Review of GRADE & Overview of State Designated ETCs and Laboratory Response Network

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November 3, 2021

Overview

- Review outcomes evaluated by GRADE (presented during February 2020 meeting)
- State designated Ebola treatment centers
  - Define population
  - Review vaccine acceptability survey results
- Laboratory Response Network facilities
  - Define population
  - Review vaccine acceptability survey results

Review of GRADE: rVSVΔG-ZEBOV-GP Ebola vaccine (February 2020)

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 (BSL-4) 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 available 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)

Critical Outcomes Evaluated by GRADE

- **Benefits (Efficacy)**
  1. Development of Ebola-related symptomatic illness
- **Safety**
  1. Incidence of arthralgia
  2. Severity of arthralgia: events of grade 3 (severe) arthralgia
  3. Incidence of arthritis
  4. Vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within in 2 months of vaccination
  5. Detection of rVSV vaccine virus in blood or plasma (viremia), saliva (viral shedding), and urine (viral shedding)
  6. Serious adverse events related to vaccination

Benefits: Development of Ebola-related symptomatic illness

1 study with unvaccinated comparator [Henao-Restrepo, 2017]

- 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
  - **Vaccine efficacy at the cluster level: 100% [95% CI: 68.9 – 100, p=0.0045]**
  - **RR at the participant level: 0.04 [95% CI: 0.0001 – 0.74]**
  - **AR at the participant level: 5 fewer per 1,000 (from 5 fewer to 1 fewer)**

Safety: Incidence of Arthralgia (0-42 days)

8 studies with unvaccinated comparator solicited arthralgia within 0-42 days

- Included 6 randomized control trials:
  - Arthralgia reported in 316/1874 (16.9%) vaccinated participants compared to 42/891 (4.7%) nonvaccinated participants
  - **RR: 2.55 [95% CI: 0.94-6.91]**
  - **AR: 73 more per 1,000 (from 3 fewer to 279 more)**

Safety: Severity of Arthralgia (0-42 days)

6 studies with unvaccinated comparator reported arthralgia severity within 0-42 days

- Included 4 randomized control trials:
  - Grade 3 arthralgia reported in 2/333 (0.6%) vaccinated participants compared to 0/264 (0.0%) nonvaccinated participants
  - **RR: 6.40 [95% CI: 0.0001-27950.69]**
  - **AR: 0 fewer per 1,000 (from 0 fewer to 0 fewer)**

Safety: Incidence of Arthritis (5-56 days)

6 studies with unvaccinated comparator

- Included 4 randomized control trials
  - Arthritis reported in 39/1776 (2.2%) vaccinated participants compared to 16/868 (1.8%) nonvaccinated participants
  - **RR: 1.80 [95% CI: 0.21-15.13]**
  - **AR: 23 more per 1,000 (from 22 fewer to 400 more)**

3 studies performed synovial fluid testing

- Vaccine virus has been detected by RT-PCR in four out of seven vaccinated participants that have had synovial fluid tested

Safety: Vaccine-related adverse pregnancy outcomes

1 study with unvaccinated comparator [Legardy-Williams, 2020]

- Primary outcome: incidence of pregnancy loss in women inadvertently vaccinated while pregnant and women who became pregnant within 2 months of vaccination
  - Pregnancy loss experienced by 14/31 (45%) immediately vaccinated pregnant women compared to 11/33 (33%) unvaccinated pregnant women
  - **RR: 1.35 [95% CI 0.73-2.52]**
  - **AR: 117 more per 1,000 (from 90 fewer to 507 more)**
  - Overall, 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

Safety: Detection of rVSV vaccine virus in blood or plasma, saliva, and urine

Specimen type	Number of studies included in GRADE	Vaccine virus detected by rRT-PCR	Longest recorded positive rRT-PCR (dpv)	Culture of vaccine virus attempted	Vaccine virus detected by culture
Blood	8	Yes	14*	Yes†	No
Saliva	4	Yes	14*	No	Not performed
Urine	4	Yes	7*	No	Not performed
Skin vesicles‡	NA	Yes	20	Yes	Yes§

Abbreviation: dpv = days postvaccination; rRT-PCR = reverse transcriptase-polymerase chain reaction.

*One study also tested at 28 dpv and 0/38 samples were positive [Heppner, 2017]

†One study performed viral isolation on selected blood specimens, all negative [Agnandji, 2016]

‡Not included in GRADE assessment, data from Ervebo Package Insert

§ Of three participants with rash in one study, all were positive by rRT-PCR up to 17 dpv. Virus isolation was positive in one specimen with the highest RNA level 9 dpv [Agnandji, 2016]

Note: true estimate of duration of shedding is unknown because daily collection not performed

Safety: Vaccine-related serious adverse events

12 clinical trials and two additional publications reported on vaccine-related serious adverse events (SAEs)

- **3/17,119 (0.02%)** vaccinees judged to have a SAE related or possibly related to the vaccine were reported
  - 2 SAEs related to vaccination: a **febrile reaction** and **anaphylaxis**, both which resolved without sequelae [Henao-Restrepo, 2017]
  - 1 SAE possibly related to the vaccine: **influenza like illness**, which resolved without sequelae [Henao-Restrepo, 2017]
- An **additional case of anaphylaxis** was identified in data provided to the FDA and resolved without sequelae

