

Extraordinary meeting of the Strategic Advisory Group of Experts on Immunization on Ebola vaccination, May 2024: conclusions and recommendations

Final draft

Full meeting report to be published in the WHO Weekly Epidemiological Record on 5 July 2024

The Strategic Advisory Group of Experts (SAGE) on Immunization convened for an extraordinary meeting on 7 May 2024. This report summarizes the discussions, conclusions and recommendations of the meeting. All SAGE recommendations are made using evidence-based methods¹ and are informed by a systematic review and appraisal of evidence on the safety and impact of the assessed interventions. This review, as well as additional evidence and the SAGE declaration of interest assessment, is included in the background materials of the meeting which are available on the SAGE website.²

These recommendations supersede the interim recommendations issued by SAGE in October 2018,³ February 2019⁴ and May 2019.⁵

Background

Orthoebolavirus zairense (EBOV), the virus responsible for Ebola virus disease (EVD), is transmitted through direct or indirect contact with the blood, body fluids or secretions (stool, urine, saliva, semen) of infected individuals. EVD is rare but may lead to severe illness with a case fatality rate ranging from 25% to 90% from 1976 to 2022 and an average of approximately 60% (95% CI: 52–

¹ Development of WHO immunization policy and strategic guidance. Geneva: World Health Organization; 2024 (www.who.int/publications/i/item/9789240090729, accessed 8 May 2024).

² Strategic Advisory Group of Experts on Immunization (SAGE), Extraordinary Meeting, 7 May 2024. Geneva: World Health Organization; 2024 ([www.who.int/news-room/events/detail/2024/05/07/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-\(sage\)-7-may-2024](http://www.who.int/news-room/events/detail/2024/05/07/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-(sage)-7-may-2024), accessed 8 May 2024).

³ Report of the Strategic Advisory Group of Experts (SAGE) on Immunization, October 2018. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/bitstream/handle/10665/276544/WER9349.pdf>, accessed 30 May 2024).

⁴ SAGE Interim Recommendations on Vaccination against Ebola Virus Disease (EVD), February 2019. Geneva: World Health Organization (www.who.int/immunization/interimEbolaRecommendationsFeb2019.pdf, accessed April 2019).

⁵ Interim recommendations for Ebola vaccines. Geneva: World Health Organization; 2019 (www.who.int/publications/m/item/interim-recommendations-for-ebola-vaccines, accessed 8 May 2024).

69%).⁶ Since the discovery of EBOV in 1976, major outbreaks of EVD have been reported,⁷ mostly from west and central Africa where the disease is endemic. The two largest outbreaks occurred in multiple countries in west Africa in 2014–2016 and in 2018–2020. In the first of these outbreaks, widespread cases were reported from Guinea, Liberia and Sierra Leone during 2014–2016, with localized or imported cases in additional countries, leading to 28 652 reported cases and 11 325 deaths. The second of the outbreaks was in eastern Democratic Republic of the Congo (DRC) and Uganda in 2018–2020, resulting in 3481 cases and 2299 deaths.

Vaccines

Two types of Ebola vaccines have been licensed and prequalified by WHO – the live, attenuated, single-dose rVSVΔG-ZEBOV-GP vaccine (Ervebo, Merck & Co.) and the heterologous, two-dose Ad26.ZEBOV and MVA-BN-Filo vaccine regimen (Zabdeno and Mvabea, Janssen Pharmaceutica). rVSVΔG-ZEBOV-GP vaccine was first used during clinical trials in the 2014–2015 west African outbreak, then under a compassionate use protocol in Guinea during 2015, and again in the outbreak in eastern DRC during 2018–2020.

rVSVΔG-ZEBOV-GP vaccine

rVSVΔG-ZEBOV-GP is indicated for the immunization of individuals aged 1 year and older. Based on a recent Cochrane review, clinical efficacy estimated from a cluster-randomized ring vaccination trial of one dose of rVSVΔG-ZEBOV-GP vaccine for prevention of EVD was estimated to be 100% (95% CI: 69–100%) in adults aged ≥18 years and not pregnant, breastfeeding or severely ill).⁸ Observational data from the 2018–2020 outbreak in DRC suggests 94% (95% CI: 88–97%) vaccine effectiveness against EVD onset.⁹

Duration of protective clinical efficacy has not been formally assessed but Ebola-specific antibodies after rVSVΔG-ZEBOV-GP vaccination have been shown to remain at similar levels without evidence of waning for at least 5 years.¹⁰

The Cochrane review identified 17 studies which contributed to the evidence base on the safety of rVSVΔG-ZEBOV-GP vaccine. Based on the available randomized controlled trials (RCTs), local and systemic adverse events were higher following vaccination with rVSVΔG-ZEBOV-GP compared to

⁶ Izundi J et al. Case fatality rate for Ebola disease, 1976–2022: a meta-analysis of global data. *J Infect Public Health*. 2024;17:25–34.

