, or some were already vaccinated individuals (i.e., in the same chain of transmission of another case, probably already infected and incubating at the time of vaccination). (1)	

			This individual data collection permitted the detailed evaluation of the EVD risk for HCW/FLW.:. The risks of infection were: 6.2 per 1,000 among contacts of cases (incl. HCWs/FLWs who were contacts whose risk was 3.7 per 1,000); 0.2 per 1,000 among contacts of contacts (incl, 0.6 per 1,000 among HCWs/FLWs who were contacts of contacts); and none among 3rd level contacts. (1,2) The HCWs/FLWs vaccinated within rings had 30-day EVD risks of 1.9 per 1000, similar to the 30-day risks of 2.0 per 1000 among other ring members who were not HCWs/FLWs. The EVD infection risk within 0-9 days of vaccination following ring definition was 0.1 per 1,000 per 1,000 among HCWs/FLWs in areas with cases but outside the rings (increasing to 0.5 per 1,000 by day 365); and 'little to none' among HCWs/FLWs where the outbreak was likely to spread. This is compared to 6.2 per 1,000 among contacts of cases (incl. HCWs/FLWs who are contacts whose risk was 3.7 per 1,000). (2)	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Primary series clinical efficacy of the Ad26/MVA vaccine for prevention of EVD in humans has not been established. Immunobridging studies have demonstrated that Ad/MVA triggers an immune response that can provide protection against Ebola virus disease. (4) Five main studies showed that Ad26.ZEBOV, when used with MVA-BN-Filo, can trigger the production of antibodies capable of providing protection against Zaire ebolavirus. The studies involved a total of 3,585 adults and children. Based on animal studies with a fully lethal dose of the virus, the antibody level generated in humans following vaccination with Ad26.ZEBOV	A study analyzed longitudinal data on IgG-binding antibody concentrations from 487 participants enrolled in six Phase I and II clinical trials.

			and MVA-BN-Filo would be expected to lead to around 53% survival if infected with a fully lethal dose. However, the method used in the animal studies results in more severe infection than natural infection in humans. Although the vaccine regimen can provide protection against Ebola virus disease, the level and duration of protection are not yet known[2]. Three of the studies available demonstrating immune response 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. (4) 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. (4) Unpublished data from Johnson & Johnson show 98-100% response rate at 21 days post-dose 2. Binding antibody kinetics decline between 21 days post-dose 2 and 6 months post-dose 1, followed by a plateau for at least 4.5 years (n=26 at 4.5 years). (15)	The researchers used a mathematical model to estimate the longevity of the humoral immune response induced by this vaccine regimen. They found that the half-life of the long-lived antibody-secreting cells (ASCs) is at least 15 years[3].

[2] https://www.ema.europa.eu/en/documents/overview/Ad26.ZEBOV-epar-medicine-overview_en.pdf

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8752100/ and https://www.nature.com/articles/s41541-023-00767-y

	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	In a pooled review of all available RCTs: (4) **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). **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). **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.	Time to full protection given the two-dose series is an important consideration when used in the context of outbreak response.
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	This is a two-dose vaccine with a good safety profile and good immunogenicity data. The benefits of assumed protective immunogenicity outweighs the harms of the expected AEs of vaccination.	

	What is the overall quality of this evidence for the critical outcomes?	Efficacy of the intervention *No included studies* ☒ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☐ Duration of protective immunity *No included studies* *Very low* *Low* *Moderate* *High* Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐	Primary series clinical efficacy of the Ad26/MVA vaccine for prevention of EVD in humans has not been established. Immunobridging studies have demonstrated that Ad/MVA triggers an immune response that can provide protection against Ebola virus disease. (4) Based on the search results, the Ad26.ZEBOV and MVA-BN-Filo two-dose Ebola vaccine regimen appears to provide durable long-term protection: Moderate certainty evidence for the serious adverse events. (4) For further details, please see the Cochrane review.	Safety: Refer to GACVS December 2019 review (8)

VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☒ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	While there is no research evidence, it is assumed that there is no important uncertainty or variability in how the target populations values the disease outcomes.	Given high efficacy and durability of protection of the vaccine among people at risk and high case fatality rate, the desirable outcome (sustained protection from EVD) is likely to be important compared to the undesirable outcomes (primarily short-lasting mild AEFIs).

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	Yes, the desirable effects largely outweigh the undesirable effects. The high risk of EVD infection for contacts and the case fatality rate of EVD versus the safety profile inform this statement. Regarding HCWs/FLWs in a trial, those who opted to participate and be vaccinated were motivated by a desire to save and protect themselves and others, contribute to scientific progress, or lead by example. Non-participants expressed concerns around the fear of unknown side effects following vaccination, and distrust or fear of stigmatization. (9)	
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	The locations where outbreaks occur (often with access and security concerns), the clear differences in risk of EVD infection by various population groups, the effectiveness of the ring vaccination strategy and the market availability and high price of Ebola vaccines makes access to these vaccines focused to those with very high and high risk of EVD infection. The Gavi Alliance has been a key supporter and partner to countries at risk of Ebola and the establishment and funding of a global vaccine stockpile led by WHO, which supports manufacturing and rapid availability of vaccines during outbreaks. The Ebola vaccine stockpile has been included in the Gavi Vaccine Investment Strategy. Operational costs for delivery are also required, including preparation of the vaccination, planning, implementing, and monitoring. Vaccine storage and transport costs are also required given the cold chain specific requirements of the vaccine.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Cost-effectiveness in low- and middle-income countries of the vaccination of HCWs/FLWs in this context still needs to be assessed.	

