ACIP Evidence to Recommendations Framework

https://www.cdc.gov/vaccines/acip/recs/grade/ebola-vaccine-etr.html

The ETR framework was prepared and presented in February 2020.

Question: Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended for healthy, non-pregnant, non-lactating adults 18 years of age or older in the U.S. population who are at potential occupational risk to exposure to Ebola virus (species *Zaire ebolavirus)* for the prevention Ebola virus disease (EVD)?

Population: Healthy, non-pregnant, non-lactating adults 18 years of age or older in the U.S. population who are at risk of occupational exposure to Ebola virus (species *Zaire ebolavirus*); Subgroups: 1) Individuals responding to an outbreak of EVD due to Ebola virus (species *Zaire ebolavirus*); 2) healthcare personnel involved in the care and transport of confirmed EVD patients at federally-designated Ebola Treatment Centers in the United States; 3) laboratorians and support staff working at biosafety level 4 (BSL-4) laboratories

Comparison(s): No vaccine

Outcomes:

- Development of Ebola-related symptomatic illness (Critical)
- Vaccine-related joint pain or swelling (arthritis or arthralgia) (Critical)
- Vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within in 2 months of vaccination (Critical)
- Transmissibility of rVSV vaccine virus: Surrogate assessed with viral dissemination/shedding of the rVSV vaccine virus (Critical)
- Serious adverse events related to the vaccination (Critical)

Background: With case fatality rates of 70-90% when untreated, Ebola virus (species *Zaire ebolavirus*) is the most lethal of the 4 viruses that cause EVD in humans. In addition, the virus is highly transmissible and can be found in all body fluids of an infected individual, including urine, blood, salvia, sweat, feces, vomit, semen, and breastmilk. Death is rapid, usually occurring 7-10 days after symptom onset. In survivors, Ebola virus (species *Zaire ebolavirus*) has been known to persist in immune-privileged sites, and in some instances, has resulted in continued disease transmission and disease recrudescence. In addition, sequalae have been reported in EVD survivors including uveitis, arthralgia, myalgia, chronic abdominal pain and fatigue.Currently there is no FDA-approved treatment for EVD.

Ebola virus (species *Zaire ebolavirus*) is responsible for the majority of reported EVD outbreaks (18/28; 64%), including the largest EVD outbreak in history (2014-2016 West Africa). Worldwide, outbreaks due to Ebola virus (species *Zaire ebolavirus*) have infected >31,000 persons and resulted in >12,000 deaths. In total, 11 individuals infected with Ebola virus (species *Zaire ebolavirus*) were treated in the United States; all were associated with the 2014-2016 West Africa outbreak. Of these 11 individuals, 9 were infected in West Africa; two (nurses) were infected in the United States while caring for a returning traveler. Also, during both the 2014-2016 West Africa outbreak and the ongoing DRC outbreak, additional individuals were repatriated to the United States following high-risk exposures to confirmed EVD patients, none tested positive for Ebola virus.

On August 1, 2018, an outbreak of EVD due to Ebola virus (species *Zaire ebolavirus*) was declared in eastern Democratic Republic of Congo (DRC). Following an increase in EVD cases in eastern DRC and travel-associated cases in Uganda, the World Health Organization (WHO) Emergency Committee declared the outbreak a public health emergency of international concern (PHEIC) on July 17, 2019. On February 12, 2020, the committee unanimously re-affirmed that the outbreak still constitutes as a PHEIC. As of February 15, 2020, the ongoing outbreak in DRC has infected >3000 persons and resulted in >2000 deaths.