⁷ Outbreaks and Emergencies Bulletin. Brazzaville: WHO Regional Office for Africa; 2024 (www.afro.who.int/health-topics/disease-outbreaks/outbreaks-and-other-emergencies-updates, accessed 30 May 2024).

⁸ Henao-Restrepo AM 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.

⁹ Muyembe JJ et al. 2022. Evidence on the efficacy of ring vaccination with rVSVΔG-ZEBOV-GP. DRC Paper. Presentation to the SAGE Ebola Vaccine Working Group [unpublished].

¹⁰ Huttner A et al. Antibody responses to recombinant vesicular stomatitis virus-Zaire Ebolavirus vaccination for Ebola virus disease across doses and continents: 5-year durability. *Clin Microbiol Infect*. 2023;29(12):1587–94.

the control. The rate of serious adverse events was similar between vaccine and control groups, including in children over 1 year of age and adolescents.

The identified RCTs did not include pregnant women; consequently, there are few data on pregnancy outcomes. Evidence on rVSVΔG-ZEBOV-GP vaccination from these trials does not suggest any major pregnancy-related safety concerns. Similarly, no data on vaccination of infants are available from clinical trials .

The overall good safety profile of rVSVΔG-ZEBOV-GP vaccination was confirmed by observational studies as well as by post-implementation vaccine surveillance data from DRC from more than 300 000 vaccinees, including infants aged 6–12 months (n=6397), children aged 1–10 years (n=48 520) and pregnant women (n=1663). No stratified data are available on vaccination by gestational age.

Ad26.ZEBOV and MVA-BN-Filo

Ad26.ZEBOV and MVA-BN-Filo is indicated for active immunization in individuals aged 1 year and older.

Six RCTs and observational studies were identified that reported on specific antibodies following vaccination by Ad26.ZEBOV and MVA-BN-Filo in the general population of countries at risk of EVD outbreaks. Five RCTs and observational studies reported on the level of specific antibodies following Ad26.ZEBOV and MVA-BN-Filo vaccination in children and adolescents. On the basis of these data, Ad26.ZEBOV and MVA-BN-Filo is highly immunogenic across population groups.

On the basis of animal studies with a fully lethal dose of the virus, the antibody level generated in humans following vaccination with Ad26.ZEBOV and MVA-BN-Filo would be expected to result in 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. No real-world data on protection against EVD are available as yet; hence the level of protection and duration of protection are not yet known.¹¹ However, antibody titres have been documented to remain at a similar level without evidence of waning for at least 5 years.¹²

In total, 15 studies identified by the Cochrane review reported on the safety of Ad26.ZEBOV and MVA-BN-Filo. While being slightly more reactogenic than the control, no elevated risk of vaccine-related serious adverse events was identified after either the first or second dose of vaccine, including in children over 1 year of age and adolescents.

¹¹ European Medicines Agency. Zabdeno (Ad26.ZEBOV-GP, recombinant).

(www.ema.europa.eu/en/documents/overview/zabdeno-epar-medicine-overview_en.pdf, accessed 30 May 2024).

¹² Cochrane Response. A systematic review of safety, efficacy, immunogenicity, and duration of protection of licensed Ebola virus vaccines. 2024 ([www.who.int/news-room/events/detail/2024/05/07/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-\(sage\)-7-may-2024](http://www.who.int/news-room/events/detail/2024/05/07/default-calendar/extraordinary-meeting-of-the-strategic-advisory-group-of-experts-on-immunization-(sage)-7-may-2024), accessed 6 June 2024).

Analysis of serious adverse events in 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: 0.03–15.08, p=0.79).

Vaccination in the context of outbreaks

SAGE was informed about the ring vaccination¹³ strategy and its impact on mitigating outbreaks while being implemented together with other control strategies, as has been the strategy of choice since 2016.

