Evidence to Recommendations for Pre-Exposure Vaccination with rVSVΔG-ZEBOV-GP Vaccine for At-Risk Adults in the United States

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Policy 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 prevention of Ebola virus infection?

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 Ebola virus disease 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 (BSL4) laboratories that handle a) cultures or b) animals infected with replication-competent Ebola virus or c) diagnostic or clinical specimens containing replication-competent Ebola virus
Intervention	Pre-exposure intramuscular immunization with a single licensed dose of the rVSVΔG-ZEBOV-GP vaccine
Comparison	No vaccine
Outcomes deemed "Critical" or "Important" by ACIP Ebola vaccine Work Group	▪ **Development of Ebola-related symptomatic illness (Critical)** ▪ Ebola-related mortality (Critical) –No Data ▪ **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)** ▪ Incidence and severity of oral or skin lesions (Important) ▪ Interaction or cross-reactivity with monoclonal antibody-based therapeutics or other VSV-backboned vaccines (Important)

Problem: Ebola Virus Disease Due to Ebola Virus (species *Zaire ebolavirus*)

Is the problem of public health importance ?

☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

Problem: Ebola Virus Disease Due to Ebola Virus (species *Zaire ebolavirus*)

- Ebola virus (species *Zaire ebolavirus*) is the most lethal of the 4 viruses that cause Ebola virus disease (EVD) in humans
- Highly transmissible; found in all body fluids of an infected individual
- Severe disease, with death usually occurring 7-10 days after symptom onset
- In survivors, virus has been known to persist in immuno-privileged sites, and in some instances, has resulted in continued disease transmission and disease recrudescence
- No FDA-approved treatment

International Public Health Threat

- Responsible for the majority of reported EVD outbreaks (64%; 18/28) to include the largest EVD outbreak in history (2014 West Africa)
- Infected >31,000 persons and resulted in >12,000 deaths*
- August 1, 2018, EVD outbreak due to Ebola virus (species *Zaire ebolavirus*) declared in eastern Democratic Republic of Congo
  - July 17, 2019: outbreak declared a “Public Health Emergency of International Concern” (PHEIC)
  - February 12, 2020: Emergency Committee unanimously agreed that the outbreak still constitutes a PHEIC
  - >3,000 persons infected with >2,000 deaths

* Does not include ongoing 2018 DRC outbreak

U.S. Public Health Threat

- 11 individuals infected with Ebola virus (species *Zaire ebolavirus*) were treated in the United States
  - All associated with 2014 West Africa Outbreak
  - 9 were infected in West Africa
  - 2 infected in the United States while caring for a returned traveler
- Additional persons were repatriated to the United States following high-risk exposures to confirmed EVD patients (2014 West Africa Outbreak, 2018 DRC outbreak); none developed EVD

Problem: Ebola Virus Disease Due to Ebola Virus (species *Zaire ebolavirus*)

Is the problem of public health importance?

☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

- Virus is responsible for the majority of reported EVD outbreaks
- >31,000 persons infected, resulting in >12,000 deaths
- International and U.S. public health threat
- High case fatality rate (70-90% when untreated)
- No FDA-approved treatment

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Benefits

How substantial are the desirable anticipated effects?
☐ Minimal ☐ Small ☐ Moderate ☐ Large ☐ Don’t know ☐ Varies

- One study evaluated using GRADE provided data on vaccine efficacy;
- Demonstrated protective effect from vaccination at the participant level (RR:0.04 [95%CI: 0.0001 – 0.74]) = 96% risk reduction

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Harms

How substantial are the undesirable anticipated effects?

☐ Minimal ☐ Small ☐ Moderate ☐ Large ☐ Don't know ☐ Varies

- Arthralgia is more commonly reported among vacinees (RR*: 2.55)
- Severe arthralgia is more commonly reported among vaccinated recipients; overall uncommon (RR*: 6.40)
- Arthritis is more commonly reported among vacinees (RR*: 1.80)
- Pregnancy loss in vaccinated women not significantly higher than in non-vaccinated women (RR*: 1.35)
- rVSV vaccine virus detected post-vaccination in blood, saliva, urine, synovial fluid
- Vaccine-related SAEs are rare

*Reported RR for RCTs

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Benefit/Harms

Do the desirable effects outweigh the undesirable effects?

☐ Favors intervention ☐ Favors comparison ☐ Favors both ☐ Favors neither ☐ Unclear

- Documented protective efficacy of the vaccine
- High severity of illness
- High transmissibility of the virus
- Virus persistence; instances of continued disease transmission and disease recrudescence
- Lack of FDA-approved treatment
- Vaccine-related SAEs are rare

Benefit/Harms

Do the desirable effects outweigh the undesirable effects?
[X] **Favors intervention** [ ] Favors comparison [ ] Favors both [ ] Favors neither [ ] Unclear

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Overall Certainty for Evidence: Effectiveness

Effectiveness of the intervention
☐ No included studies ☐ Very low ☐ Low ☐ Moderate ☐ High

- One study evaluated using the GRADE process demonstrated protective effect from vaccination

Overall Certainty for Evidence: Effectiveness

Effectiveness of the intervention				
☐ No included studies	☐ Very low	☐ Low	☒ **Moderate**	☐ High

- One study evaluated using the GRADE process demonstrated protective effect from vaccination
- At the participant level, the overall certainty in the evidence for effectiveness is “Moderate”

Overall Certainty for Evidence: Safety

Safety of the intervention
☐ No included studies ☐ Very low ☐ Low ☐ Moderate ☐ High

Certainty for Evidence: Post-Vaccination Arthralgia (0-42 days)

