Evidence for Expansion of Recommendations for Pre-Exposure Vaccination with rVSVΔG-ZEBOV-GP Ebola Vaccine for Special Pathogens Treatment Centers and Laboratory Response Network Facilities

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Policy Question 1

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended for healthcare personnel* involved in the care and transport of suspect or confirmed Ebola virus disease patients at Special Pathogens Treatment Centers?

Policy Question 2

Should pre-exposure vaccination with the rVSVΔG-ZEBOV-GP vaccine be recommended for laboratorians and support staff at Laboratory Response Network (LRN) facilities that handle specimens that may contain replication-competent Ebola virus (species *Zaire ebolavirus*) in the United States?

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

International Public Health Threat

- Ebola virus (species *Zaire ebolavirus*) is responsible for the majority of reported EVD outbreaks, including the largest EVD outbreak in history (2014 West Africa)
- Infected >31,000 persons and resulted in >12,000 deaths*

* Does not include ongoing 2018 DRC outbreak

U.S. Public Health Threat

- 11 individuals infected with Ebola virus (species *Zaire ebolavirus*) have been 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)

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

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- High case fatality rate (70-90% when untreated)

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 vaccine 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 [95% CI: 0.73–2.52])
- rVSV vaccine virus detected post-vaccination in blood, saliva, urine, synovial fluid
- Vaccine-related serious adverse events (SAEs) are uncommon (3 events / 17,119 vaccine recipients)

*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 Ebola virus
- Ebola virus persistence in survivors; instances of continued disease transmission and disease recrudescence
- Vaccine-related SAEs are uncommon

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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
- At the participant level, the overall certainty in the evidence for effectiveness is “Moderate” (level 2)
- At the cluster level, overall certainty in the evidence for effectiveness is “Low” (level 3)

Overall Certainty for Evidence: Effectiveness

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Overall Certainty for Evidence: Safety

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

Overall Certainty for Evidence: Safety

Safety of the intervention

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

Outcome	Findings	Evidence type[b]
Incidence of arthralgia	Arthralgia is more commonly reported among vaccine recipients compared to placebo	4
Severity of arthralgia	Severe (grade 3) arthralgia is more commonly reported among vaccine recipients compared to placebo or unvaccinated, but is overall uncommon	4
Incidence of arthritis	Arthritis is more commonly reported among vaccine recipients compared to placebo	4
Pregnancy-related adverse events due to vaccination	The rate of pregnancy loss among pregnant women who received immediate vaccination was not significantly higher than the rate of pregnancy loss among unvaccinated pregnant women	4
Transmissibility of vaccine-virus[a]	rVSVΔG-ZEBOV-GP has been detected in blood/plasma up to 14 days, saliva 7 days, and urine 7 days post-vaccination; however, true duration of shedding and potential for transmissibility is uncertain	4
Vaccine-related serious adverse events[a]	Vaccine-related SAEs are an uncommon occurrence (3 events in 17,119 vaccine recipients across 12 studies)	3

a. Outcome data was only collected from the vaccinated study arm from these studies; therefore they were considered observational for these outcomes
b. Overall evidence type for each outcome is determined by taking the lowest certainty value (highest evidence type) across both RCT and Obs for each outcome

Overall Certainty for Evidence: Safety

Safety of the intervention

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Target Population Sentiments — HCP at Special Pathogens Treatment Centers

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 — HCP at Special Pathogens Treatment Centers

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

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

- **54%** of the study population expressed interest in receiving the vaccine if eligible and offered the vaccine today
- When people were given the choice to get vaccinated at different time points (when there was an EVD case in the U.S. or their state), interest in vaccine increased to **81%**
- **53%** of the survey population thought ACIP should vote to "recommend" the vaccine to HCP at Special Pathogens Treatment Centers

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Target Population Sentiments — HCP at Special Pathogens Treatment Centers

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

- Mixed response to vaccination amongst HCP at Special Pathogens Treatment Centers, but interest in the vaccine increased markedly with perceived risk

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Stakeholder Sentiments — HCP at Special Pathogens Centers

Is the intervention acceptable to key stakeholders?