GRADE Summary

Comparison: One dose rVSVΔG-ZEBOV-GP versus placebo or no vaccine in adults ≥18

Outcome	Design (# of studies)	Findings	Evidence type†
Benefits			
Prevent Ebola virus disease	RCT (1)	rVSVΔG-ZEBOV-GP is effective at preventing Ebola virus disease	**3**
Safety			
Incidence of arthralgia	RCT (6) Obs (1)	Arthralgia is more commonly reported among vaccine recipients compared to placebo	**4**
Severity of arthralgia	RCT (4) Obs (1)	Severe (grade 3) arthralgia is more commonly reported among vaccine recipients compared to placebo or unvaccinated, but is overall uncommon	**4**
Incidence of arthritis	RCT (5) Obs (1)	Arthritis is more commonly reported among vaccine recipients compared to placebo	**4**
Pregnancy-related adverse events due to vaccination	Obs (1)	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 Blood/plasma Saliva Urine	 Obs* (7) Obs* (4) Obs* (4)	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	Obs* (12)	Vaccine-related SAEs are an uncommon occurrence (3 events in 17,119 vaccine recipients across 12 studies)	**3**

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

†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

Populations of Interest

Recap of Ebola Virus Vaccine Session, February 2021

- Identified 2 additional U.S. populations at risk for *potential* occupational exposure to Ebola virus (species *Zaire ebolavirus*)
  - **Healthcare personnel* (HCP) at state designated Ebola Treatment Centers involved in the care and transport of suspect or confirmed EVD patients**
  - Individuals who work as laboratorians and support staff at Laboratory Response Network (LRN) facilities that handle replication competent Ebola virus (species *Zaire ebolavirus*)

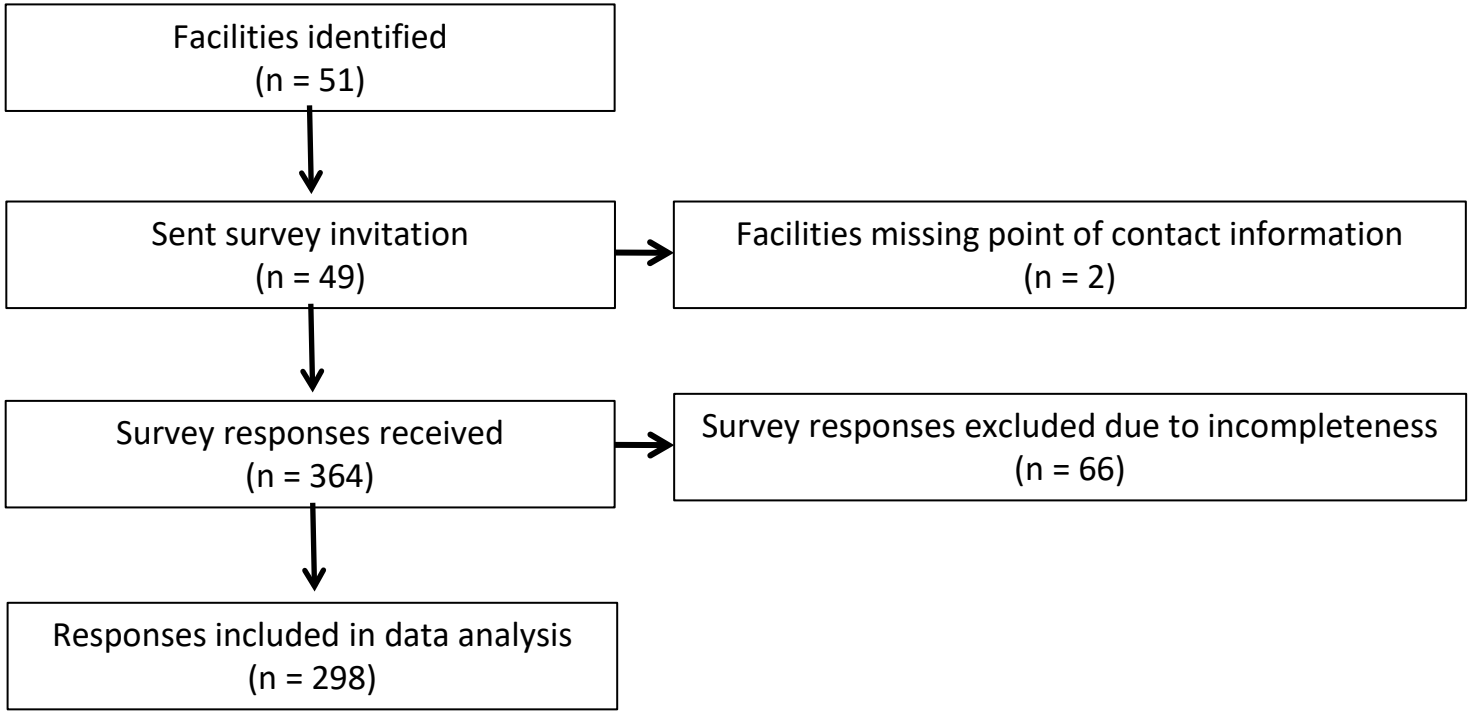
*See slide #31

State Designated ETCs

- Designated by states
- Council of State and Territorial Epidemiologists (CSTE) WG has determined the preferred terminology for these facilities: **Special Pathogens Treatment Centers (SPTC)**
- SPTCs have been defined as*:
  - Healthcare facilities that intend to receive and are able to provide care for a suspect or confirmed patient with Ebola virus disease (EVD) for the duration of their illness, as assessed by their state health department. In addition to EVD, these facilities may also be designated by the states to treat other high consequence pathogens.
- Currently **55 SPTC facilities** identified