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	The at-risk countries are primarily low-income countries. Access to Ebola vaccine would reduce health inequities in vaccine access between individuals at low risk (e.g., international responders) versus HCWs/FLWs in areas with cases in low-income countries. Vaccination of HCW/ FLWs in these areas are supported by the ethical principles of solidarity and reciprocity.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Ministries of Health have supported rapid deployment of Ebola vaccines to support outbreak response since such vaccines were available and interim recommendations from SAGE guided their use. Vaccines have been administered to over 400,000 individuals at risk since 2016 in areas with outbreaks and to HCWs/FLWs in areas at risk of the outbreak spreading.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	As documented by the high coverage achieved, individual-level demand for Ebola vaccines in general during outbreaks in areas with cases and in areas where the outbreak is expected to spread is anticipated to continue to be high. That said, there are no specific data on this vaccine regimen.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	A 2-dose vaccine with a 56-day interval between doses may add complexity to the ability to vaccinate individuals with a full course in an emergency setting. Should the outbreak move to that specific area, having two different vaccines with different strategies for implementation and different schedules, this is likely to trigger difficulties in implementation. HCWs/FLWs in areas where the outbreak is likely to spread may not likely to be highly mobile within a 2-month time-span, depending on the context.	

<table>
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☐</td></tr>
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Annex 2b: DURING OUTBREAKS - OUTSIDE RINGS: Administration of rVSV ZEBOV GP vaccine outside the rings in areas with EVD cases AND in areas where an EVD outbreak is likely to spread

Question: During outbreaks and outside rings, should rVSV ZEBOV GP vaccine be administered to HCWs/FLWs in areas with confirmed cases AND in areas where outbreak is likely to spread?

Population: HCWs/FLWs in areas with confirmed cases and in areas where outbreak is likely to spread
Intervention: One-dose regimen of rVSV ZEBOV GP vaccine
Comparison(s): No vaccine/ placebo
Outcome: Immunogenicity**,** Efficacy, Effectiveness, Duration of Protection, Safety

Background:

Ebola virus disease (EVD) is a rare but severe illness in humans, with a high mortality which varies with the EBOV species from 25% to 90% (average 50%). There are six species in the genus Ebolavirus, three of which (Bundibugyo, Sudan and Zaire) have previously caused large outbreaks. Since 1976 when it was first identified, there have been 25 outbreaks of Ebolavirus with local transmission, of which 17 (71%) of these were caused by *Orthoebolavirus zairense*. The largest epidemic of Ebola since its discovery occurred from 2014-2016 in West Africa, wherein an estimated 28,600 persons were infected and 11,325 died.

During an outbreak response, rapid high levels of protection and a good safety profile are important vaccine characteristics. Therefore, a single-dose regimen with rapid onset of immunity (within 10 days) is highly preferred. The ring vaccination approach has been used since the first Ebola vaccine was available. Approximately 350,000 contacts and contacts of contacts have been promptly vaccinated with rVSVΔGZEBOV-GP - GP during the Ebola Zaire outbreaks since 2016. The ring vaccination strategy has proven highly effective in contributing to stop EVD outbreaks.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Zaire Ebola virus has been the cause of approximately 71% (17/24) of Ebola virus outbreaks since its discovery. Mortality rates are very high, ranging from 25-90%. During the EVD outbreak in West Africa, it was reported that HCW were between 21 and 32 times more likely to be infected with Ebola virus than the people in the general adult population, especially in the first months of the outbreak (13). In a review of EVD outbreaks from 2018 to 2023, a total of 3,716 cases were reported. Of these cases, 216 (6%) were healthcare workers. HCWs often comprise a greater proportion of all cases at the start of an outbreak compared to later stages of the outbreak when infection prevention and control measures are implemented. (14) However, these figures referred to proportion of cases and do not include denominators of people at risk that would allow adequate estimation of their risks and comparison to other groups. The risk of EVD infection varies by proximity to the EVD case. In the DRC 2018-20 outbreak of the 3,323 confirmed EVD cases during the entire outbreak 3,317/3,323 (95.7%) have their contacts and contacts of contacts enumerated in the vaccination rings. The majority were the index cases around which the rings were formed, or some were already vaccinated individuals (i.e., in the same chain of transmission of another case, probably already infected and incubating at the time of vaccination). (1)	

			This detailed individual data collection permitted the evaluation of the EVD risk of infection per 1,000 within 0-9 days following ring definition and vaccination when the vaccine is expected to have little or no effect. The risks were: 6.2% per 1,000 among contacts of cases (incl. HCWs/FLWs who were contacts whose risk was 3.7%); 0.2% per 1,000 among contacts of contacts (incl, 0.6% among HCWs/FLWs who were contacts of contacts); and none among 3rd level contacts. (1,2) The HCWs/FLWs vaccinated within rings had 30-day EVD risks of 1.9 per 1000, similar to the 30-day risks of 2.0 per 1000 among other ring members who were not HCWs/FLWs. The EVD infection risk within 0-9 days of vaccination following ring definition was 0.1% per 1,000 among HCWs/FLWs in areas with cases but outside the rings (increasing to 0.5% by day 365); and 'little to none' among HCWs/FLWs where the outbreak was likely to spread. This is compared to 6.2% among contacts of cases (incl. HCWs/FLWs who are contacts whose risk was 3.7%). (2)	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	One-dose vaccine efficacy for prevention of EVD: Estimated to be 100% (95% CI: 68.9 to 100.0) among those vaccinated immediately. (4,5) The observational data from the DRC 2018-2020 outbreak suggests 94% (CI 88-97%) vaccine efficacy against EVD onset. (3) Isolation of cases, other EVD control measures, and ring vaccination with single-dose live rVSVΔG-ZEBOV-GP vaccine can substantially alter the course of outbreaks of the Zaire species of Ebola virus. About 6 days after intervention with isolation of any recent cases and ring vaccination the incidence of EVD started to	