- [ ] No
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Stakeholder Sentiments — HCP at Special Pathogens Centers

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Target Population Sentiments — Staff at LRN Facilities

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

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Target Population Sentiments — Staff at LRN Facilities

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

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- **59%** of the study population expressed interest in receiving the vaccine if eligible and offered the vaccine today
- When people were given the choice to get vaccinated at different time points (when there was an EVD case in the U.S. or their state), interest in vaccine increased to **86%**
- **59%** of the survey population thought ACIP should vote to "recommend" the vaccine to staff at LRN facilities

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Target Population Sentiments — Staff at LRN Facilities

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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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Health Equity

What would be the impact on health equity?

☐ Reduced ☐ Probably reduced ☐ Probably no impact ☐ Probably increased ☐ Increased

☐ Varies ☐ Don't know

- Only age, sex, and profession (job title) collected
- Race/ethnicity data from respondents not collected

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Feasibility

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

- Licensed doses are available through the Strategic National Stockpile

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Balance of Consequences for SPTCs and LRNs

☐ 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
X **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 17,119 persons vaccinated in the U.S., Europe, Africa evaluated using GRADE
- Available data from vaccine acceptability surveys from both target populations

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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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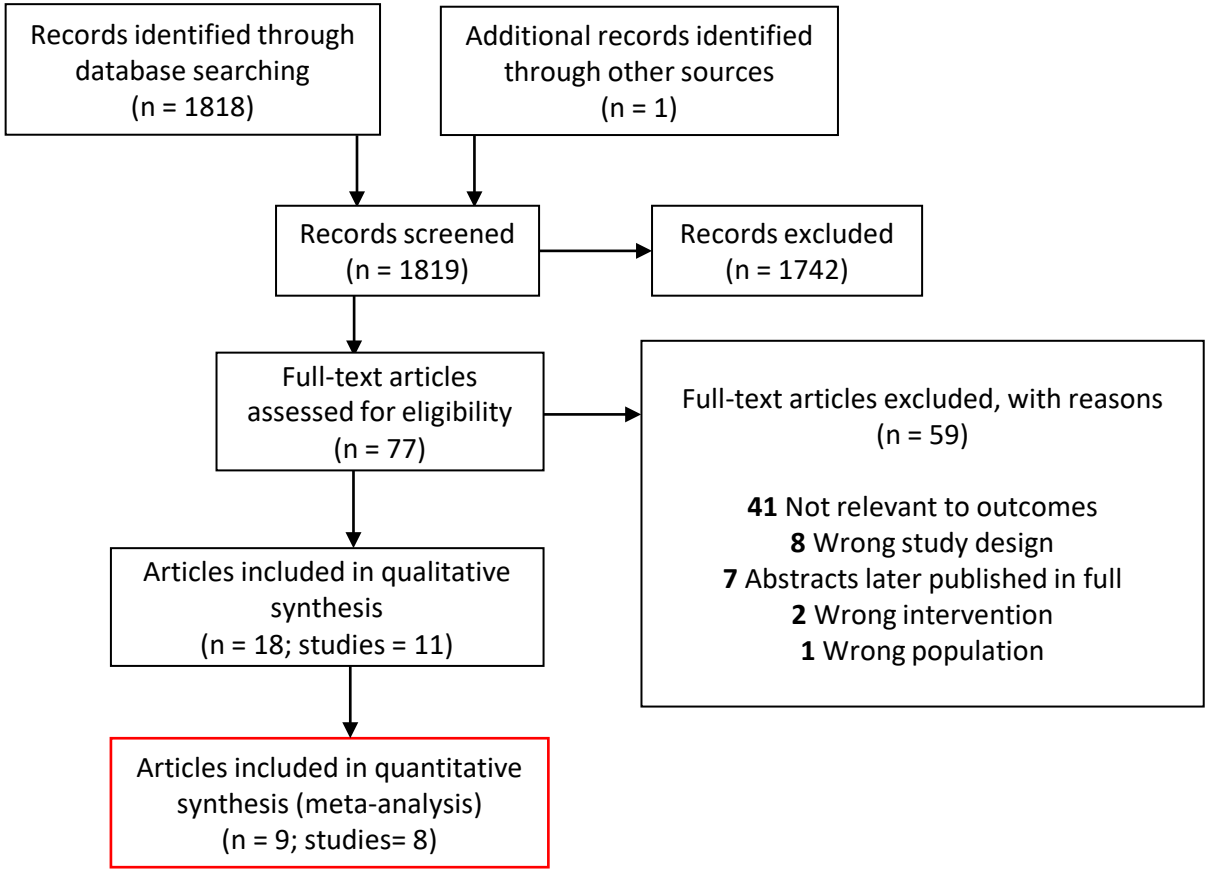
Included in meta-analyses (RCT or NRS with comparator); Not included in meta-analyses (NRS, without comparator)