Since 2016, ring vaccination was implemented within 7–14 days of outbreak declaration around approximately 95% (352/3721) of all reported EVD cases. Over 90% (335 806/371 546) of individuals at high and very high risk have been vaccinated, despite security and access challenges in outbreak settings.

SAGE was further presented with an evaluation of EVD risk among specific target populations inside and outside of rings. The EVD risks (risk provided in ‰) in the 0–9 days from index case (onset of symptoms) until vaccination (i.e. the period when the vaccine is expected to have little or no effect) provide information on the baseline risks of these populations. The baseline risk inside the rings, as evaluated in the DRC outbreak of 2018–2020, was 6.2‰ for EVD contacts, 0.2‰ for contacts of contacts and little-to-no risk for third-level contacts. EVD risk among contacts was lower if the index case was a vaccinee (ratio 0.43, 95%CI: 0.29–0.65), and the overall case fatality rate among vaccinees was 23% (106/462), as against 75% among other cases in this outbreak.

Health-care workers (HCWs) can be among the first victims of an EVD outbreak while they play a critical role in treating the patients, controlling the outbreak and maintaining a functional health system. By expressing the number of EVD cases within HCWs and front-line workers (FLWs) as a percentage of the total number of cases we see that about 5% of all confirmed EBOV cases reported from outbreaks in Africa (1976–2024) were among HCWs. During the EVD outbreak in West Africa during 2015–2016, it was estimated that HCWs were between 21 and 32 times more likely to be infected with EBOV than people in the general adult population, especially in the first months of the outbreak.¹⁴ During the 2018–2020 outbreak in DRC, inside the rings, the risk was 3.7‰ for HCWs/FLWs that were contacts (compared to 6.2‰ of a contact that was not an HCW or FLW). Outside the rings, the risk for all HCWs/FLWs in areas with incident-confirmed cases was 1–

¹³ Each ring includes contacts as any person having been exposed to a confirmed case of Ebola virus infection less than 21 days before the identification as a contact by surveillance teams, in at least one of the following ways: slept in the same household with a case; direct physical contact with the case (alive or dead) during the illness; direct physical contact with the (dead) case at the funeral, touched his/her blood or body fluids during the illness; touched his/her clothes or linen; or been breastfed by a patient (baby). Contacts of contacts include neighbours, family or extended family members living within the nearest geographical boundary of all contacts, plus household members of any high-risk contacts. Where HCWs/FLWs are known contacts or contacts of contacts, they should be included in the ring vaccination.

¹⁴ Health worker Ebola infections in Guinea, Liberia and Sierra Leone: a preliminary report, 21 May 2015. Geneva: World Health Organization (www.who.int/publications/i/item/WHO-EVD-SDS-REPORT-2015.1, accessed 30 May 2024).

3‰. During this prolonged outbreak, the risk among HCWs/FLWs who were vaccinated despite not being in any ring but who were living in areas with incident EVD cases rose from 0.1‰ on day 30 to 0.5‰ over one year. The risk to HCWs and FLWs in areas where the outbreak is likely to spread is very low, and no cases have been reported in past outbreaks.

SAGE recommended that ring vaccination should continue to be the strategy of choice for EVD outbreaks. SAGE reiterated that the rapidity of launching ring vaccination targeting contacts and contacts of contacts of incident EVD cases during an EVD outbreak response is paramount. Vaccination of third-level contacts of EVD cases should be implemented only when vaccination of contacts and contacts of contacts is completed and if vaccine doses and human resources allow. SAGE reconfirmed the use of a single dose of rVSVΔG-ZEBOV-GP vaccine in these situations, in which high efficacy has been demonstrated from day 10 post-vaccination onwards. Vaccination of those identified as part of a ring should target all contacts and contacts of incident cases, including children from birth, pregnant women and lactating women. This recommendation, which is in part off-label, was made by SAGE taking account of the potential for severe disease outcomes in pregnant women and in infants. SAGE noted that a two-dose vaccine regimen, such as that of the Ad26.ZEBOV and MVA-BN-Filo vaccines, is not suitable in the context of vaccination inside the rings for outbreak response, where rapid high levels of protection are important (a single dose of rVSVΔG-ZEBOV-GP vaccine with rapid onset of immunity is greatly preferred).¹⁵

For affected areas with incident-confirmed cases of EVD, although outside of the immediate rings, SAGE recommended immunizing HCWs and FLWs with a single dose of rVSVΔG-ZEBOV-GP vaccine.