			decrease substantially, and after another six days few further cases arose. The sooner after index case onset this intervention occurred the sooner the incidence of EVD in case-contacts decreased. Initial response after vaccination ranges from 80-100% of vaccinees demonstrating seroresponse ≥4-fold increase from baseline. Studies with slightly lower seroresponse rates (80-95%) showed slight decline over the 6-month to 1-year study periods, with no declines greater than 10%, where as those with high initial responses (>95%) maintained this level of seropositivity at the Year 2 follow up time point. (4) Available studies suggest high and sustained levels specific antibodies and neutralizing antibodies in adults at 3- and 5-year time points following primary series vaccination (GP-ELISA GMT month 6: 713.8 [661.4, 770.3]; GMT month 60: 785.9 [722.3, 855.2]; with 85.8% [81.9, 89.1] with GP-ELISA $\geq$2-fold increase over baseline and ≥200 EU/mL at month 60). (4,6) Multiple studies have shown high seroresponse (≥4-fold increase from baseline) to Ebola specific antibodies over time after rVSVΔG-ZEBOV-GP vaccination. Case-fatality rates also decline following vaccination. In the DRC 2018-2020 outbreak, of the 462 cases among vaccinated individuals (contacts or, contacts of contacts), case-fatality rate was 26%, 14%, and 5% if the case was vaccinated 0-9, 10-29 days, or 30+ days pre-symptom onset, respectively. (3) Risk of transmission was also reduced among those vaccinated compared to those not vaccinated. Contacts of a recently-vaccinated index case had lower EVD infection rate of 3.4/1,000,	

			compared to contacts of a never vaccinated index case at 6.9/1,000. (3) Modeling using the DRC outbreak data reported that the ring vaccination strategy may have resulted in a reduction of about 60% of EVD cases during the outbreak, and that it is three times more efficient (in terms of doses and resources used) compared to targeted or mass vaccination strategies. (7)	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	Seventeen studies reported on **serious adverse events** following rVSVΔG-ZEBOV-GP vaccination. Nine of these were randomized controlled trials (RCTs) comparing rVSVΔG-ZEBOV-GP with placebo or with no intervention. In the RCTs, serious adverse events were collected from 12 weeks to 24 months following vaccination. Pooled results showed little to no difference between rVSVΔG-ZEBOV-GP and control (moderate certainty evidence; risk difference [RD] 3 more per 1000, 95% CI 4 fewer to 14 more; 9 trials, 12,364 participants). (4) Pooled results found 246 more cases of **solicited local adverse events** per 1000 participants in the rVSVΔG-ZEBOV-GP 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, I2= 7%). (4) Pooled results found 289 more cases of **solicited systemic adverse events** per 1000 participants in the rVSVΔG-ZEBOV-GP 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, I2= 76%). (4) Children were vaccinated throughout the outbreak in DRC 2018-2020. I latter part of the study included infants more than 6 months old, lactating women and pregnant women after the first	Time to full protection given the two-dose series is an important consideration when used in the context of outbreak response. Therefore the vaccine is not recommended for individuals at high and very high risk of infection within rings.

			trimester. Although the study did not involve a placebo-controlled comparison, no serious side-effects were apparent and the safety profile was similar to that of (non-pregnant) adults. (3)	
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	This is a single-dose vaccine with a good safety profile and very high efficacy. When implemented in ring vaccination approach it has demonstrated the ability to rapidly protect people at very high and high risk of EVD (i.e. Contacts and contacts of contacts) from a disease with a very high case-fatality rate. Vaccination has also been shown to reduce case fatality rates among those vaccinated, even if vaccinated a short time before infection, and reduce risk of secondary transmission to next-level contacts.	
	What is the overall quality of this evidence for the critical outcomes?	Efficacy of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☒ Safety of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐	The available evidence indicates the rVSVΔG-ZEBOV-GP can provide durable protection for at least 3 – 5 years, and potentially longer, based on the sustained antibody responses observed in clinical trials. Moderate certainty evidence for the serious adverse events. (4)	Safety: Acceptable safety profile. Most adverse events (AE) are mild and resolve within days without sequelae. Refer to GACVS December 2019 review (8)

VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☒ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	While there is no research evidence, it is assumed that there is no important uncertainty or variability in how the target populations values the disease outcomes.	Given high efficacy and durability of protection of the vaccine among people at risk and high case fatality rate, the desirable outcome (sustained protection from EVD) is likely to be important compared to the undesirable outcomes (primarily short-lasting mild AEFIs).

	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ *Varies* ☐	The desirable effects of the intervention largely outweigh the undesirable effects. The high risk of EVD infection for <u>contacts</u> and the case fatality rate of EVD versus the safety profile inform this statement. Following previous recommendations for vaccinating at-risk HCWs during outbreaks, approx. 107,000 HCWs/FLWs have been vaccinated since 2016 in Guinea, DRC, Rwanda, Burundi, Uganda, Sierra Leone, Cote d'Ivoire, and South Sudan, another approximately 194,000 in DRC, Guinea Bissau, and Uganda have been vaccinated preventively using repurposed doses with short shelf-life from the stockpile. (17) Regarding HCWs/FLWs in a trial, those who opted to participate and be vaccinated were motivated by a desire to save and protect themselves and others, contribute to scientific progress, or lead by example. Non-participants expressed concerns around the fear of unknown side effects following vaccination, and distrust or fear of stigmatization. (9)	
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	The locations where outbreaks occur (often with access and security concerns), the clear differences in risk of EVD infection by various population groups, the effectiveness of the ring vaccination strategy and the market availability and high price of Ebola vaccines makes access to these vaccines focused to those with very high and high risk of EVD infection. The Gavi Alliance has been a key supporter and partner to countries at risk of Ebola and the establishment and funding of a global vaccine stockpile managed by the ICG, which supports manufacturing and rapid availability of vaccines during outbreaks. The Ebola vaccine stockpile has been included in the Gavi Vaccine Investment Strategy. rVSVΔG-ZEBOV-GP is currently offered to Gavi for procurement for the Ebola vaccine stockpile at approximately USD $99/dose including the service component	