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Evidence Retrieval



Outcome 1: Development of Ebola-related symptomatic illness

Studies with unvaccinated comparator (n=1)

Henao-Restrepo, 2017: Ça Suffit Trial, Guinea

- Two-part Phase III cluster-randomized open-label, ring vaccination trial
  - **Initial study:** contacts and contacts of contacts of confirmed EVD cases offered immediate vaccination vs delayed vaccination (21 days after randomization)
  - **Follow-up study:** clusters were offered immediate vaccination following cessation of the randomized trial
- Primary outcome: incidence of EVD with onset 10 days or more from randomization
  - Accounts for incubation period and unknown time for vaccinees to develop protective immunity

Outcome 1: Development of Ebola-related symptomatic illness

Henao-Restrepo, 2017: Ça Suffit Trial, Guinea (Final Results)

	Immediately Vaccinated N=Participants (clusters)	Delayed/Never vaccinated N= Participants (clusters)
All participants, randomized and non-randomized	3775 (70)	4507 (104) [a]
Development of EVD ≥ *10 days* after randomization, all participants [b]	0 (0)	23 (11)
Development of EVD < *10 days* of randomization, all participants [b]	21 (11)	31 (22)
Randomized participants	2108 (51)	3075 (47) [c]
Development of EVD ≥ *10 days* after randomization, randomized participants	0 (0)	16 (7)

Vaccine efficacy 100% (95% CI: 68.9 – 100, p=0.0045) [d]

a. Refers to all eligible in delayed plus all eligible never-vaccinated in immediate group
b. For non-randomized participants the date of inclusion in the ring was used
c. Refers to all eligible participants (clusters) randomized to delayed/never vaccinated group
d. Efficacy calculation based on randomized participants who developed EVD ≥ 10 day after randomization

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GRADE Evidence Assessment Criteria

- **Initial evidence type (certainty level) determined by study design**
  - Initial evidence type 1 (high certainty): A body of evidence from randomized controlled trials
  - Initial evidence type 3 (low certainty): A body of evidence from observational studies
- **Risk of bias:** Can include failure to conceal allocation, failure to blind, loss to follow-up. Risk of bias may vary across outcomes.
- **Inconsistency:** Criteria for evaluating include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2
- **Indirectness:** Considers the generalizability of the evidence to the original PICO components (i.e. pre-exposure immunization in the U.S. population)
- **Imprecision:** Considers the fragility of the relative and absolute effect measures based on the interpretation of the 95% CIs and the optimal information size
- **Other considerations:** Includes publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding

Overall Evidence Types (Certainty Levels)

- **Type 1 (high certainty):** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Type 2 (moderate certainty):** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Type 3 (low certainty):** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Type 4 (very low certainty):** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

Evidence Table: Development of Ebola-related symptomatic illness

Summary: rVSVΔG-ZEBOV-GP is effective at preventing Ebola virus disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rVSV-vaccine	no rVSV-vaccine	Relative (95% CI)	Absolute (95% CI)		
1 [9]	Randomized [a] (clusters)	not serious	not serious	serious [b]	serious [c]	none	0/51 (0.0%)	7/47 (14.9%)	**RR 0.06** [g] (0.0001 to 1.05)	**140 fewer per 1,000** (from 149 fewer to 7 more)	LOW Evidence type 3	CRITICAL
1 [9]	Observational [d] (participants)	not serious	not serious	serious [b]	not serious	strong association [e]	0/2108 [f] (0.0%)	16/3075 (0.5%)	**RR 0.04** [g] (0.0001 to 0.74)	**5 fewer per 1,000** (from 5 fewer to 1 fewer	MODERATE [e] Evidence type 2	CRITICAL

Note: Outcome assessed with laboratory confirmed case of EVD

Explanations

a. Henao-Restrepo 2017 was a cluster randomized trial where units of randomization were clusters; cluster-level data presented here
b. Concern for indirectness to US population: population consists of contacts and contacts of contacts of EVD case, ring vaccination strategy which may include post-exposure vaccination
c. Because this study was done at a time when the 2014-2015 West Africa outbreak was waning in Guinea and there are few events reported it does not meet optimal information size and suggests fragility in the estimate; 95% C.I. contains the potential for desirable as well as undesirable effects
d. Henao-Restrepo 2017 was a cluster randomized trial (i.e. units of randomization were clusters); participant-level data presented here
e. The concerns with indirectness pose no inflationary effect; therefore, the evidence was rated up based on a very large magnitude of effect from the 96% RR reduction and overall certainty was upgraded two levels
f. Denominator represents participants from the clusters randomized to received immediate vaccination
g. RR calculated using the standard continuity correction of 0.5