*Definition adapted from: https://www.cdc.gov/vhf/ebola/healthcare-us/preparing/treatment-centers.html

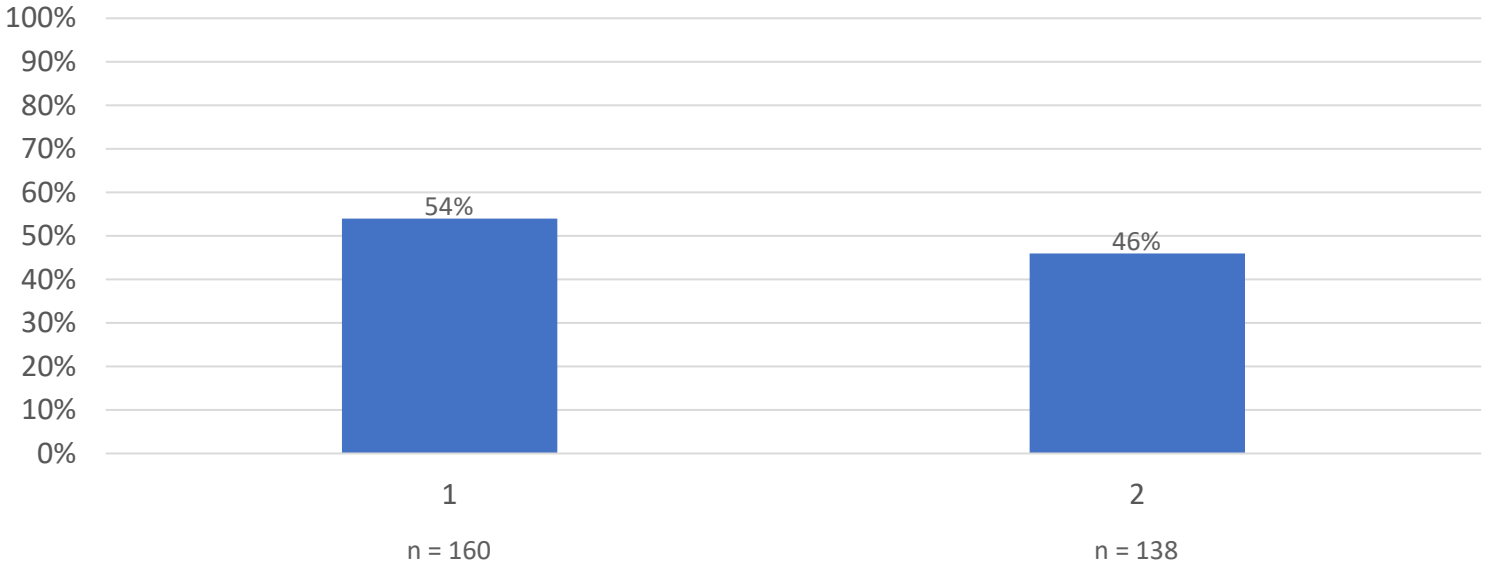
Vaccine Acceptability Survey: Special Pathogen Treatment Centers



Demographics: Profession (n = 298)

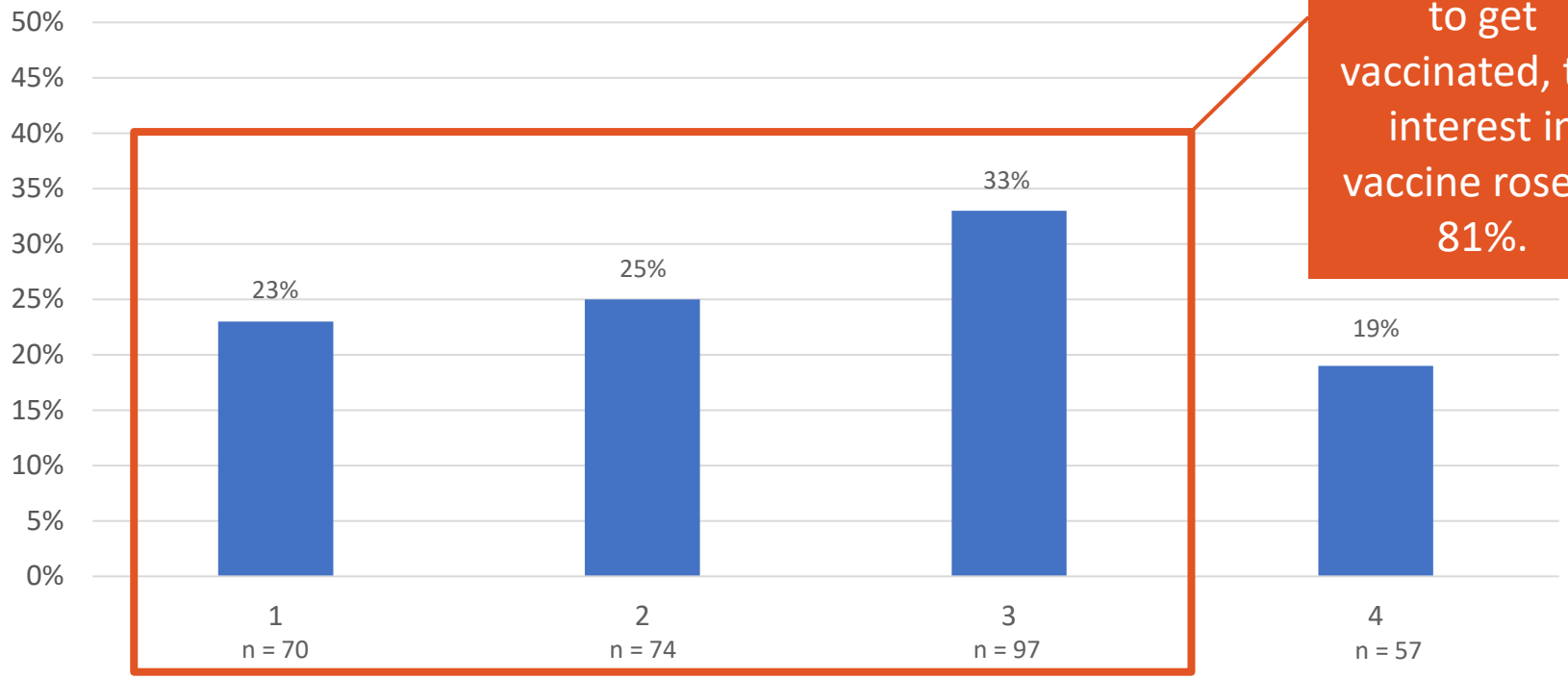
Profession	n	%
Nurse	116	39%
Doctor	67	22%
Respiratory Therapist	25	8%
EMT	22	7%
Advanced Practice Provider	22	7%
Laboratory Technician	20	7%
Manager/Safety Officer	14	5%
Other	9	3%
Environmental Services	3	1%