			of managing, storing, maintaining, and replenishing of Ebola vaccine stockpile. (10) Operational costs for delivery are also required, including preparation of the vaccination, planning, implementing, and monitoring. Vaccine storage and transport costs are also required given the cold chain specific requirements of the vaccine.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Cost-effectiveness in low- and middle-income countries of the vaccination of HCWs/FLWs in this context still needs to be assessed.	Speed of response is one of the key factor in limiting outbreak spread.
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	The at-risk countries are primarily low-income countries. Access to rVSVΔG-ZEBOV-GP would reduce health inequities in vaccine access between individuals at low risk (e.g., international responders) versus HCWs/FLWs in areas with cases in low-income countries.	Availability and access to Ebola vaccines through a global emergency stockpile for outbreak response greatly improves timeliness of effective response to EVD outbreaks.

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Ministries of Health have requested rapid deployment of Ebola vaccines to support outbreak response since such vaccines were available and interim recommendations from SAGE guided their use. Vaccines have been administered to over 400,000 individuals since 2016 in areas with outbreaks and to HCWs/FLWs in areas at risk of the outbreak spreading.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Individual-level demand for Ebola vaccines during outbreaks in areas with cases and in areas where the outbreak is expected to spread is anticipated to continue to be high. Regarding HCWs/FLWs in a trial, those who opted to participate and be vaccinated were motivated by a desire to save and protect themselves and others, contribute to scientific progress, or lead by example. Non-participants expressed concerns around the fear of unknown side effects following vaccination, and distrust or fear of stigmatization. (9)	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	The one dose schedule is conducive to feasible implementation. Ring vaccination outside of a clinical trial has demonstrated that the strategy can be rapidly and safely implemented. Vaccination was initiated within 7-14 days after outbreak declaration and the same pattern has been observed in every outbreak since 2016. Ring vaccination has been implemented rapidly and successfully in countries declaring outbreaks including DRC, Guinea, and Uganda. It is estimated that among 3,721 cases confirmed from 2016-2022, vaccination rings were formed around all but 195 of them (5%), and vaccination rates within the rings were very high (>90%). (12)	

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Annex 3: DURING THE INTER-EPIDEMIC PERIOD: Administration of rVSVΔG-ZEBOV-GP or Ad26.ZEBOV and MVA-BN-Filo vaccines in countries at risk of EVD outbreaks

Question: During the inter-epidemic period and in countries at risk of EVD outbreaks, should rVSVΔG-ZEBOV-GP vaccine or Ad26.ZEBOV and MVA-BN-Filo vaccines be administered to certain target populations?

Populations:

- HCW/FLWs in areas with history of EVD outbreaks including health workers, front-line workers, national response teams;
- Others who may be exposed to EVD including laboratory and research workers, and international responders who regularly support EVD responses;
- EVD Survivors and contacts of survivors.

Intervention: One dose of Ebola virus vaccine (rVSVΔG-ZEBOV-GP) or two doses of Ad26.ZEBOV and MVA-BN-Filo vaccines
Comparison(s): No vaccine/placebo
Outcome: Immunogenicity, efficacy, effectiveness, duration of protection, safety

Background:

EVD is a rare but severe illness in humans, with a high mortality which varies with the Ebola virus species from 25% to 90% (average 50%). Following the first detection of Ebola virus disease in 1976, there have been 16 major outbreaks of Ebola Zaire virus detected in 8 countries, the largest of these being the epidemic in West Africa in 2014-2016 wherein an estimated 28,600 persons were infected and 11,325 died.

rVSVΔG-ZEBOV-GP is a live-attenuated recombinant vesicular stomatitis virus vaccine, which expresses the glycoprotein (GP) of the Zaire Ebola Virus (ZEBOV) and was the first licensed and WHO pre-qualified vaccine against Ebola zaire disease. The single-dose vaccine has proven to be highly efficacious in the prevention of EVD and is currently recommended as the first-choice vaccine for at-risk individuals during an EVD outbreak.

Health and frontline workers

Recent estimates of health workforce indicate that there are approximately 2 million health care workers (including community health workers and support staff) in the 16 countries with previous documented EBOV case(s), of whom 1.6 million are located in Nigeria, South Africa, and DRC. (16) Following previous recommendations for vaccinating at-risk HCWs during outbreaks, approx. 107,000 HCWs/FLWs have been vaccinated since 2016 in Guinea, DRC, Rwanda, Burundi, Uganda, Sierra Leone, Cote d'Ivoire, and South Sudan, another approximately 194,000 in DRC, Guinea Bissau, and Uganda have been vaccinated preventively using repurposed doses with short shelf-life from the stockpile. (17)

EVD survivors & contacts

Following the large EVD outbreaks in West Africa (2014-2016) and more recently in DRC (2018-2020), cohorts of EVD survivors were followed longitudinally to observe the duration of time that *Ebolazaire virus* (EBOV) could be detected in bodily fluids. Multiple studies have shown that EBOV RNA can remain in semen for one year or longer. (18-21) There is uncertainty regarding the risk factors associated with persistent excretion as the Ebola virus remains in "immunological privileged" sites, including the anterior chamber of the eye, the testes and the brain, where immune reactions would cause more harm than good. Antigens in these sites do not normally elicit an immune response.