On December 19, 2019, the FDA approved rVSVΔG-ZEBOV-GP vaccine (ERVEBO®, Merck) for the prevention of disease caused by *Zaire ebolavirus* in individuals 18 years of age or older. The vaccine is a replication-competent, recombinant vesicular stomatitis virus-based vaccine that protects only against Ebola virus (species *Zaire ebolavirus*). This vaccine is currently being administered in the eastern DRC EVD outbreak using a post-exposure ring vaccination strategy in outbreak affected areas (DRC, Uganda) and pre-exposure vaccination in frontline workers in DRC and high-risk surrounding countries (Uganda, Rwanda, South Sudan, and Burundi). The vaccine is currently available in the U.S. to individuals at potential occupational risk through the PREPARE clinical trial.

	CRITERIA	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☒ | *Varies* ☐	Ebola virus, species *Zaire Ebolavirus,* is responsible for 18/28 (64%) of EVD outbreaks reported since 1976, including the two largest EVD outbreaks in history (2014 West Africa Outbreak, ongoing outbreak in the Democratic Republic of Congo). In total, >31,000 people have been infected resulting in >12,000 deaths. Currently, there is no FDA-approved treatment for EVD. With the widespread use of modern transportation, a disease that was limited to remote regions of Africa, is now a global threat, as evidenced by the 2014 West Africa Outbreak. As such, domestic EVD preparedness activities, to include a vaccinated workforce that able to quickly respond to	

			current and future outbreaks, care for Ebola-infected patients in the United States and carry out research to better understand the virus and develop new countermeasures is a public health priority.	
BENEFITS & HARMS	How substantial are the desirable anticipated effects?	Minimal ☐ Small ☐ Moderate ☐ Large ☒ Don't know ☐ Varies ☐	Only one study evaluated using the GRADE process provided data on efficacy. At the participant level, the risk ratio (RR) was 0.04 with a 95% confidence interval (95% CI) of 0.0001 – 0.74 [absolute risk (AR) 5 fewer per 1,000; 95% CI 5 fewer to 1 fewer], demonstrating a protective effect from vaccination.	
	CRITERIA	WORK GROUP JUDGMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	How substantial are the undesirable anticipated effects?	Minimal ☐ Small ☐ Moderate ☒ Large ☐ Don't know ☐ Varies ☐	Arthralgia is more commonly reported among vaccinees (RR:2.55 for RCTs). Severe arthralgia is more commonly reported among vaccinees (RR:6.40 for RCTs). Arthritis is more commonly reported among vaccinees (RR: 1.80 for RCTs). Pregnancy loss in vaccinated women was not significantly higher than in non-vaccinated women (RR: 1.35). vaccine virus (rVSV) was detected post-	

			vaccination in blood, saliva, urine, and synovial fluid by reverse transcriptase polymerase chain reaction (RT-PCR). Vaccine-related severe adverse events are rare	
	Do the desirable effects outweigh the undesirable effects?	*Favors intervention* [X] *Favors comparison* [ ] *Favors both* [ ] *Favors neither* [ ] *Unclear* [ ]	The documented protective efficacy of the vaccine against EVD is considered to be of high clinical benefit. Vaccine-related severe adverse reactions were uncommon. This, taken in consideration with the high mortality rate in infected individuals, high transmissibility of the virus, disease sequalae, and lack of an FDA-approved treatment factor into the assessment that the desirable effects of vaccination outweigh the undesirable effects.	This falls under Situation 1 (Condition: When low quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high) of the five paradigmatic situations in which a strong recommendation may be warranted despite low or very low confidence in effect estimates. Reference: Andrews JC, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013 Jul; 66(7):726-35).
	What is the overall certainty of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* [ ] *4 Very low* [ ] *3 Low* [ ] *2 Moderate* [X] *1 High* [ ] Safety of the intervention *No included studies* [ ] *4 Very low* [X] *3 Low* [ ] *2 Moderate* [ ] *1 High* [ ]	One study evaluated using the GRADE process provided data on efficacy. At the participant level the overall certainty in the evidence for effectiveness is "moderate". The overall certainty in the evidence is "very low" for the safety outcomes based on the lowest of the critical outcomes. The certainty of evidence for arthralgia 0-42 days after vaccination was	"Low" and "very low" certainty of evidence for arthralgia, severe arthralgia, and arthritis may be due to variability between studies in the definition of these outcomes, methodology used to diagnosis these outcomes, availability of specialized care/radiographic imaging, and timing when these outcomes were assessed. Low certainty for severe adverse events was low due to extraction of vaccinated-arm data only, thus rendering the data observational.