If you were eligible for vaccination and offered the rVSV Ebola vaccine today*, would you choose to be vaccinated? (n=298)



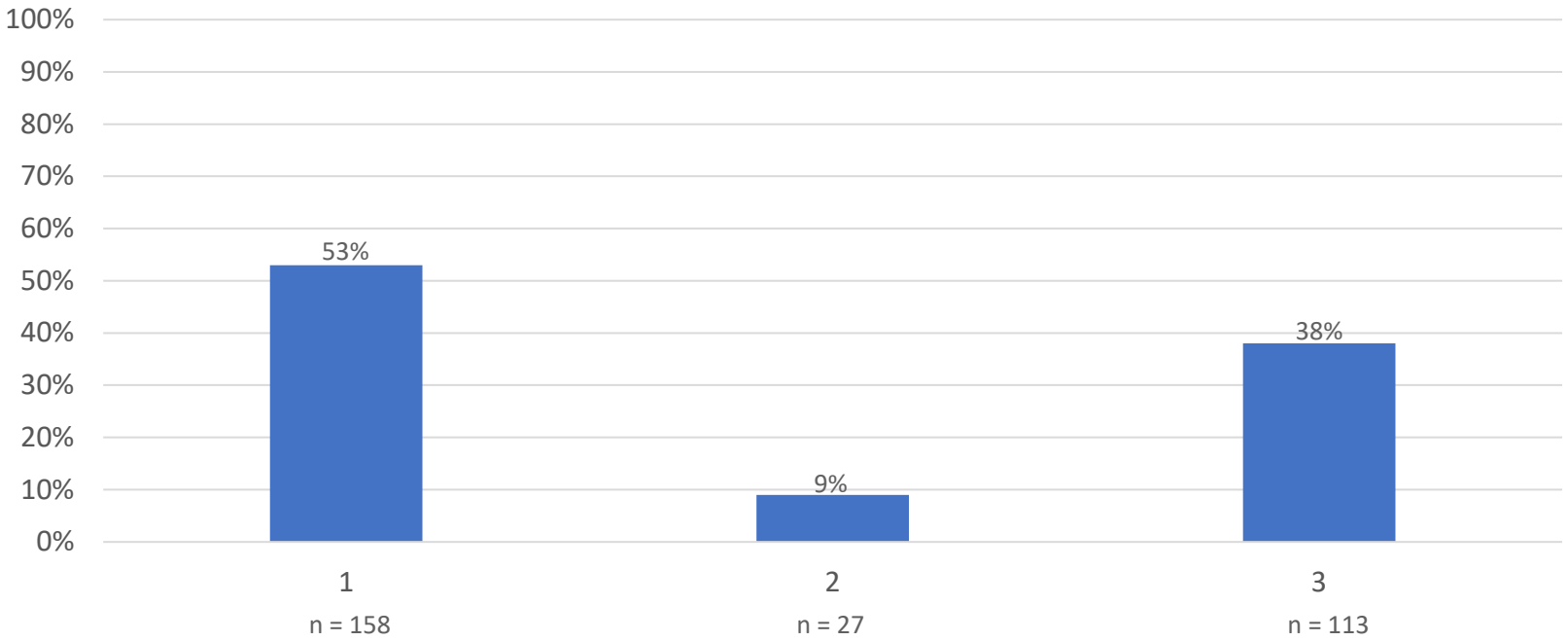
*Today refers to the time between October 14th – January 22nd 2021 when the individual took the survey. During this time, the Ebola outbreak in Equateur Province, DRC was declared over on November 18th, 2020.

When would you choose to get vaccinated: (n=298)



When we gave participants an option of choosing when to get vaccinated, the interest in vaccine rose to 81%.

Do you think ACIP should vote to “recommend” the rVSV vaccine to healthcare personnel at your facility[1]? (n=298)



*Did not ask about “Shared Clinical Decision Making”.