- Arthralgia is more commonly reported among vaccine recipients compared to placebo
- Certainty for evidence “Very Low”
  - Low certainty may be due to variability between studies in the definition of arthralgia, evaluation of arthralgia, availability of specialized care/radiographic imaging, and timing at which arthralgia was ascertained

Certainty of Evidence: Severe Arthralgia

- Severe arthralgia is more commonly reported among vaccine recipients compared to placebo or unvaccinated, but overall is uncommon
- Certainty of evidence “Low/ “Very Low” (RCTs/Obs)
- Low certainty may be due to variability between studies in evaluation of arthralgia and timing at which arthralgia was ascertained

Certainty of Evidence: Post-Vaccination Arthritis (0-56 days)

- Arthritis is more commonly reported among vaccine recipients compared to placebo; rVSV vaccine virus detected by RT-PCR in synovial fluid of 4 vaccinated participants[4,6,11]

- Certainty of evidence “Low”/ ”Very Low” (RCTS/Obs)
  - May be due to variability between studies in the definition of arthritis, methodology used to diagnosis arthritis, availability of specialized care/radiographic imaging, and timing at which arthritis was ascertained

Certainty of Evidence: Vaccine-related Adverse Pregnancy Outcomes

- Pregnancy loss among vaccinated pregnant women was not significantly higher than pregnancy loss among unvaccinated pregnant women
- Certainty of evidence “Very Low”

Certainty of Evidence: Vaccine-related Severe Adverse Events

- Across 12 studies/19,184 vaccinated persons, 2 vaccine-related and 1 *possibly* vaccine-related SAEs; all resolved without sequelae
  - Anaphylaxis, febrile reaction, influenza-like illness
- Certainty of evidence “Low”
  - Due to extraction of vaccinated-arm data only, thus rendering the data observational
- Vaccine-related SAEs are rare

Certainty of Evidence: Transmissibility of Vaccine Virus

- No data available on vaccine virus transmissibility to non-vaccinated persons or animals
- Assessed viral dissemination and shedding as an indirect surrogate
- Certainty of evidence: “Very Low”
  - Outcome data was only collected from vaccinated study arms, thus rendering the data observational

Overall Certainty for Evidence

Safety of the intervention

☐ No included studies ☐ Very low ☐ Low ☐ Moderate ☐ High

Outcome	Low Certainty	Very Low Certainty
Arthralgia		RCT/Obs
Severe arthralgia	RCT	Obs
Arthritis	RCT	Obs
Pregnancy outcomes		Obs
Vaccine virus transmission		Obs
SAEs	Obs	

Target Population Sentiments

Does the target population feel that the desirable effects are large relative to undesirable effects

- [ ] No
- [ ] Probably no
- [ ] Uncertain
- [ ] Probably yes
- [ ] Yes
- [ ] Varies

Target Population Sentiments

- No Knowledge, Attitudes, and Practices (KAP) surveys have been conducted amongst our 3 populations of interest
- Persons responding to EVD outbreaks and HCP[1] at federally-designated Ebola Treatment Centers will likely think the desirable effects outweigh undesirable
  - Some enrolled in a clinical trial offering the vaccine (PREPARE)
  - 10/11 EVD patients treated in the U.S. were either responding to an EVD outbreak and/or were healthcare workers

Target Population Sentiments

- BSL-4 personnel, response to vaccination mixed
  - Some enrolled in a clinical trial offering the vaccine (PREPARE)
  - Others unable to enroll in PREPARE due to logistical challenges, but *expressed interest* in accessing the licensed vaccine when it is available outside of the 3 PREPARE clinical trial sites
  - Anecdotal reports of some declining to be vaccinated 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

Target Population Sentiments

Does the target population feel that the desirable effects are large relative to undesirable effects

☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

- No KAP survey data available
- Individuals responding to an EVD outbreak and HCP at federally-designated Ebola Treatment Centers likely think desirable effects are large relative to undesirable effects
- Mixed response to vaccination amongst BSL-4 laboratorians/support staff

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Target Population Sentiments

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

- Individuals responding to an EVD outbreak and HCP at federally-designated Ebola Treatment Centers likely think desirable effects are large relative to undesirable effects
- Mixed response to vaccination amongst BSL-4 laboratorians/support staff but most think desirable effects are large relative to undesirable effects

Target Population Sentiments

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Stakeholder Sentiments

Is the intervention acceptable to key stakeholders
☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

- No KAP survey data available
- Acceptable to the majority of the 3 populations of interest
- NGOs, federally-designated Ebola Treatment Centers, governmental organizations, BSL-4 laboratories have been supportive of staff receiving the vaccine through the clinical trial (PREPARE)

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Resource Allocation

Is the intervention a reasonable and efficient allocation of resources
☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes

- Cost effectiveness evaluation not performed as this vaccine is intended for use in preparedness scenarios in limited populations and not as routine vaccination in the general population
- At this time, the vaccine will be stored and made available through the U.S. government

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Feasibility

Is the intervention feasible to implement
☐ No ☐ Probably no ☐ Uncertain ☐ Probably yes ☐ Yes ☐ Varies

- As it appears now, licensed vaccine will likely become available Q3/Q4 2020
- Vaccine is currently available through the PREPARE clinical trial
- Ongoing discussions 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

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Balance of Consequences

☐ Undesirable consequences clearly outweigh desirable consequences in most settings	☐ Undesirable consequences probably outweigh desirable consequences in most settings	☐ 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

Sufficiency of Information

Is there sufficient information to move forward with a recommendation?
☐ Yes ☐ No

- Available efficacy data in an outbreak setting
- Safety data for 19,184 persons vaccinated in the U.S., Europe, Africa evaluated using GRADE

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Healthcare Personnel Definition

1 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

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For more information, contact CDC
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