			”very low” for RCTs and observational studies. Certainty of evidence for severe arthralgia was “low” for RCTS and “very low” for observational studies. Certainty of evidence of arthritis (0-56 days after vaccination) was “low” for RCTs and “very low” for observational studies. Certainty of evidence for vaccine-related adverse pregnancy outcomes was “very low” for observational studies. Certainty of evidence for severe adverse events (SAE)was “low” for observational studies. Vaccine related SAEs were rare. No data were available on vaccine virus transmissibility to non-vaccinated persons or animals, as such viral dissemination and shedding were used as indirect surrogates. The certainty of evidence for transmissibility of vaccine virus is “very low” for observational studies.	

VALUES	Does the target population feel that the desirable effects are large relative to undesirable effects?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably Yes* ☐☐ *Yes* ☐ *Varies* ☒	No Knowledge, Attitudes, and Practices surveys have been conducted amongst our 3 populations of interest as it pertains to the rVSVΔG-ZEBOV-GP vaccine. Although exact numbers are unavailable, BSL-4 laboratorians and support staff, healthcare personnel[1] from the federally-designated Ebola Treatment Centers, and individuals responding to an EVD outbreak have participated in in a clinical trial offering the vaccine which would suggest at least some within these groups feel that the desirable effects are large relative to undesirable effects. Given that 10/11 individuals infected with EBOV and treated in the United States were either responding to an EVD outbreak and/or were healthcare workers, work group members think that persons responding to an EVD outbreak and HCP at federally designated Ebola Treatment Centers would feel that the desirable effects are relative to undesirable effects. For BSL-4 laboratorians and support staff, response to vaccination has been	

			mixed. Some have enrolled in a clinical trial offering the vaccine (PREPARE). Others were unable to enroll in PREPARE due to logistical challenges but expressed interest in accessing the licensed vaccine when it is available outside of the three PREPARE clinical trial sites. In addition, there are anecdotal reports of some BSL-4 laboratorians and support staff declining vaccination because the additional level of protection afforded by vaccination, in the backdrop of strict biosafety measures already in place in BSL-4 laboratories, was considered to be minimal compared to the potential undesirable effects of vaccination.	
CRITERIA	WORK GROUP JUDGMENTS		RESEARCH EVIDENCE	ADDITIONAL INFORMATION
Is there important uncertainty about or variability in how much people value the main 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* ☐		Given the high mortality associated with EVD, the lack of an FDA-approved treatment, the high transmissibility of the virus, this vaccine's demonstrated efficacy in preventing EVD, and their interest and participation in a clinical trial offering vaccination, we believe that most individuals within our three	

			populations of interest would be interested in being vaccinated. Although the response to vaccination amongst BSL-4 laboratorians and support staff have been mixed, the work group thinks that most in this population will feel that desirable effects are large relative to the undesirable effects.	
ACCEPTABILITY	Is the intervention acceptable to key stakeholders?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☒ *Varies* ☐	No Knowledge, Attitudes, and Practices (KAP) surveys have been conducted amongst US healthcare workers related to the rVSVΔG-ZEBOV-GP. However, individuals within the 3 populations at potential occupational risk of exposure to the virus have enrolled in the ongoing PREPARE trial and have received the vaccine. Given the high mortality associated with EVD, the lack of an FDA-approved treatment, the high transmissibility of the virus, and this vaccine's demonstrated efficacy, acceptability is expected to continue despite the moderate anticipated undesirable effects.	Stakeholders include 1) Individuals responding to an outbreak of EVD; 2) healthcare workers and support staff involved in the care and transport of confirmed EVD patients at the ten regional Special Pathogen Centers in the United States; 3)Laboratorians and support staff working at the ten biosafety level 4 (BSL4) laboratories in the United States 4) administrators at public health institutions involved in EVD response activities 5)administrators at non-governmental organizations involved in EVD response activities 6) administrators at Special Pathogen Centers 7) administrators at BSL4 laboratories.