Conclusions

- **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%**
- Concern for a **serious adverse event** and **transmission of the vaccine virus** to others were top concerns for study participants

*Today refers to the time between October 14th – January 22nd 2021 when the individual took the survey. During this time, the Ebola outbreak in Equateur Province, DRC was declared over on November 18th, 2020.

Recap of Ebola Virus Vaccine Session, February 2021

- Identified 2 additional U.S. populations at risk for *potential* occupational exposure to Ebola virus (species *Zaire ebolavirus*)
  - Healthcare personnel* (HCP) at a state designated Ebola Treatment Centers involved in the care and transport of suspect or confirmed EVD patients
  - **Individuals who work as laboratorians and support staff at Laboratory Response Network (LRN) facilities that handle replication competent Ebola virus (species *Zaire ebolavirus*)**

*See slide #31

Defining Laboratory Response Network Facilities

- The Laboratory Response Network (LRN) quickly responds to biological and chemical threats and other public health emergencies
- Ebola testing is available at **~58 LRN labs** in the US
- Estimate 10-15 laboratorians who can do Ebola testing per facility

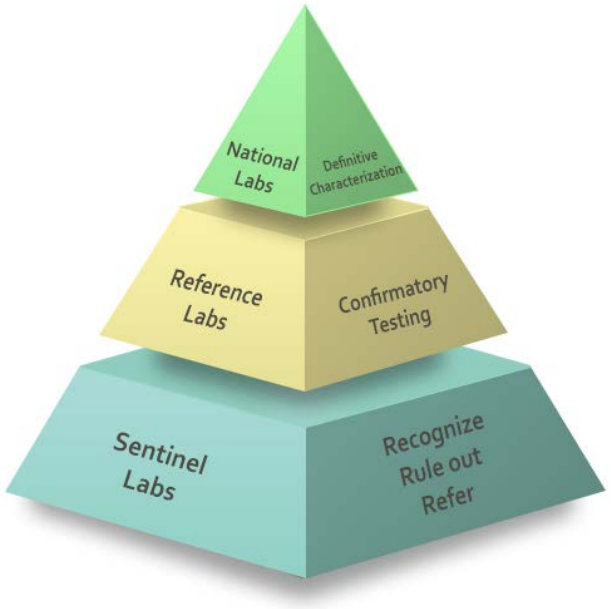
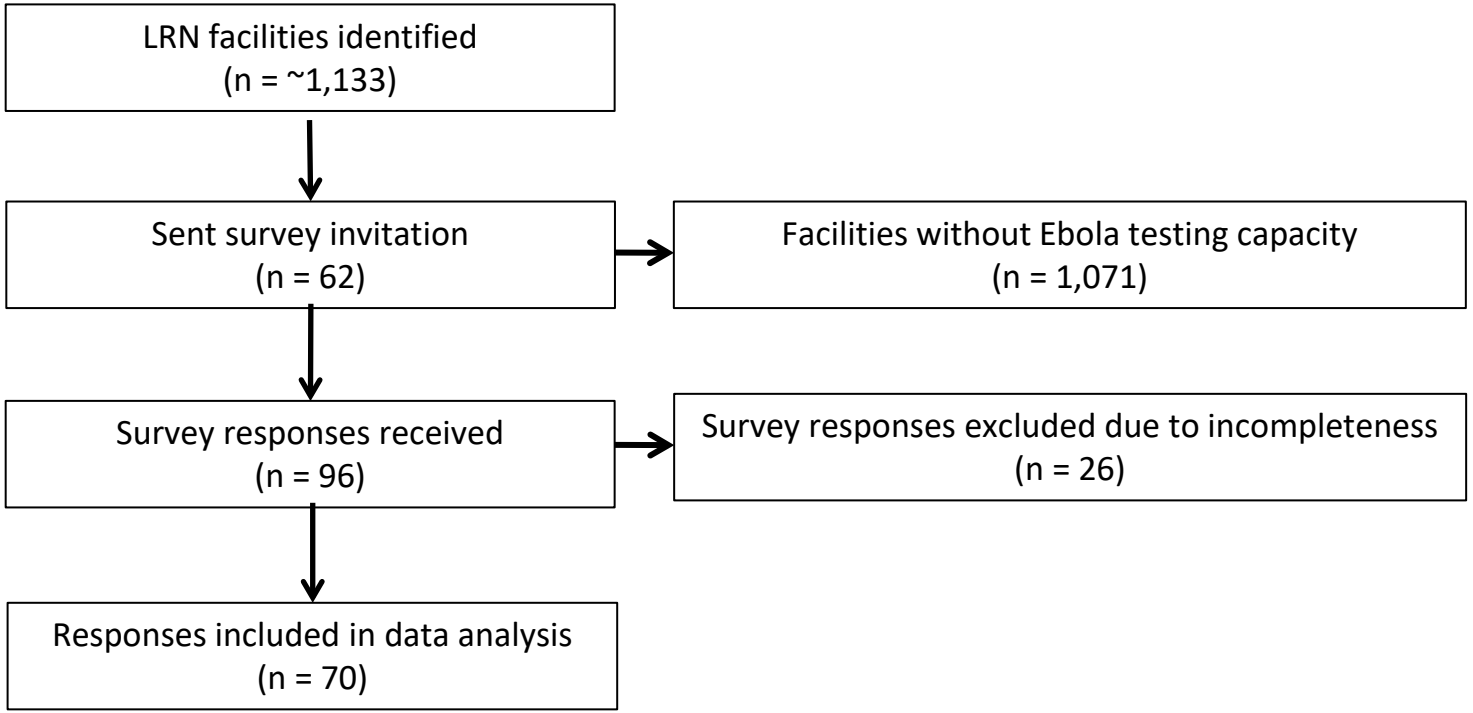