Outbreaks have rarely been linked to the persistent excretion of virus in survivors, though a few have been documented. Several studies have demonstrated that EVD outbreaks and clusters of EVD cases have been genetically linked to previous virus clades, indicating that individuals with persistent or relapse EVD infection (both male and female) may be the cause of re-emergence of EVD in a community. (20,22)
The magnitude of the risk of transmission from survivors to unvaccinated or vaccinated close contacts and their role in future outbreaks is unknown. Vaccination of survivors and their contacts has been proposed by some as a potential additional strategy to reduce the risk of transmission from survivors to their close contacts. However, there is no evidence that vaccination of survivors will reduce the risk of persistent viral excretion (i.e., whether vaccination would elicit an immune response in those immunological privileged sites) or have an effect on transmission from survivors to their close contacts.

EVD Survivors: It is estimated that from EVD outbreaks between 2018-2022, there are 1,304 survivors, the majority of whom are from the 2018 DRC outbreak (1,183). (23)

Contacts of survivors: It is estimated that there are approximately 195 EVD cases between 2016-2022 that did not have rings formed around them because ring vaccination was not able to be established. In 3,526 EVD cases ring vaccination was conducted. This results in approximately 5,850 contacts not in rings and not vaccinated, and an additional 952 contacts in rings who were not vaccinated (assuming 90% vaccination coverage within rings). (23) In addition, over time, new contacts are likely to be identified, some of them likely not vaccinated.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION

PROBLEM	Is the problem a public health priority?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	<u>Risk for HCW/FLW</u> In a prolonged outbreak in DRC from 2018-2020, overall risk of HCW/FLW infection among vaccinated individuals living in areas with EVD cases but outside of defined EVD rings was estimated at 0.1 per 1,000 during days 0-9 following ring definition and vaccination, increasing to 0.5 per 1,000 by day 365 post-vaccination. During outbreaks the risk increases to 3.7 per 1,000 if contact of a case (compared to 6.2% among general population that is contact of a case) in days 0-9. (1,2). None of the HCWs/FLWs vaccinated outside the affected areas or in areas where the outbreak was judged likely to spread got infected with EVD. during a newly emerging outbreak, the proportion of HCW/FLW among Ebola cases can be significant (about 1/3) <u>Survivor/contacts of survivor</u> EVD survivors can harbor persistent Ebola virus in certain immune privileged body sites, even after recovery. Waning immunity and viral persistence in survivors may contribute to the reemergence of Ebola virus outbreaks. Ebola virus can be detected in the body fluids of survivors months or years after initial infection. Some researchers argue that EVD survivors may have "more efficient antibody immunity than vaccinees despite	While the emergence to date of EBOV is limited to a subset of countries in Sub-Saharan Africa, experience from past epidemics has demonstrated the global health security risk these outbreaks represent, with cases exported to both neighboring and connected (via flight) countries. *HCW/FLW* HCWs are also typically the first point of contact for cases imported into other countries and therefore may be at higher risk than the general population and a source of disease propagation. In addition, equity must be considered and infection prevention prioritized for HCW, as HCW put themselves at a higher risk to care for others who are ill. *Survivor/contact of survivor* The availability of EBV for emergency vaccination, with a focus on the ring vaccination approach of vaccinating all contacts and contacts of contacts of EVD cases, has resulted in smaller chains of transmission and a majority of at-risk contacts of

			similar levels of circulating antibodies". Therefore, the available evidence indicates that EVD survivors, due to potential viral persistence and unique immune responses, may play a role in the resurgence or start of Ebola outbreaks. For example, in Sierra Leone, 62% (26/42) of male EVD survivors had detectable levels of EBOV RNA in their semen 4-6 months post-discharge; 4 of 26 (15%) continued to have detectable levels of RNA at 10-12 months; 1 of 25 (4%) at 16-18 months; 0 of 12 (0%) at 19 or more months (19). In Liberia, 63% of the 9% of survivors who initially tested positive for Ebola virus RNA detected in their semen had detectable RNA at 12 months or longer after EVD recovery, with the longest duration of detection of 565 days post-discharge (18). Several studies have also genetically linked clusters of EVD cases to individuals with persistent or relapse EVD infection (both male [22] and female [20]). Since 2020, five of the six Zaire Ebola outbreaks are suspected to have begun as result of a relapse from an EVD survivor (DRC (4); Guinea (1)). (24) Transmission from survivors is expected to have occurred in the 2014-2016 West Africa outbreak as well, with one documented outbreak case study (20).	survivors already being vaccinated during the emergency response activities.

			The magnitude of the risk of transmission from survivors to unvaccinated or vaccinated close contacts and their role in future outbreaks is unknown. Data from 2016 to date indicates that a very small percentage of contacts and contacts of contacts of survivors are currently unvaccinated (about 25,000 individuals located across 4 countries). In addition, they often reside in hard-to-reach geographic areas. Estimating the number of new contacts is challenging but may represent additional unvaccinated people.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	For HCW/ FLW *No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐ For contacts of survivors *No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐ For survivors *No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	<u>HCW/FLW and other populations at risk of EVD exposure</u> At a population level, the benefits of preventive vaccination of HCWs/FLWs and other at-risk populations who are often the first responders in an outbreak and critical for further control of the spread of the outbreak are deemed to outweigh the risks. For these reasons, infection prevention for HCW should also be prioritized (27). Preventive vaccination of HCWs may also reduce EVD outbreak size, given it may reduce amplification of disease transmission. <u>Contacts of survivors</u>	

			There is no evidence that vaccination of survivors will reduce the risk of persistent viral excretion (i.e.. whether vaccination would elicit an immune response in those immunological privileged sites) or have an effect on transmission from survivors to their close contacts. The Cochrane review reported one study (Proches 2016) that reported on specific antibodies after rVSVΔG-ZEBOV-GP in 1403 contacts of survivors. Results were stratified by seropositivity at baseline and age. 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). 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%). (4) <u>In those with prior EVD exposure</u>:	