RESOURCE USE	Is the intervention a reasonable and efficient allocation of resources?	No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒	A cost effectiveness evaluation was not performed because this vaccine is intended for use in emergency response and preparedness scenarios in limited populations, and not as routine vaccination in the general population. At this time in the U.S., the vaccine will be stored and made available through the US Government.	
FEASIBILITY	Is the intervention feasible to implement?	No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☒ Varies ☐	As it appears now, no licensed vaccine will be available until Q3/Q4 of 2020. The vaccine is currently available through the PREPARE clinical trial. Discussions are ongoing on mechanisms to allow for limited quantities of investigational-labeled vaccine to be made available for ACIP-recommended populations in the interim period between ACIP recommendations and availability of licensed product outside the setting of a clinical trial.	The vaccine has stringent cold chain requirements (-60 to -80C).

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	There is insufficient evidence to determine the balance of consequences
	☐	☐	☐	☒	☐	☐

Is there sufficient information to move forward with a recommendation? Yes [x] No			
Policy options for ACIP consideration	ACIP does not recommend the intervention* *Intervention may be used within FDA licensed indications ☐	ACIP recommends the intervention for individuals based on shared clinical decision-making ☐	ACIP recommends the intervention ☒
Draft recommendation (text)	Please provide the draft recommendations proposed to ACIP. 1. Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for adults 18 years of age or older in the U.S. population who are responding to an outbreak of EVD due to Ebola virus (species *Zaire ebolavirus*) 2. Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for adults 18 years of age or older who work as healthcare personnel[1] at a federally-designated Ebola Treatment Center in the United States 3. Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for adults 18 years of age or older who work as laboratorians and support staff at biosafety-level 4 facilities in the U.S. who are at potential risk for occupational exposure to Ebola virus (species *Zaire ebolavirus*) Healthcare personnel (HCP) refers to all paid and unpaid persons serving in healthcare settings who have the potential for direct or indirect exposure to patients or infectious materials, including body substances (e.g., blood, tissue, and specific body fluids); contaminated medical supplies, devices, and equipment; contaminated environmental surfaces; or contaminated air. These HCP include, but are not limited to, emergency medical service personnel, nurses, nursing assistants, physicians, technicians, *clinical laboratory personnel, autopsy personnel,* therapists, phlebotomists, pharmacists, students and trainees, contractual staff not employed by the healthcare facility, and persons not directly involved in patient care, but who could be exposed to infectious agents that can be transmitted in the healthcare setting (e.g., clerical, dietary, environmental services, laundry, security, engineering and facilities management, administrative, billing, and volunteer personnel). Adapted from https://www.cdc.gov/infectioncontrol/guidelines/healthcare-personnel/index.html		

Additional considerations (optional)	rVSVΔG-ZEBOV Ebola vaccine is currently no commercially available in the U.S. The vaccine will be stored and made available for U.S. civilians through the US Government in accordance with ACIP recommendations upon receipt of request.

Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend the intervention* *Intervention may be used within FDA licensed indications ☐	ACIP recommends the intervention for individuals based on shared clinical decision-making ☐	ACIP recommends the intervention ☒
Additional ACIP considerations	Pre-exposure vaccination with rVSVΔG-ZEBOV-GP vaccine is recommended for adults 18 years of age or older in the United States population who are at potential risk of exposure to Ebola vaccine (species *Zaire ebolavirus*) because they: • Are responding to an outbreak of EVD; or • Work as healthcare personnel at a federally-designated Ebola Treatment Center in the United States; or • Work as laboratorians or other staff at biosafety-level 4 facilities in the United States.		