Image received from https://www.cdc.gov/anthrax/lab-testing/isitanthrax.html

Vaccine Acceptability Survey: Laboratory Response Network Facilities

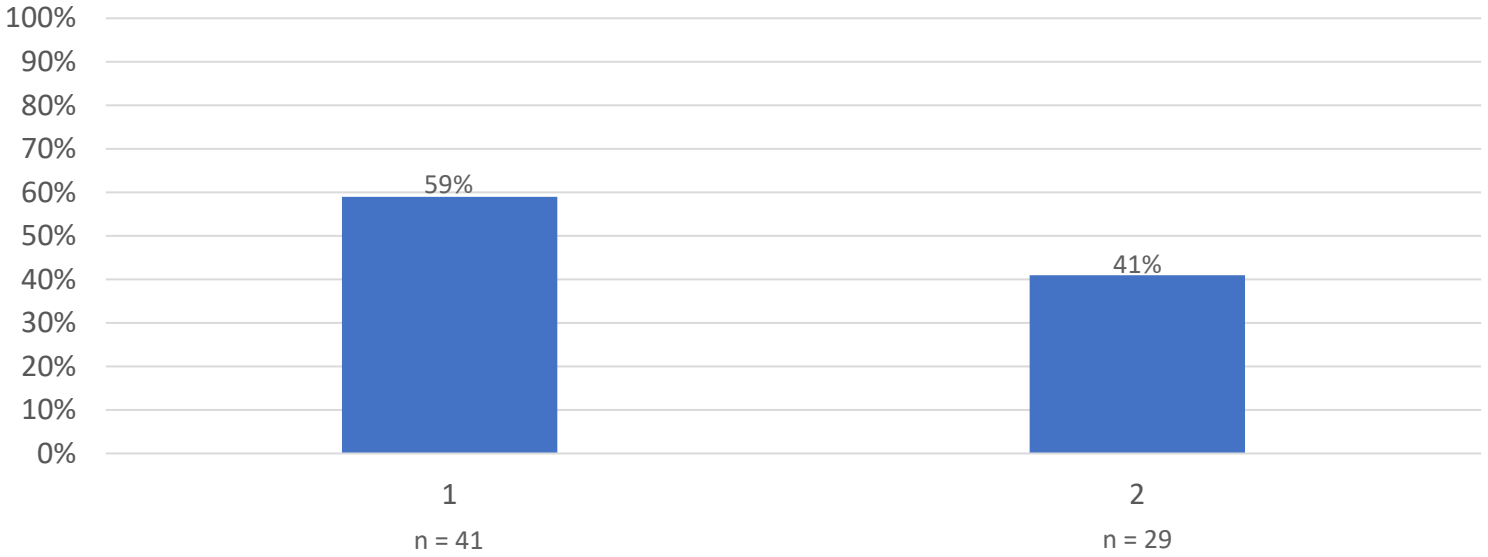


Demographics: Profession (n = 70)

Profession	n	%
Laboratory Scientist	45	64%
Management	21	30%
Other	4	6%

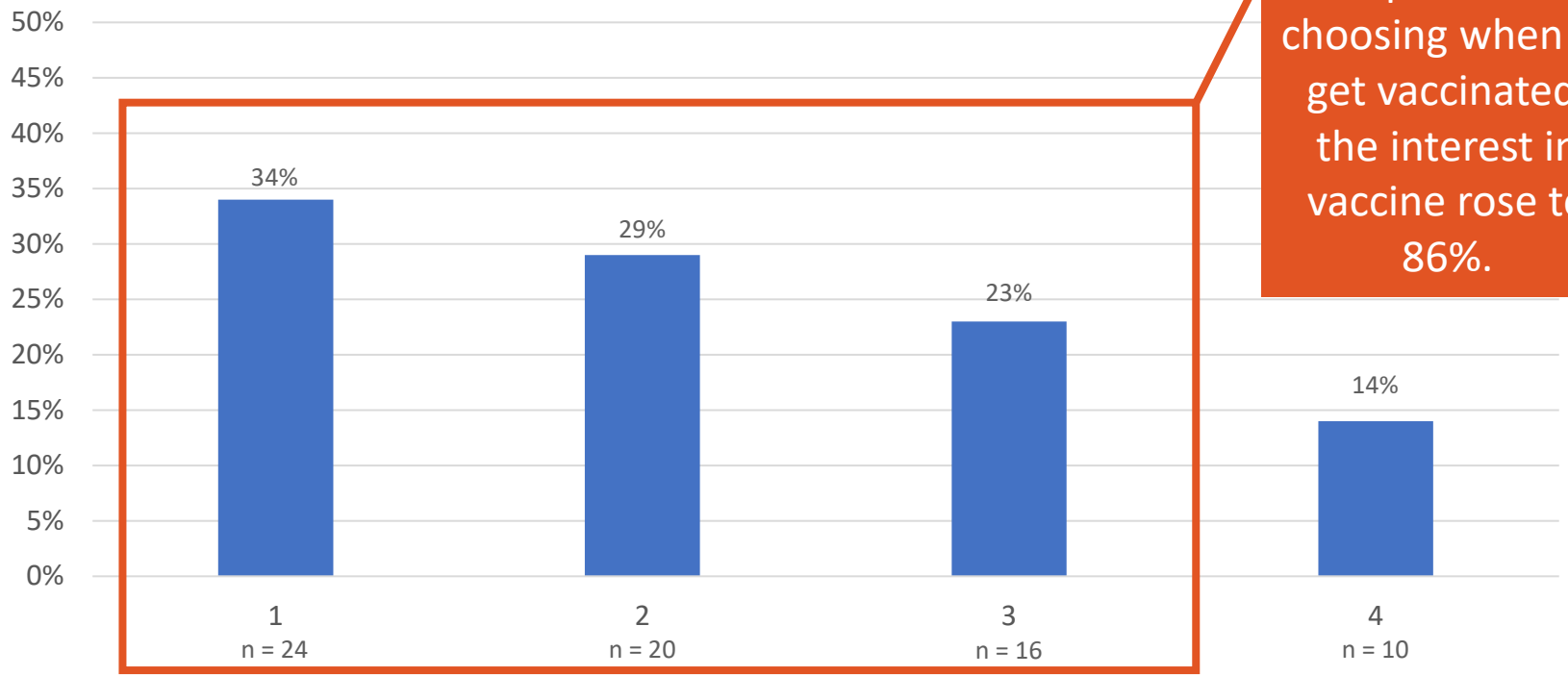
- Survey respondents were given the options of: laboratory scientist, clerk or receptionist, environmental services, manager, or other.
- Of the four individuals who self-identified as other, all four described themselves as Director or Laboratory Director.

If you were eligible for vaccination and offered the rVSV Ebola vaccine today*, would you choose to be vaccinated? (n=70)



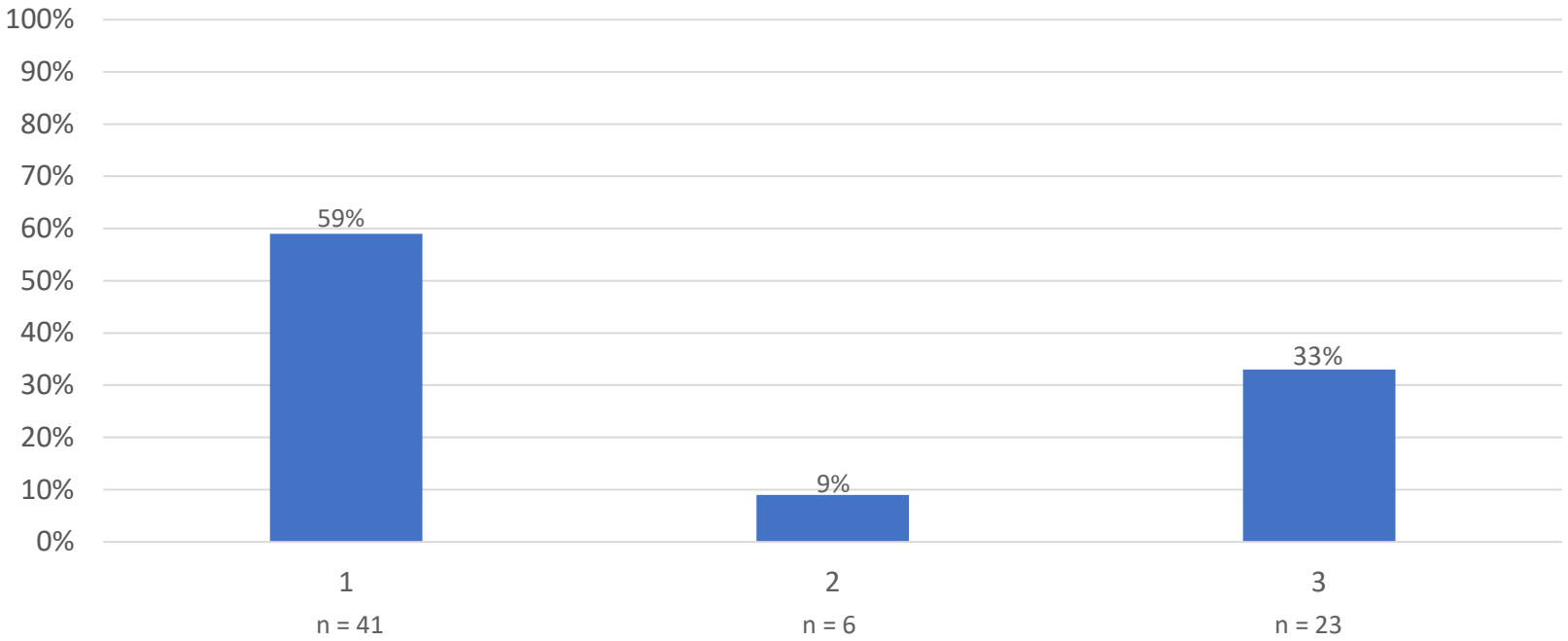
*Today refers to the time between December 29th – January 21st 2021 when the individual took the survey. During this time, there were no active Ebola virus outbreaks in the world.

When would you choose to get vaccinated (n=70):



When we gave participants an option of choosing when to get vaccinated, the interest in vaccine rose to 86%.

Do you think ACIP should vote to “recommend” the rVSV vaccine to staff at LRN facilities*? (n=70)



*Did not ask about “Shared Clinical Decision Making”.