			One study examined variation in immune response to rVSVΔG-ZEBOV-GP based on varying baseline IgG status. The study demonstrated rVSVΔG-ZEBOV-GP vaccination is safe and immunogenic in people with and without raised baseline Ebolavirus IgG antibodies. Seroconversion 28 days after vaccination was ~80%. There was no sign of blunted immune response to vaccination in those with baseline seropositivity. (25)	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	For HCW/ FLW *No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐ For contacts of survivors *No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐ For survivors *No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	<u>HCWs/FLWs and other populations at high risk of EVD exposure</u> The safety profile of the interventions in these populations are assumed to be equal to the risk in the general population. <u>Contacts of survivors</u> Cochrane review reported one study (Proches 2016) among contacts of survivors. The safety profile was similar to that of other studies. <u>In those with prior EVD exposure</u>: One study examined variation in immune response to rVSVΔG-ZEBOV-GP based on varying baseline IgG status, as well as the **rates of AEs and SAEs by baseline serostatus**. The study demonstrated rVSVΔG-ZEBOV-GP vaccination is safe and immunogenic in people with and without raised baseline Ebolavirus IgG antibodies.	

			The adverse events profile was favorable, similar between the sero-groups, and with some data suggesting the possibility of fewer events and less severe events in those seropositive. In those seropositive at baseline, 63.6% (110/173) had any adverse event, compared to 66.1% (553/837) that were seronegative at baseline. No SAEs were documented. (25)	
	Balance between benefits and harms	For HCW/ FLW *Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐ For contacts of survivors and survivors	While there is evidence of adverse events resulting from rVSVΔG-ZEBOV-GP (primarily side effects such as headache, fever, muscle pain), they typically resolve within 1 week and are mild to moderate in nature. (26) Considering the severity of EVD and risk of death, at an individual level the benefits of vaccination are deemed to outweigh the risk of these adverse events. *HCW/FLW* ***and other populations at high risk of EVD exposure*** At a population level, the benefits of preventive vaccination of HCWs/FLWs and other at-risk populations who are often the first responders in an outbreak and critical for further control of the spread of the outbreak are deemed to outweigh the risks of these adverse events. For these reasons, infection prevention for HCW should also be prioritized (27). Preventive vaccination of HCWs may also reduce EVD	

		Favours intervention ☐ Favours comparison ☐ Favours both ☐ Favours neither ☐ Unclear ☒	outbreak size, given it may reduce amplification of disease transmission. *Survivor/contact of survivor* Given the high persistence of EBOV among survivors, especially in the first year following discharge, vaccination of survivors and their contacts may minimize the likelihood of an outbreak occurring as a result of recurrence or spread of EVD from a survivor. However, there is limited to no evidence of the effectiveness of this vaccination approach in preventive further occurrence of EVD.	
	What is the overall quality of this evidence for the critical outcomes?	Efficacy of the intervention (HCW/FLW) No included studies ☒ Very low ☐ Low ☐ Moderate ☐ High ☒ Safety of the intervention (HCW/FLW) No included studies ☐ Very low ☐ Low ☐ Moderate ☒ High ☐ No studies on efficacy of rVSV-ZEBOV in contacts of survivors were identified. Unpublished (ungraded) data available	In the general population, efficacy of rVSVΔG-ZEBOV-GP: GRADE HIGH (4) Data on efficacy of rVSV-ZEBOV in HCWs and FLWs in labs working with Ebola virus comes from one case report. No studies were identified that reported on the efficacy of Ad26.ZEBOV, MVA-BN-Filo vaccination in humans. Moderate certainty evidence for the serious adverse events (rVSV-ZEBOV and Ad26.ZEBOV, MVA-BN-Filo. (4) For further details, please see the Cochrane review.	Safety: Refer to GACVS December 2019 review (8)

		on safety/ immunogenicity of vaccination of (contacts of) survivors.		
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☒ *No important uncertainty or variability* ☐ *No known undesirable outcomes* ☐	<u>HCWs/FLWs and other populations at high risk of EVD exposure</u> There does not seem to be any substantial item on the undesirable outcome. Hence, it is likely that the uncertainty/variability is not important. <u>Survivors and contacts of survivors</u> There is no evidence that vaccination of survivors will reduce the risk of persistent viral excretion (ie. whether vaccination would elicit an immune response in those immunological privileged sites) or have an effect on transmission from survivors to their close contacts. The latter could of course change over time.	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☒ *Yes* ☐ *Varies* ☐	No evidence was retrieved on the values and preferences of the target population, but it would be assumed that on the individual's level, avoidance of EVD would outweigh the undesirable effected related to immunization (pain during immunization, AEFIs). <u>HCW/FLW and other populations at high risk of EVD exposure</u> However, as with other diseases (e.g., Covid-19, cholera), vaccine demand is typically higher when there is a present risk (i.e., during an outbreak) than when	

			the vaccine is offered preventively. Given the target population, especially HCWs may be more hesitant to take a vaccine with known side effects, especially if this limits their ability to work immediately following vaccination. Other target groups, such as traditional healers, may also be hesitant to be vaccinated. <u>*Survivor/contact of survivor*</u> There could be stigma with the vaccination if their EVD survivor status were revealed to those who did not know it previously. The experience from the "Proches" study in Guinea indicate that specialized training of health staff and intense community engagement is required.	
RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	<u>HCWs/FLWs</u> ***<u>and other populations at high risk of EVD exposure</u>*** rVSVΔG-ZEBOV-GP is currently offered to Gavi for procurement for the Ebola vaccine stockpile at approximately USD $99/dose (10) including the service component of managing, storing, maintaining and replenishing of Ebola vaccine stockpile. High income countries may be able to allocate resources for this vaccine for a small number of at-risk persons, whereas most middle and all low income countries without external resources are unlikely to	

			be able to afford procurement of this vaccine for their at-risk populations. The Gavi Alliance has been a key supporter of the Ebola vaccine programme and stockpile, and the preventive Ebola vaccination programme has been approved and funded by Gavi's Board contingent upon SAGE recommendation for preventive vaccination. In terms of additional resources for vaccine delivery, vaccine would be delivered in one-time targeted preventive campaigns, using fixed and mobile approaches. Operational costs to support vaccine demand generation and vaccine delivery, including cold chain costs, would be required. While envisioned to be a targeted campaign, it will require adult vaccination outside of the routine immunization schedule. <u>For survivors & contacts of survivors T</u>he number of persons likely to be vaccinated through this preventive vaccination strategy is <u>currently very small</u> and the unvaccinated contacts are distributed in a large, difficult to access area with security challenges, and is expected to remain so especially if outbreaks remain contained and contacts are vaccinated through ring vaccination approach during outbreaks.	