CI: Confidence interval; **RR:** Relative risk

Objective 2: Incidence of Arthralgia (0-42 days)

Summary: Arthralgia is more commonly reported among vaccine recipients compared to unvaccinated

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rVSV-ZEBOV vaccine	no rVSV-ZEBOV vaccine	Relative (95% CI)	Absolute (95% CI)		
6 [1,2,4,5,6,7]	Randomized trials	serious [a]	serious [b]	not serious	serious [c]	none	316/1874 (16.9%)	42/891 (4.7%)	**RR 2.55**[e] (0.94 to 6.91)	**73 more per 1,000** (from 3 fewer to 279 more)	VERY LOW Evidence type 4	CRITICAL
2 [3,6]	Observational studies	not serious	not serious	not serious	serious [d]	none	75/469 (16.0%)	8/99 (8.1%)	**RR 1.63**[e] (0.0001 to 986.24)	**51 more per 1,000** (from 81 fewer to 1,000 more)	VERY LOW Evidence type 4	CRITICAL

Note: Observational studies with no comparator groups are not included in evidence table, but would be considered of very low certainty (evidence type 4)

Explanations

a. Participants, healthcare personnel, and outcome assessors were not blinded in Huttner 2015 or Samai 2018 potentially influencing events reported for this subjective outcome. Concern for possible underreporting in Kennedy because arthralgia was only solicited at one week and at one month for the majority of participants; Huttner only solicited arthralgia for low dose participants

b. Concerns with heterogeneity (I^2=70%) some may be explained by concerns with risk of bias (poor randomization or outcome definition)

c. The 95% confidence interval includes potential for possible harms as well as benefits

d. Few events reported do not meet optimal information size and suggest fragility in the estimate.

e. RR calculated using the standard continuity correction of 0.5

CI: Confidence interval; **RR:** Relative risk

Outcome 3: Severity of arthralgia (0-42 days)

Summary: Severe (grade 3) arthralgia is more commonly reported among vaccine recipients compared to unvaccinated, but is overall uncommon

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rVSV-ZEBOV vaccine	no rVSV-ZEBOV vaccine	Relative (95% CI)	Absolute (95% CI)		
4 [1,5,6,7]	Randomized trials	serious [a]	not serious	not serious	serious [b]	none	2/333 (0.6%)	0/264 (0.0%)	**RR 6.40** [c] (0.0001 to 27950.69)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	LOW Evidence type 3	CRITICAL
2 [3,6]	Observational studies	not serious	not serious	not serious	serious [b]	none	No events of grade 3 arthralgia were reported among 469 vaccinated and 99 non-vaccinated participants [d]				VERY LOW Evidence type 4	CRITICAL

Note: Observational studies with no comparator groups are not included in evidence table, but would be considered of very low certainty (evidence type 4)

Explanations

a. Participants, healthcare personnel, and outcome assessors were not blinded in Huttner 2015 or Samai 2018 potentially influencing events reported for this subjective outcome. Huttner only solicited arthralgia for low dose participants.

b. Few events reported do not meet optimal information size and suggest fragility in the estimate.

c. Risk ratios (RR) were calculated using a 0.1 continuity correction due to low numbers of reported events.

d. Huttner 2015 did not solicit arthralgia for high-dose participants; these data were excluded from analysis.

CI: Confidence interval; **RR:** Relative risk

Outcome 4: Incidence of arthritis (5-56 days)

Summary: Arthritis is more commonly reported among vaccine recipients compared to unvaccinated

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rVSV-ZEBOV vaccine	no rVSV-ZEBOV vaccine	Relative (95% CI)	Absolute (95% CI)		
4 [1,2,4,5]	Randomized trials	serious [a]	not serious	not serious	serious [b]	none	39/1776 (2.2%)	16/868 (1.8%)	**RR 1.80**[d] (0.21 to 15.13)	**23 more per 1,000** (from 22 fewer to 400 more)	LOW Evidence type 3	CRITICAL
2 [3,6]	Observational studies	not serious	not serious	not serious	very serious [b,c]	none	43/520 (8.3%)	3/107 (2.8%)	**RR 2.06**[d] (0.0001 to 7739.16)	**33 more per 1,000** (from 28 fewer to 1,000 more)	VERY LOW Evidence type 4	CRITICAL