In areas where the outbreak is considered likely to spread, HCWs and FLWs are at very low risk of EVD. SAGE recommended that in these low-risk areas HCWs and FLWs should be offered the vaccine and that either of the WHO-prequalified Ebola vaccines may be used, depending on availability. However, SAGE noted that rVSVΔG-ZEBOV-GP vaccine should be used only if there is sufficient supply to vaccinate higher-risk populations (inside the rings) and is available for the duration of the outbreak.

Revaccination

In response to any new outbreak, the newly enumerated ring members who previously received either one dose of rVSVΔG-ZEBOV-GP or the two-dose regimen of Ad26.ZEBOV and MVA-BN-Filo vaccines during the preceding 6 months do not require an additional dose. Any incomplete schedule of Ad26.ZEBOV/ MVA-BN-Filo vaccination should be completed. As a precautionary measure, given their EVD risks, an additional dose of rVSVΔG-ZEBOV-GP vaccine should be offered to those ring members previously vaccinated with a full schedule of either vaccine more than 6 months earlier.

¹⁵ Ebola Virus Disease (EVD) Vaccine Target Product Profile. Geneva: World Health Organization; 2016 ([www.who.int/publications/m/item/ebola-virus-disease-\(evd\)-vaccine-target-product-profile](http://www.who.int/publications/m/item/ebola-virus-disease-(evd)-vaccine-target-product-profile), accessed 30 May 2024).

SAGE took note of the lack of data on the benefit–risk of administering more than two doses of rVSV-ZEBOV vaccine or additional doses of Ad26.ZEBOV/ MVA-BN-Filo vaccine. The need for, and feasibility of, administering additional doses should be assessed locally, taking account of the risk of exposure, vaccine supply and access, security concerns and community acceptance.

Preventive vaccination in the absence of outbreaks

SAGE recommended that countries at risk of EVD (i.e. countries with a history of EBOV outbreaks or in their neighbouring areas) should evaluate the transmission risk on the basis of outbreak epidemiology and available local evidence and should identify in each country priority areas and target populations for preventive vaccination. Given the available data on risks, SAGE does not recommend widespread vaccination of the general population.

Health-care and front-line workers

In order to mitigate the impact of future outbreaks, SAGE recommends preventive vaccination of HCW and FLWs in the priority areas of countries with a history of EBOV outbreaks, or in neighboring their areas. Further, national Ebola response teams, international responders, laboratory workers with possible exposure to Ebola virus, and those working in specialized EBOV research units and in Ebola treatment units who may treat future EVD patients should be considered for preventive vaccination. SAGE noted that either of the available Ebola vaccines (rVSVΔG-ZEBOV-GP or Ad26.ZEBOV/ MVA-BN-Filo vaccines, depending on local availability) may be used according to their respective schedules.

Survivors and close contacts of survivors

EBOV outbreaks have been linked to persistent virus excretion from some survivors and it has been shown that the virus can hide in immunologically privileged sites such as placenta, testes and central nervous system, as well as in synovial fluid and ocular fluid.¹⁶ Survivors may shed virus in semen for at least 5 years post-recovery and in vaginal fluid and breastmilk for an unknown period of time. From 2020 to 2021, three outbreaks were linked to persistent infection from a survivor. Further, limited evidence^{17,18} from survivors show a risk of relapse of acute EVD more than 6 months after initial disease onset.

A prospective cohort study of contacts of survivors from the 2014–2016 outbreak in Guinea evaluated the impact of pre-existing immunity, given that up to 10% of the contacts have detectable antibody titres despite being asymptomatic. The study reported that rVSV-ZEBOV vaccination is safe and immunogenic both in individuals who were seropositive and in those who were seronegative for Ebolavirus IgG antibodies. Seroconversion 28 days after vaccination was 81% (95%CI: 79–83%) in those who were seronegative at baseline. There was no evidence of interference of the immune responses to vaccination in those who were seropositive at baseline.

¹⁶ Doshi RH et al. Vaccination of contacts of Ebola virus disease survivors to prevent further transmission. *Lancet Glob Health*. 2020;8(12):e1455–6.

¹⁷ Jacobs M et al. Late Ebola virus relapse causing meningoencephalitis: a case report. *Lancet*. 2016;388:498–503.