			However, those who were not vaccinated during outbreaks are likely to live in hard-to-reach areas. Central level cold chain capacities are expected to be sufficient in countries at risk given recent investments in cold storage during the Covid-19 pandemic, and the relatively small volume of vaccine required for targeted preventive Ebola vaccination. The vaccination activity could be used to share information on other EVD detection and prevention measures among HCWs/FLWs at risk.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Cost-effectiveness needs to be assessed.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies ☐	HCWs/FLWs ***and other populations at high risk of EVD exposure*** Preventive vaccination and vaccination of HCW/FLWs during outbreaks in areas at risk would be primarily in low-income countries that are unable to afford this vaccine. This intervention would therefore reduce the inequity of access to Ebola vaccine between those who might provide care for EVD cases in high income compared to low-income settings.	

			Preventive vaccination of at risk HCWs/FLWs will protect those who may have a higher occupational risk than the general population. Including FLWs will protect groups that have high risk of infection but often lower levels of education and access to health care services than HCWs, such as traditional healers, health care facility auxiliary staff (morticians, janitors) and burial workers, and provide the opportunity to educate on EVD prevention beyond vaccination.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Ministries of Health and Immunization Managers approached by WHO to implement preventive vaccination using expiring doses have expressed interest in the vaccination activity, if costs were furnished by partners. However, given competing priorities, MOHs have had challenges to plan the activity on short notice and are therefore not as interested in doses with short shelf-life (<3 months). It is presumed that interest from MOHs will be greater when preventive vaccination is able to be planned further in advance and the partner funding for implementation is clear. Global partners have expressed the need for protection of HCWs/FLWs from EVD. Gavi Alliance has made substantial	EVD survivor care program have been established to help survivors with sequelae and to provide semen testing and safer sex counselling. These programmes showed excellent participation rates in the DRC and in Guinea with over 90% attendance rate to monthly visit. These programmes could be useful and be the platform to offer the vaccine to survivor and their contacts.

			commitments to finance both emergency and preventive vaccination, in alignment with SAGE recommendations. Global partners have encouraged countries to pursue pre-emptive and preventive vaccination of at-risk individuals to minimize the risk of EVD outbreaks.	
	Which option is acceptable to target group?	*Intervention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	It is presumed from past pre-emptive vaccination during outbreaks and preventive vaccination using expiring Ebola vaccine stock that the intervention option would be acceptable to the target groups if the costs are covered by the health care provider/other partner, the workplace facilitates vaccination access and recuperation time as required, and side effects can be managed. <u>Survivors/contacts of survivors</u> Given the known side effects and, for survivors and contacts the risk of stigma, some vaccine refusals can be expected.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☒ | *Varies* ☐	With the availability of partner funding for vaccine procurement and vaccine delivery costs, this intervention is feasible in middle and lower income countries that face financial constraints and multiple public health priorities. Vaccination targeting groups at low or no risk greatly expands the level of effort required across the health system. Opportunity	

			costs of vaccination can be minimized by providing the vaccination only to those at high risk and very high risk of infection. Operational costs for reaching survivors & contacts could be minimized if this strategy were implemented in an integrated manner with preventive vaccination of HCWs/FLWs as the geographic areas targeted for vaccination are likely to overlap. Testing and follow up of all survivors to determine eligibility for vaccination based on viral secretion may be challenging in some settings, while programme implemented in the DRC and in Guinea showed good participation rate with more than 90% of eligible males providing semen samples until obtention of two consecutive negative results. Gavi Alliance will make available funds for vaccination operational costs and technical assistance in Gavi-eligible countries. Vaccine supply has been maintained at the desired stockpile level of approximately 500,000 doses (28) since early 2023, and suppliers have indicated their ability to produce additional quantities based on demand. Gavi Alliance market shaping efforts are planned in order to improve market health, such as the predictability of demand and the availability of affordable Ebola vaccines.	

<table>
<tr><td>Balance of consequences</td><td>Undesirable consequences
clearly outweigh
desirable consequences
in most settings
☐</td><td>Undesirable consequences
probably outweigh
desirable consequences
in most settings
☐</td><td>The balance between
desirable and undesirable
consequences
is closely balanced or uncertain

For survivors/contacts of survivors
☒</td><td>Desirable consequences
probably outweigh
undesirable consequences
in most settings
☐</td><td>Desirable consequences
clearly outweigh
undesirable consequences
in most settings

For HCWs/FLWs
☒</td></tr>
<tr><td>Type of recommendation</td><td>We recommend the intervention

For HCWs/FLWs
☒</td><td colspan="2">We suggest considering recommendation of the intervention
For survivors and contacts of survivors
☒ Only in the context of rigorous research
☒ Only with targeted monitoring and evaluation
☐ Only in specific contexts or specific (sub)populations</td><td>We recommend the comparison

☐</td><td>We recommend against the intervention
and the comparison

☐</td></tr>
<tr><td>Recommendation (text)</td><td colspan="5">Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.</td></tr>
<tr><td>Implementation considerations</td><td colspan="5">Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.</td></tr>
<tr><td>Monitoring and evaluation</td><td colspan="5">Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.</td></tr>
<tr><td>Research priorities</td><td colspan="5">Please see Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations : www.who.int/publications/i/item/WER-9927-351-362.</td></tr>
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References:

1. Muyembe JJ et al 2022 (submitted). Evidence on the efficacy of ring vaccination with rVSVΔGZEBOV-GP -GP. DRC Paper. June 2022. Presentation to the SAGE Ebola Vaccine Working Group. [Unpublished]
2. World Health Organization Risk of EVD by population group and by vaccination strategy. December 2023. Prepared for SAGE Ebola Vaccine Working Group. [Unpublished]
3. Muyembe JJ et al 2022 (submitted). Evidence on the efficacy of ring vaccination with rVSVΔGZEBOV-GP -GP. DRC Paper. June 2022. Presentation to the SAGE Ebola Vaccine Working Group. [Unpublished]
4. Cochrane Response. Systematic review of safety, efficacy, immunogenicity, and duration of protection of licensed Ebola virus vaccines. 2023. [unpublished]
5. Henao-Restrepo AM, Longini I, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet 2015; 386: 857–66.
6. Merck. Update on Durability of Immunogenicity of rVSVΔG-ZEBOV-GP (ERVEBO®) for SAGE-WG. Nov2023. Presentation to SAGE Ebola Vaccine Working Group. [unpublished]
7. Vespignani A, Longini I et al. Assessment of the impact of different vaccination strategies. June 2022. Presentation to the SAGE Ebola Vaccine Working Group. [Unpublished]
8. World Health Organization Global Advisory Committee on Vaccine Safety, 4–5 December 2019. Wkly EpidemiolRec 2020; 95, No. 4: 25-36.
9. Grantz KH, Claudot P, Kambala M, et al. Factors influencing participation in an Ebola vaccine trial among frontline workers in Guinea. Vaccine 2019; 37: 7165–7170.
10. UNICEF. Ebola Vaccine Prices 11012021. Available at: Link. Accessed 22 March 2024.
11. Gsell PS, Camacho A, Kucharski A, et al. Ring vaccination with rVSVΔGZEBOV-GP under expanded access in response to an outbreak of Ebola virus disease in Guinea, 2016: an operational and vaccine safety report. Lancet Infect Dis 2017; 17: 1276–1284.
12. World Health Organization. Summary of EVD cases with rings around them, estimated contacts vaccinated and not vaccinated, and survivors. Recent outbreaks 2016-2022. December 2023. Prepared for SAGE Ebola Vaccine Working Group. [Unpublished]
13. World Health Organization. Health worker Ebola infections in Guinea, Liberia and Sierra Leone: a preliminary report 21 May 2015. Available at: https://www.who.int/publications-detail-redirect/WHO-EVD-SDS-REPORT-2015.1. Accessed 22 March 2024.
14. Legand, A et al. Healthcare workers and pregnant women among confirmed and probable Ebola virus disease cases. December 6, 2023. Presentation to SAGE Ebola Vaccine Working Group. [Unpublished]

15. Luhn, K. Janssen Ebola Vaccine Regimen Ad26.ZEBOV, MVA-BN-Filo: Update for the SAGE Ebola Vaccine Working Group. June 20, 2022. Presentation to the SAGE Ebola Vaccine Working Group. [Unpublished]
16. World Health Organization. Number of health workers by country and selected cadres in countries at risk of EVD. Compiled for SAGE Ebola Vaccine Working Group December 2023. [unpublished]
17. Ebola vaccination of HCWs/FLWs (Ring + Preventive vaccination) [Excel]. Compiled for SAGE Ebola Vaccine Working Group December 2023. [unpublished]
18. Soka M, Choi M, Baller A, et al. Prevention of sexual transmission of Ebola in Liberia through a national semen testing and counselling programme for survivors: an analysis of Ebola virus RNA results and behavioural data. Lancet Glob Health 2016; 4: e736–43.
19. Deen G, Broutet N, Xu W, et al. Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors — Final Report. N Engl J Med 2017; 377: 1428-37.
20. Dokubo EK, Wendland A, Mate S, et al. Persistence of Ebola virus after the end of widespread transmission in Liberia: an outbreak report. Lancet Infect Dis 2018; 18: 1015–24.
21. Kofnan A. Risk Factors for Ebola virus Persistence in Semen of Survivors – Liberia. June 21, 2022. Presentation to SAGE Ebola Vaccine Working Group. [unpublished]
22. Mbala-Kingebeni P, Pratt C, Mutafali-Ruffin M, et al. Ebola Virus Transmission Initiated by Relapse of Systemic Ebola Virus Disease. N Engl J Med 2021; 384: 1240-7.
23. World Health Organization Summary of EVD cases with rings around them, estimated contacts vaccinated and not vaccinated, and survivors. [Excel]. Compiled for SAGE Ebola Vaccine Working Group December 2023. [unpublished]
24. World Health Organization. The potential source of outbreaks Survivors and contacts of survivors and vaccination status. December 14-15, 2023. Presentation to the SAGE Ebola Vaccine Working Group. [Unpublished]
25. Watson C, Carroll M. Ebola vaccination in close contacts of survivors: immune response and safety in asymptomatic seropositive persons. June 2022. Presentation to SAGE Ebola Vaccine Working Group. [unpublished]
26. Merck. rVSVΔG-ZEBOV-GP Safety Summary. June 2022. Presentation to the SAGE Ebola Vaccine Working Group. [Unpublished]
27. Wilkason C, Lee C, Sauer L, et al. Assessing and Reducing Risk to Healthcare Workers in Outbreaks. Health Security 2020; 18: 3.
28. UNICEF. Ebola Vaccine Emergency Stockpile. Available at: Link. Accessed 22 March 2024.