Conclusions

- **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 US or their state), interest in vaccine increased to **86%**
- Common reasons for not wanting the vaccine were **low risk of exposure** and **concerns about potential side effects** (especially arthritis)

*Today refers to the time between December 29th – January 21st 2021 when the individual took the survey. During this time, there were no active Ebola virus outbreaks in the world.

Healthcare Personnel Definition

* 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

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.

Additional Slides

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?

Evidence Retrieval

- Literature search of multiple biomedical and interdisciplinary bibliographic databases including: Medline, Embase, Global Health, CINAHL, Cochrane Library, Scopus and Clinicaltrials.gov
- A broad and rigorous strategy incorporating terms related to the concept of vaccination against Ebola virus using the rVSVΔG-ZEBOV-GP vaccine, without date or language restrictions, was used to identify potentially relevant studies
- Results were compiled in an Endnote Library and duplicate records were removed
- The search was updated on January 31, 2020 to screen recent records not captured in the original search
- We contacted subject matter experts and the manufacturer in an effort to obtain unpublished or other relevant data not included in the search and received permission to use one additional record: Legardy-Williams, 2020 (now published)

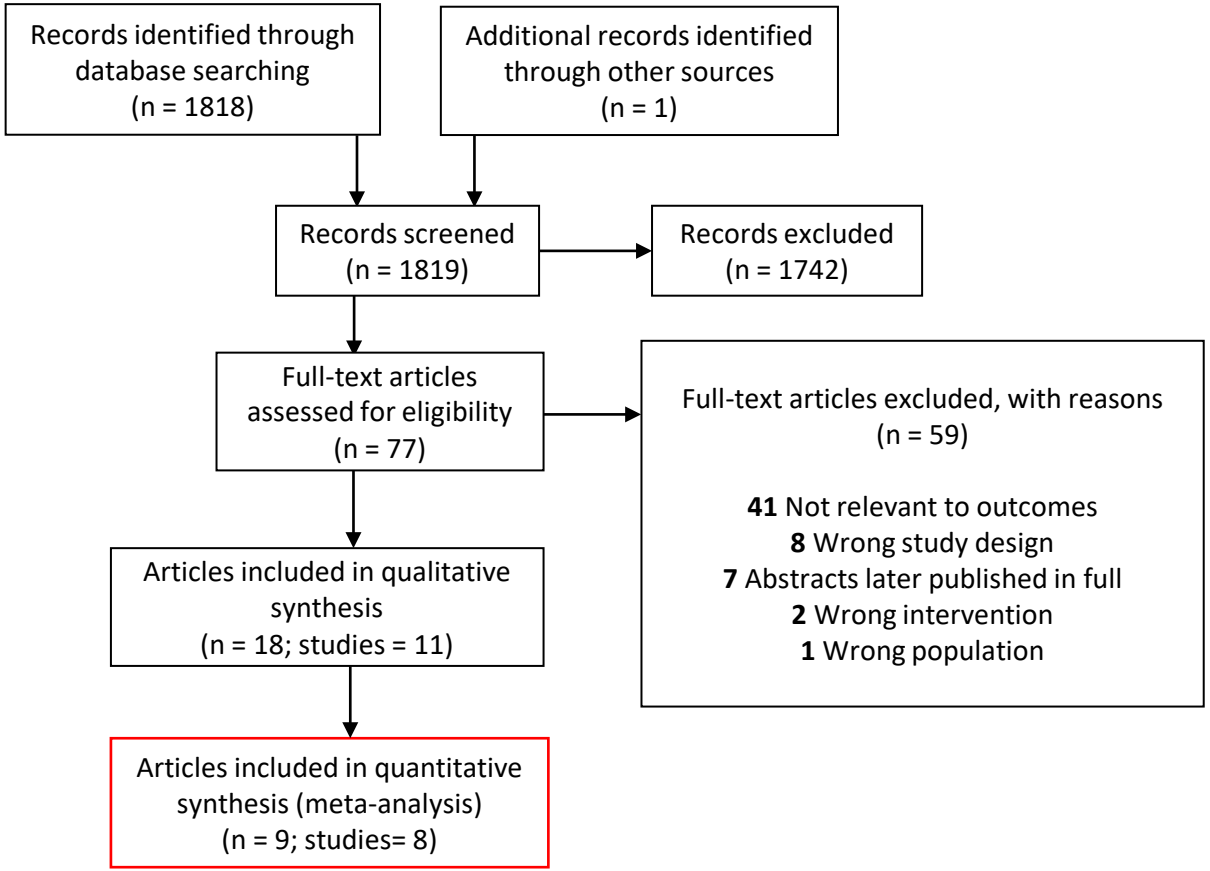
Evidence Retrieval (cont.)

Records were included if they presented data on the rVSVΔG-ZEBOV-GP Ebola virus vaccine **and**:

- Involved immunocompetent adults 18 years of age or older regardless of pregnancy status [a]
- Included data for intervention of interest (rVSVΔG-ZEBOV-GP, pre-exposure, single dose, any PFU)
- Included data relevant to the outcome measures being assessed
- Reported primary data from comparative or single-arm studies; randomized control trials, prospective or retrospective cohort, case-control, cross-sectional studies [b]

a. Data from animal or *in vitro* studies or data from humans <18 years of age were excluded
b. Records that did not provide primary data (e.g. literature reviews or summaries, editorials, commentaries, opinions, clinical trial registries or protocols) and case reports or case studies were excluded

Evidence Retrieval



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 [1,3,5,6,7,9,10,11,12,13,14,15]	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.

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