¹⁸ Mbala-Kingebeni P et al. Ebola virus transmission initiated by relapse of systemic Ebola Virus Disease. *N Engl J Med*. 2021;384:1240–7.

The adverse events profile was favourable and was similar between the serogroups, with some data suggesting the possibility of fewer events and less-severe events in those who were seropositive.¹⁹ There is currently 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 immunologically privileged sites) or will have an effect on transmission from survivors to their close contacts.

On the basis of expert opinion, SAGE recommended that survivors with documented recent persistent virus excretion could be considered for vaccination if resources and vaccine doses are available and in the context of a research protocol. The risk–benefit of vaccination and the feasibility of offering vaccination to survivors should be assessed locally, together with access, security concerns and community acceptance.

In addition, people who have not previously been vaccinated and who have close contact with a survivor with documented recent persistent virus excretion should be offered a dose of rVSV ZEBOV.

Pregnant or lactating women should be vaccinated if they belong to a target group for which preventive vaccination is recommended.

For preventive vaccination in the absence of an outbreak, SAGE did not recommend revaccination of previously vaccinated individuals. Those who have received only one dose of Ad26.ZEBOV vaccine 56 days or more earlier should complete the vaccination schedule with the recommended dose of MVA-BN-Filo Ebola vaccine.

Vaccine stockpile

In 2021, following a SAGE recommendation, a global stockpile of 500 000 doses of rVSVΔG-ZEBOV-GP vaccine was established under the International Coordinating Group (ICG) on vaccine provision to ensure equitable, timely access to vaccine doses for Ebola outbreaks. Since its establishment up until 2023,²⁰ some 145 690 doses have been deployed from the ICG stockpile; 95% of doses (139 120 doses) shipped from the stockpile have been used for preventive vaccination of HCWs in countries with a history of EVD outbreaks, while 5% of the doses have been used for outbreak response (6570 doses) resulting in the rapid containment of the few outbreaks that have occurred since 2021. A total of 208 390 (40%) doses in the current stockpile are scheduled to expire by the end 2024.

Countries should use vaccines for preventive or outbreak response vaccination in accordance with the outlined recommendations. Shelf-life and expiry dates should be monitored and reassessed if possible.

¹⁹ Watson CH.et al. Rvsv-Zebov Vaccination in People with Pre-Existing Immunity to Ebolavirus: An Open-Label Safety and Immunogenicity Study in Guinean Communities Affected by Ebola Virus Disease (L'Essai Proches). Available at SSRN: <https://ssrn.com/abstract=4819274> or <http://dx.doi.org/10.2139/ssrn.4819274>

²⁰ See No. 17, 2024, 99, 193–202.

SAGE called on partners and funders supporting outbreak response and the outbreak stockpile to ensure that sufficient doses of both vaccines (rVSVΔG-ZEBOV-GP vaccine and Ad26.ZEBOV plus MVA-BN-Filo vaccines) are available.

Moreover, beyond the existing mechanism for procurement of outbreak response vaccines, SAGE recommended the use or creation of a suitable mechanism to fund procurement and implementation of the preventive vaccination recommendations.

Research priorities

SAGE issued research recommendations with the aim of addressing the knowledge gaps noted above. In conducting this research, every effort should be made to prioritize leadership by local researchers in the disease-endemic countries.

SAGE encouraged the generation of longer-term data on vaccine-induced duration of protection and the benefits of additional doses for both vaccines. In addition, SAGE recommended continued safety monitoring of administered vaccine doses in order to expand the evidence base on safety and immunogenicity/efficacy of administration of additional doses of both vaccines, as well as on co-administration with other vaccines and on the interchangeability of the available Ebola vaccines.

The magnitude of the risk of transmission from survivors to unvaccinated or vaccinated close contacts and their role in future outbreaks remains unknown. SAGE underlined the importance of assessing the impact of vaccination on reduction of risk of persistent viral excretion. Beyond vaccination, consideration of the role of therapeutics²¹ and other preventive measures to reduce the risk of viral excretion in survivors is warranted.

In the context of survivor programmes, research should be conducted on effectiveness, acceptance and uptake of Ebola vaccination by contacts of survivors.

SAGE commended the researchers from Guinea, DRC and the other affected countries for the quality of the data generated despite research being conducted in hard-to-reach and insecure contexts.

²¹ Therapeutics for Ebola virus disease. Geneva: World Health Organization; 2022 (www.who.int/publications/i/item/9789240055742, accessed 30 May 2024).