Note: Observational studies with no comparator groups are not included in evidence table, but would be considered of very low certainty (evidence type 4)

Explanations

a. Studies used variable definitions and methods for diagnosing and reporting arthritis. In addition, participants, healthcare personnel, and outcome assessors were not blinded in Huttner 2015 or Samai 2018 potentially influencing events reported for this subjective outcome.

b. The 95% CI includes the potential for possible harms, as well as possible benefit.

c. Few events reported do not meet optimal information size and suggest fragility in the estimate.

d. Risk ratios (RR) calculated using the standard continuity correction of 0.5

CI: Confidence interval; **RR:** Relative risk

Outcome 5: Vaccine-related pregnancy adverse events

Summary: The rate of pregnancy loss among pregnant women who received immediate vaccination was not significantly higher than the rate of pregnancy loss among unvaccinated pregnant women

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rVSV-ZEBOV vaccine	no rVSV-ZEBOV vaccine	Relative (95% CI)	Absolute (95% CI)		
1[8]	Observational	not serious [a]	not serious	serious [b]	very serious [c,d]	none	14/31 (45.2%)	11/33 (33.3%)	**RR 1.35** (0.73 to 2.52)	**117 more per 1,000** (from 90 fewer to 507 more)	VERY LOW Evidence type 4	CRITICAL

Note: Observational studies with no comparator groups are not included in evidence table, but would be considered of very low certainty (evidence type 4)

Explanations

a. Participants, study personnel, and outcome assessors were unblinded and could have potentially influenced risk behaviors, though likely did not have an impact on risk of bias

b. Legardy-Williams et al. report on the outcome of pregnancy loss as a measure of vaccine-related pregnancy adverse events; however, the study did not differentiate between spontaneous abortions (which includes induced abortion) and stillbirths. The outcome may not accurately distinguish between those events due to the vaccine. In addition, we are not certain about the events reported that are directly related to receipt of the vaccine.

c. The 95% CI includes the potential for possible harms, as well as possible benefit.

d. Few events reported do not meet optimal information size and suggest fragility in the estimate.

CI: Confidence interval; **RR:** Relative risk

Evidence Table: Detection of rVSV in blood/plasma by RT-PCR

Summary: rVSVΔG-ZEBOV-GP has been detected by RT-PCR in blood/plasma up to 14 days post-vaccination; however, true duration of shedding and potential for transmissibility is uncertain

Certainty assessment							Summary of Findings	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
8 [2,3,5,6,7,10,11,13]	Observational studies[a]	serious [b]	not serious	very serious [c]	not serious	none	Longest recorded positive RT-PCR in blood or plasma is 14 days post-vaccination; 26/691 (3.7%) positive at day 7; 1/501 (0.2%) vaccinees positive at day 14.	VERY LOW (Evidence type 4)	CRITICAL

Explanations

a. Outcome data was only collected from the vaccinated study arm from these studies; therefore they were considered observational for these outcomes

b. Not all who received the vaccine were tested; concern for incomplete outcome data. Heppner 2017: 46/60 were tested on day 3, 49/60 were tested on day 7, and 30/60 were tested on day 14.

c. The outcome of interest is transmissibility of the vaccine virus to humans or animals. No data is available for, so viral dissemination and shedding is assessed as an indirect surrogate. RT-PCR positivity is not synonymous with infectivity.

Evidence Table: RT-PCR detection of rVSV in saliva and urine

Summary: VSVΔG-ZEBOV-GP has been detected in saliva up to 14 days and urine up to 7 days post-vaccination; however, true duration of shedding and potential for transmissibility is uncertain

Certainty assessment							Summary of Findings	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
4[3,5,7,11]	Observational studies [a]	serious [b]	not serious	very serious [c]	not serious	none	Longest recorded positive RT-PCR in saliva is 14 days post-vaccination; 6/257 (2.3%) positive at day 7; 1/98 (1.0%) vaccinees positive at day 14. Longest recorded positive RT-PCR in urine is 7 days post-vaccination; 2/246 (0.8%) positive at day 7; 0/98 positive at day 14.	VERY LOW (Evidence type 4)	CRITICAL

Explanations

a. Outcome data was only collected from the vaccinated study arm from these studies; therefore they were considered observational for these outcomes

b. Not all who received the vaccine were tested; concern for incomplete outcome data. ElSherif: Virus in urine and saliva were only tested if viremia was detected at or above the level of quantification; Heppner 2017: 46/60 were tested on day 3, 49/60 were tested on day 7, and 30/60 were tested on day 14.

c. The outcome of interest is transmissibility of the vaccine virus to humans or animals. No data is available for, so viral dissemination and shedding is assessed as an indirect surrogate. RT-PCR positivity is not synonymous with infectivity.

Evidence Table: Vaccine-related serious adverse events

Summary: Vaccine-related SAEs are an uncommon occurrence

Certainty assessment							Summary of Findings	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
12 [1,3,4,5,6,7,10,11,12,13,14,15]	Observational studies [a]	not serious	not serious	not serious	not serious	none	Across 12 studies, 3/17,119 (0.02%) vaccinees were judged to have an SAE related to or possibly related to vaccination.	LOW (Evidence type 3)	CRITICAL

Explanations

a. Outcome data was only collected from the vaccinated study arm from these studies; therefore they were considered observational for these outcomes

b. Overall evidence type is 3 (low certainty) because these 12 studies were considered observational for these outcomes as data was only collected from the vaccinated study arm from these studies without a comparator; however there was no downgrading of the evidence.

Evidence Table: Development of Ebola-related symptomatic illness

Summary: rVSVΔG-ZEBOV-GP is effective at preventing Ebola virus disease

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	rVSV-vaccine	no rVSV-vaccine	Relative (95% CI)	Absolute (95% CI)		
1 [9]	Randomized [a] (clusters)	not serious	not serious	serious [b]	serious [c]	none	0/51 (0.0%)	7/47 (14.9%)	**RR 0.06** [g] (0.0001 to 1.05)	**140 fewer per 1,000** (from 149 fewer to 7 more)	LOW Evidence type 3	CRITICAL
1 [9]	Observational [d] (participants)	not serious	not serious	serious [b]	not serious	strong association [e]	0/2108 [f] (0.0%)	16/3075 (0.5%)	**RR 0.04** [g] (0.0001 to 0.74)	**5 fewer per 1,000** (from 5 fewer to 1 fewer	MODERATE [e] Evidence type 2	CRITICAL

Note: Outcome assessed with laboratory confirmed case of EVD

Explanations

a. Henao-Restrepo 2017 was a cluster randomized trial where units of randomization were clusters; cluster-level data presented here
b. Concern for indirectness to US population: population consists of contacts and contacts of contacts of EVD case, ring vaccination strategy which may include post-exposure vaccination
c. Because this study was done at a time when the 2014-2015 West Africa outbreak was waning in Guinea and there are few events reported it does not meet optimal information size and suggests fragility in the estimate; 95% C.I. contains the potential for desirable as well as undesirable effects
d. Henao-Restrepo 2017 was a cluster randomized trial (i.e. units of randomization were clusters); participant-level data presented here
e. The concerns with indirectness pose no inflationary effect; therefore, the evidence was rated up based on a very large magnitude of effect from the 96% RR reduction and overall certainty was upgraded two levels
f. Denominator represents participants from the clusters randomized to received immediate vaccination
g. RR calculated using the standard continuity correction of 0.5

CI: Confidence interval; **RR:** Relative risk

GRADE Evidence Assessment Criteria

- **Initial evidence type (certainty level) determined by study design**
  - Initial evidence type 1 (high certainty): A body of evidence from randomized controlled trials
  - Initial evidence type 3 (low certainty): A body of evidence from observational studies
- **Risk of bias:** Can include failure to conceal allocation, failure to blind, loss to follow-up. Risk of bias may vary across outcomes.
- **Inconsistency:** Criteria for evaluating include similarity of point estimates, extent of overlap of confidence intervals, and statistical criteria including tests of heterogeneity and I^2
- **Indirectness:** Considers the generalizability of the evidence to the original PICO components (i.e. pre-exposure immunization in the U.S. population)
- **Imprecision:** Considers the fragility of the relative and absolute effect measures based on the interpretation of the 95% CIs and the optimal information size
- **Other considerations:** Includes publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding

Overall Evidence Types (Certainty Levels)

- **Type 1 (high certainty):** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Type 2 (moderate certainty):** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Type 3 (low certainty):** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Type 4 (very low certainty):** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect