



# **Grading of Recommendations Assessment, Development and Evaluation (GRADE): rVSV $\Delta$ G-ZEBOV-GP Ebola vaccine**

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**Advisory Committee on Immunization Practices**

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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?**

|   |  |
|---|--|
| <b>Population</b>   | <p>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 <i>Zaire ebolavirus</i>); Subgroups: 1) Individuals responding to an outbreak of Ebola virus disease due to Ebola virus (species <i>Zaire ebolavirus</i>); 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</p>   |
| <b>Intervention</b>   | <p>Pre-exposure intramuscular immunization with a single licensed dose of the rVSVΔG-ZEBOV-GP vaccine</p>  |
| <b>Comparison</b>   | <p>No vaccine</p>  |
| <b>Outcomes deemed “Critical” or “Important” by ACIP Ebola vaccine Work Group</b> | <ul style="list-style-type: none"> <li>▪ Development of Ebola-related symptomatic illness (Critical)</li> <li>▪ Ebola-related mortality (Critical) –No Data</li> <li>▪ Vaccine-related joint pain or swelling (arthritis or arthralgia) (Critical)</li> <li>▪ Vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within in 2 months of vaccination (Critical)</li> <li>▪ Transmissibility of rVSV vaccine virus: Surrogate assessed with viral dissemination/shedding of the rVSV vaccine virus (Critical)</li> <li>▪ Serious adverse events related to the vaccination (Critical)</li> <li>▪ Incidence and severity of oral or skin vesicles (Important)</li> <li>▪ Interaction or cross-reactivity with monoclonal antibody-based therapeutics or other VSV-backed vaccines (Important)</li> </ul> |

|  |  |
|--|--|
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|   |   |
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# Critical Outcomes: Included for Meta-analysis

- **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)
  6. Detection of rVSV vaccine virus in saliva (viral shedding)
  7. Detection of rVSV vaccine virus in urine (viral shedding)
  8. Serious adverse events related to vaccination

# Critical Outcomes: Descriptive Analyses Only

- **Benefits (Efficacy)**

1. Development of Ebola-related symptomatic illness

- **Safety**

1. Incidence of arthralgia
2. Incidence of arthritis
3. Severity of arthralgia: events of grade 3 (severe) arthralgia
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)**
6. **Detection of rVSV vaccine virus in saliva (viral shedding)**
7. **Detection of rVSV vaccine virus in urine (viral shedding)**
8. **Serious adverse events related to vaccination**

# 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 rVSV $\Delta$ G-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

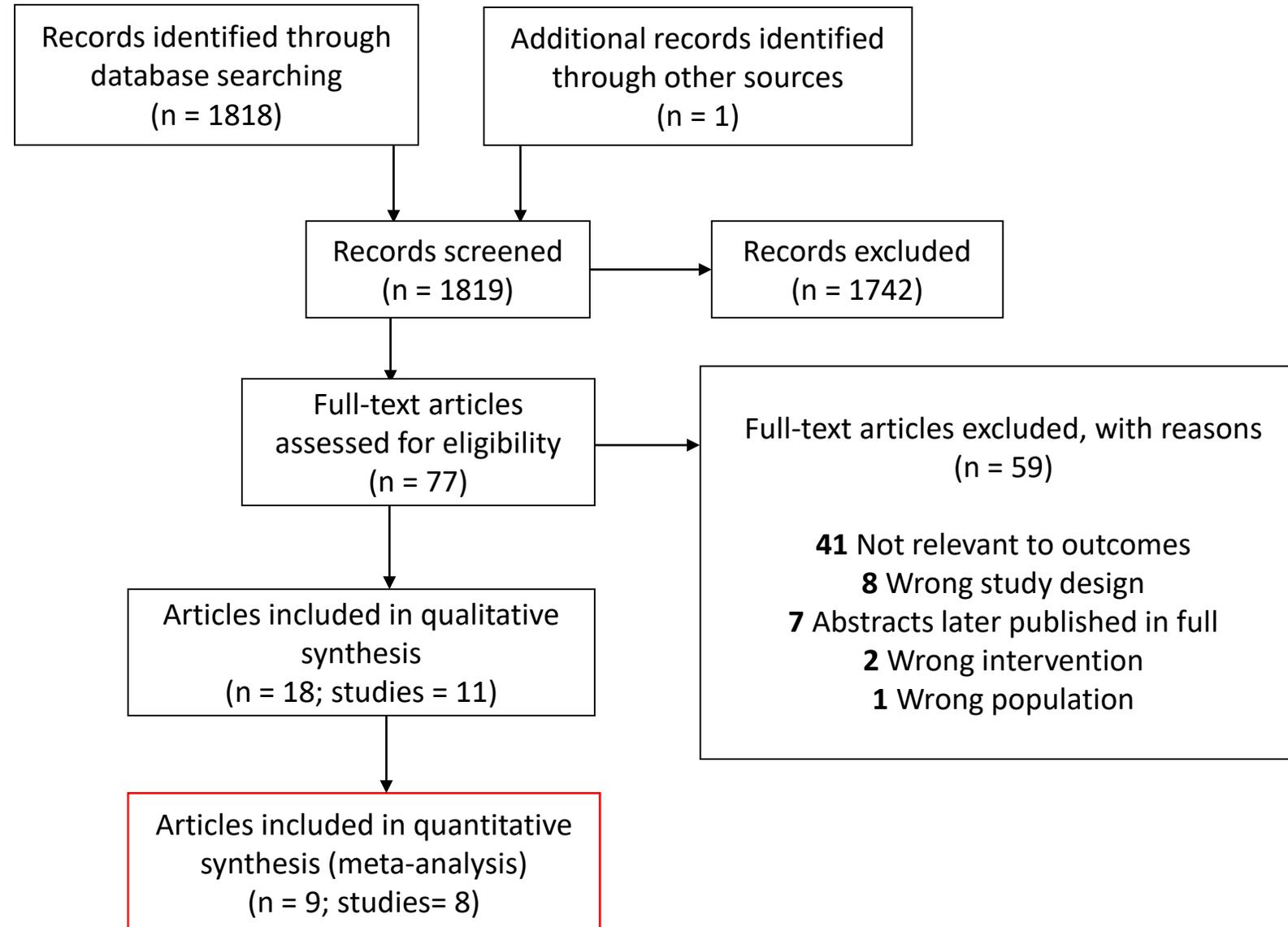
Records were included if they presented data on the rVSVΔG-ZEBOV-GP Ebola virus vaccine and:

- Involved immunocompetent adults 18 years of age or older regardless of pregnancy status <sup>a</sup>
- 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 <sup>b</sup>

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 effect

**Not measuring how well the individual studies were conducted, but how much confidence we have in the estimates of effect across each outcome**

## Evidence Profile Notes

- GRADE was conducted as it pertains to the specific population, intervention, comparison, and outcome (PICO) of interest
- Randomized control trial (RCT) refers to a trial which randomizes participants to an active intervention or a placebo or unvaccinated comparator arm
- Observational studies (Obs) refer to one-arm studies, studies for whom participants were not randomized, or studies that did not provide disaggregated data to allow for the comparison between randomized arms
- Evidence was also considered observational if only data from the vaccinated study arms were included in analysis for a given outcome

**Outcome 1: Development of Ebola-related  
symptomatic illness**

# 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<br>N=Participants (clusters) | Delayed/Never vaccinated<br>N= Participants (clusters) |
|--|---|--|
| All participants, randomized and non-randomized                                      | 3775 (70)   | 4507 (104) <sup>a</sup>                                |
| Development of EVD $\geq 10$ days after randomization, all participants <sup>b</sup> | 0 (0)   | 23 (11)  |
| Development of EVD $< 10$ days of randomization, all participants <sup>b</sup>       | 21 (11)   | 31 (22)  |
| Randomized participants  | 2108 (51)   | 3075 (47) <sup>c</sup>                                 |
| Development of EVD $\geq 10$ days after randomization, randomized participants       | 0 (0)   | 16 (7)   |

**Vaccine efficacy 100% (95% CI: 68.9 – 100, p=0.0045) <sup>d</sup>**

- 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  $\geq 10$  day after randomization

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# Evidence Table: Development of Ebola-related symptomatic illness

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

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

**Note: Outcome assessed with laboratory confirmed case of EVD**

## Explanations

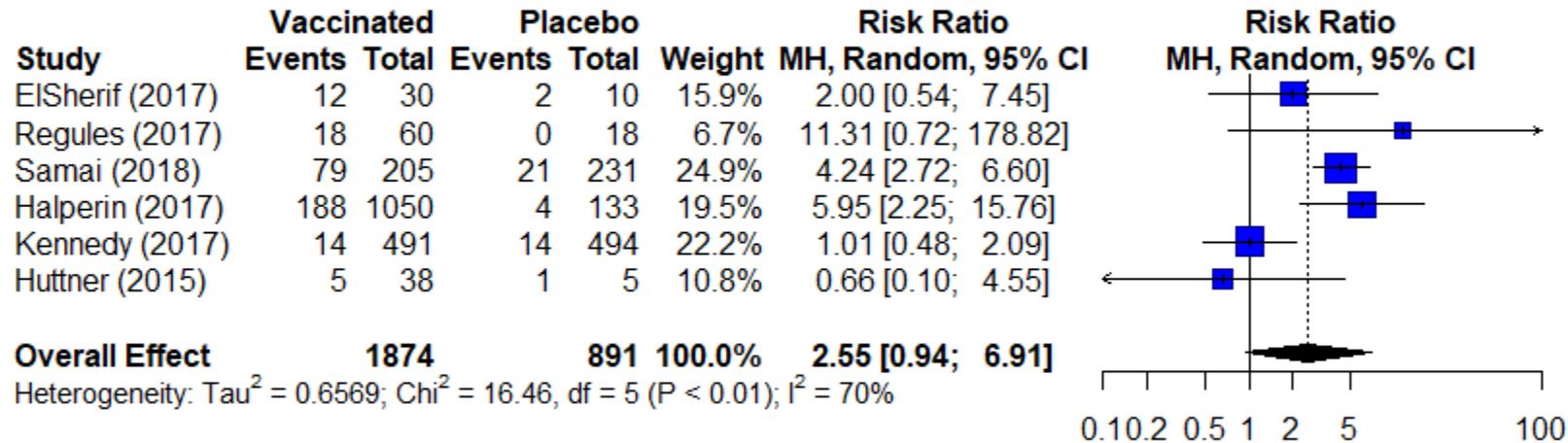
- Henao-Restrepo 2017 was a cluster randomized trial where units of randomization were clusters; cluster-level data presented here
- Concern for indirectness to US population: population consists of contacts and contacts of contacts of EVD case, ring vaccination strategy which may include post-exposure vaccination
- 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
- Henao-Restrepo 2017 was a cluster randomized trial (i.e. units of randomization were clusters); participant-level data presented here
- 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
- Denominator represents participants from the clusters randomized to received immediate vaccination
- RR calculated using the standard continuity correction of 0.5

CI: Confidence interval; RR: Relative risk

## **Outcome 2: Incidence of Arthralgia**

**Assessed with: Incidence of arthralgia or joint pain solicited within 0-42 days**

# Objective 2: Incidence of Arthralgia (0-42 days) Estimates of Effect – RCTs



## Additional Results:

- Two non-randomized studies with non-vaccinated comparators were analyzed in a separate analysis for this outcome (RR 1.63, [CI 0.0, 986.24]) [Heppner 2017; low dose, non-randomized participants in Huttner 2015]
- In 7 studies without a comparison group with 1,546/9,329 (16.5%) vaccinated participants reported arthralgia

## Considerations:

- Studies used variable definitions for arthralgia or in some cases a definition was not provided.
- Concern for underreporting because length and time of follow up/solicitation varied between studies; however, did not have an impact on effect estimates for this analysis.
- Data presented from across several doses of vaccine (strengths /varying PFUs); however, there does not seem to be a dose-response or effect on this outcome
- Huttner 2015 did not solicit arthralgia for high-dose participants; these data were excluded from analysis
- RR calculated using the standard continuity correction of 0.5

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

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

| Certainty assessment |                       |                      |                      |              |                      |                      | No of patients     |                       | Effect                                     |   | Certainty                   | Importance |
|----------------------|-----------------------|----------------------|----------------------|--------------|----------------------|----------------------|--------------------|-----------------------|--|---|-----------------------------|------------|
| No 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<br>1,2,4,5,6,7     | Randomized trials     | serious <sup>a</sup> | serious <sup>b</sup> | not serious  | serious <sup>c</sup> | none                 | 316/1874 (16.9%)   | 42/891 (4.7%)         | RR 2.55 <sup>e</sup><br>(0.94 to 6.91)     | <b>73 more per 1,000</b><br>(from 3 fewer to 279 more)    | VERY LOW<br>Evidence type 4 | CRITICAL   |
| 2 <sup>3</sup>       | Observational studies | not serious          | not serious          | not serious  | serious <sup>d</sup> | none                 | 75/469 (16.0%)     | 8/99 (8.1%)           | RR 1.63 <sup>e</sup><br>(0.0001 to 986.24) | <b>51 more per 1,000</b><br>(from 81 fewer to 1,000 more) | VERY LOW<br>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

- 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
- Concerns with heterogeneity ( $I^2=70\%$ ) some may be explained by concerns with risk of bias (poor randomization or outcome definition)
- The 95% confidence interval includes potential for possible harms as well as benefits
- Few events reported do not meet optimal information size and suggest fragility in the estimate.
- RR calculated using the standard continuity correction of 0.5

CI: Confidence interval; RR: Relative risk

## **Outcome 3: Severity of arthralgia**

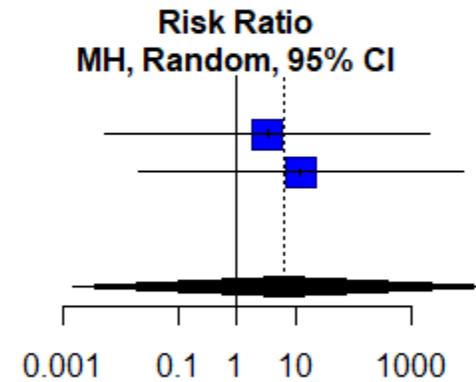
**Assessed with: Incidence of severe (Grade 3) arthralgia solicited 0 – 42 days**

**Defined as: significant joint pain or discomfort that prevents daily activity**

# Outcome 3: Incidence of severe (grade 3) arthralgia (0-42 days)

## Estimates of Effect – RCTs

| Study   | Vaccinated |       | Placebo    |       | Weight        | Risk Ratio                   |
|---|------------|-------|------------|-------|---------------|------------------------------|
|   | Events     | Total | Events     | Total |               | MH, Random, 95% CI           |
| ElSherif (2017)   | 0          | 30    | 0          | 10    | 0.0%          |                              |
| Regules (2017)  | 1          | 60    | 0          | 18    | 50.1%         | 3.31 [0.01; 2100.61]         |
| Samai (2018)  | 1          | 205   | 0          | 231   | 49.9%         | 12.39 [0.02; 8006.95]        |
| Huttner (2015)  | 0          | 38    | 0          | 5     | 0.0%          |                              |
| <b>Overall Effect</b>   | <b>333</b> |       | <b>264</b> |       | <b>100.0%</b> | <b>6.40 [0.00; 27950.69]</b> |
| Heterogeneity: Tau <sup>2</sup> = 0.0335; Chi <sup>2</sup> = 0.08, df = 1 (P = 0.78); I <sup>2</sup> = 0% |            |       |            |       |               |                              |



### Additional Results:

- Two non-randomized studies with non-vaccinated comparators were analyzed in a separate analysis and reported no events of grade 3 arthralgia among 469 vaccinated and 99 non-vaccinated participants [Heppner 2017; low dose, non-randomized participants in Huttner 2015]
- In 5 non-RCTs/observational studies with 7/7,209 (0.1%) vaccinated participants reported grade 3 arthralgia
- Halperin 2017 reported 14/1050 vs 0/133 severe arthralgia in vaccinated vs unvaccinated arms, respectively, during the follow up of 1 week to 6 months; however, de-aggregated data for 0-42 day period of follow up was not reported so this data were not included in these analyses

### Considerations:

- Studies used variable definitions for arthralgia or in some cases a definition was not provided.
- Concern for underreporting because length and time of follow up/solicitation varied between studies; however, did not have an impact on effect estimates for this analysis. There is a concern that pooling these data may under-estimate incidence because of this variability
- Data presented from across several doses of vaccine (strengths /varying PFUs); however, there does not seem to be a dose-response or effect on this outcome
- Huttner 2015 did not solicit arthralgia for high-dose participants; these data were excluded from analysis
- Risk ratios (RR) were calculated using a 0.1 continuity correction due to low numbers of reported events

# 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 |                       |                      |               |              |                      |                      | No of patients   |                       | Effect   |   | Certainty              | Importance |
|----------------------|-----------------------|----------------------|---------------|--------------|----------------------|----------------------|--|-----------------------|--|---|------------------------|------------|
| No 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 <sup>1,5,6,7</sup> | Randomized trials     | serious <sup>a</sup> | not serious   | not serious  | serious <sup>b</sup> | none                 | 2/333 (0.6%)   | 0/264 (0.0%)          | <b>RR 6.40<sup>c</sup></b><br>(0.0001 to 27950.69) | <b>0 fewer per 1,000</b><br>(from 0 fewer to 0 fewer) | LOW<br>Evidence type 3 | CRITICAL   |
| 2 <sup>3,6</sup>     | Observational studies | not serious          | not serious   | not serious  | serious <sup>b</sup> | none                 | No events of grade 3 arthralgia were reported among 469 vaccinated and 99 non-vaccinated participants <sup>d</sup> |                       |  | VERY LOW<br>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

- 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.
- Few events reported do not meet optimal information size and suggest fragility in the estimate.
- Risk ratios (RR) were calculated using a 0.1 continuity correction due to low numbers of reported events.
- Huttner 2015 did not solicit arthralgia for high-dose participants; these data were excluded from analysis.

# **Outcome 4: Incidence of arthritis**

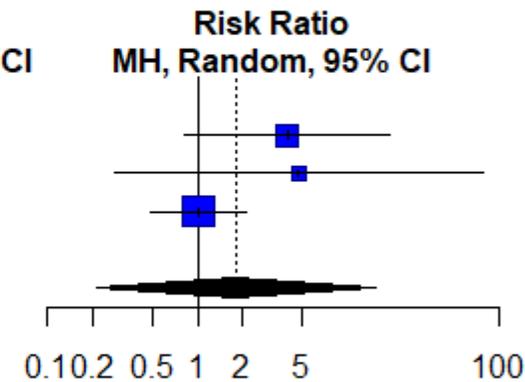
**Assessed with: Event of arthritis within 5-56 days**

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

## Estimates of Effect – RCTs

| Study                 | Vaccinated  |       | Placebo    |       | Weight        | Risk Ratio         |                      |
|-----------------------|-------------|-------|------------|-------|---------------|--------------------|----------------------|
|                       | Events      | Total | Events     | Total |               | MH, Random, 95% CI |                      |
| EISherif (2017)       | 0           | 30    | 0          | 10    | 0.0%          |                    |                      |
| Samai (2018)          | 7           | 205   | 2          | 231   | 29.2%         | 3.94               | [0.83; 18.77]        |
| Halperin (2017)       | 18          | 1050  | 0          | 133   | 12.0%         | 4.70               | [0.29; 77.57]        |
| Kennedy (2017)        | 14          | 491   | 14         | 494   | 58.8%         | 1.01               | [0.48; 2.09]         |
| <b>Overall Effect</b> | <b>1776</b> |       | <b>868</b> |       | <b>100.0%</b> | <b>1.80</b>        | <b>[0.21; 15.13]</b> |

Heterogeneity:  $\text{Tau}^2 = 0.3480$ ;  $\text{Chi}^2 = 3.19$ ,  $\text{df} = 2$  ( $P = 0.20$ );  $I^2 = 37\%$



### Additional Results:

- Two non-randomized studies with non-vaccinated comparators (Huttner 2015; Heppner 2017) were analyzed in a separate analysis with consistent effect size and lower precision for this outcome (RR 2.06, [0.00, 7739.16])
- In 2 studies without a comparison group 2/50 (4%) vaccinated participants reported arthritis

### Considerations:

- Studies defined and worked up arthritis with considerable variability.
  - Kennedy 2017: Concern for underreporting because low % of female enrolled participants (37%); Kennedy only solicited at week 1 and at month 1
  - Samai 2018: No capability of clinical diagnosis of arthritis, no rheumatology services available in Sierra Leone
  - EISherif 2017: Did not provide definition for arthritis
  - Huttner 2015: first to encounter arthritis, so thoroughly clinically investigated arthritis (all participants with arthritis referred to rheumatologist, all but 2 participants with arthritis had an u/s done); this study not included in RCT analysis because arthritis only reported in low dose participants and upon request de-aggregated data was unavailable
- Concern for underreporting because length and time of follow up/solicitation varied between studies; however, did not have an impact on effect estimates for this analysis. There is a concern that pooling these data may under-estimate incidence because of this variability
- Data presented from across several doses of vaccine (strengths /varying PFUs); however, there does not seem to be a dose-response or effect on this outcome
- Risk ratios (RR) calculated using the standard continuity correction of 0.5

# Synovial fluid testing summary

- Huttner 2015: Three participants with arthritis had synovial fluid tested via RT-PCR for vaccine virus
  - Two tested RT-PCR positive in synovial fluid
- Agnandji 2016: One synovial fluid specimen tested positive by RT-PCR on day 15; synovial viral isolation was negative
- Halperin 2017: Three participants with joint swelling had synovial fluid tested via RT-PCR for vaccine virus
  - One tested RT-PCR positive in synovial fluid on day 17 post- vaccination
  - Two tested negative (collection days 16 and 23 post-vaccination)
- **Summary:** Vaccine-virus has been detected by RT-PCR in four out of seven vaccinated participants that have had synovial fluid tested

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

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

| Certainty assessment |                       |                      |               |              |                             |                      | No of patients     |                       | Effect  |   | Certainty                   | Importance |
|----------------------|-----------------------|----------------------|---------------|--------------|-----------------------------|----------------------|--------------------|-----------------------|---|---|-----------------------------|------------|
| No 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 <sup>1,2,4,5</sup> | Randomized trials     | serious <sup>a</sup> | not serious   | not serious  | serious <sup>b</sup>        | none                 | 39/1776 (2.2%)     | 16/868 (1.8%)         | <b>RR 1.80<sup>d</sup></b><br>(0.21 to 15.13)     | <b>23 more per 1,000</b><br>(from 22 fewer to 400 more)   | LOW<br>Evidence type 3      | CRITICAL   |
| 2 <sup>3,6</sup>     | Observational studies | not serious          | not serious   | not serious  | very serious <sup>b,c</sup> | none                 | 43/520 (8.3%)      | 3/107 (2.8%)          | <b>RR 2.06<sup>d</sup></b><br>(0.0001 to 7739.16) | <b>33 more per 1,000</b><br>(from 28 fewer to 1,000 more) | VERY LOW<br>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

- 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.
- The 95% CI includes the potential for possible harms, as well as possible benefit.
- Few events reported do not meet optimal information size and suggest fragility in the estimate.
- Risk ratios (RR) calculated using the standard continuity correction of 0.5

CI: Confidence interval; RR: Relative risk

**Outcome 5: Vaccine-related adverse pregnancy outcomes for women inadvertently vaccinated while pregnant and women who become pregnant within in 2 months of vaccination**

**Assessed with: pregnancy loss (defined as spontaneous abortion and stillbirth)**

## Outcome 5: Vaccine-related adverse pregnancy outcomes

### Studies with non-vaccinated comparator (n=1)

Legardy-Williams, 2020: Non-randomized sub-study of STRIVE

- **14/31 (45%) immediately vaccinated** pregnant women experienced pregnancy loss compared to **11/33 (33%) unvaccinated** pregnant women (RR 1.35 [95% CI 0.73-2.52])
- 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
- Among live births no external congenital anomalies were detected
- Further studies with larger sample sizes would be needed to rule out a meaningful difference in the percentage of pregnancy loss, pregnancy complications, or birth defects

# Outcome 5: Vaccine-related adverse pregnancy outcomes

## Additional safety studies with no comparator, n=3

- Summary: Among 3 studies with no comparison groups, there were 3 adverse pregnancy outcomes out of 20 pregnancies (19 women); however, no conclusions can be made regarding the relationship between vaccination and adverse pregnancy outcomes based on these data

| Study Type | Studies                       | Total # vaccinated | Summary of Findings   |
|------------|-------------------------------|--------------------|---|
| RCT<br>N=1 | Halperin, 2017 <sup>a</sup>   | N= 1,042/1,061     | <ul style="list-style-type: none"> <li>5 pregnancies reported during the first 42 days post-vaccination</li> <li><b>2/5 lost to follow-up</b></li> <li><b>1/5 experienced spontaneous abortion</b></li> </ul> |
| Obs<br>N=2 | Agnandji, 2017 <sup>b</sup>   | N= 115             | <ul style="list-style-type: none"> <li>3 pregnancies reported, EDC not known</li> <li><b>0/3 experienced adverse pregnancy outcomes</b></li> </ul>  |
|            | Juan-Giner, 2019 <sup>c</sup> | N= 2,016           | <ul style="list-style-type: none"> <li>12 pregnancies in 11 women reported</li> <li><b>2/11 women experienced adverse pregnancy outcomes<sup>3</sup></b></li> </ul>   |

- Pregnancy data not reported for control group
- Dose-response study, no unvaccinated/placebo group included
- One miscarriage in 24yo woman at 5 week gestation, she was vaccinated 34 days after her last menstruation, she became pregnant 4 months later and gave birth to a healthy baby; 1 stillbirth in 21yo woman at 41 weeks, she was vaccinated 37 days after her last menstruation, she had a stillbirth 2 years prior.

# 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 |               |                          |               |                      |                             |                      | No of patients     |                       | Effect                        |   | Certainty                   | Importance |
|----------------------|---------------|--------------------------|---------------|----------------------|-----------------------------|----------------------|--------------------|-----------------------|-------------------------------|---|-----------------------------|------------|
| No 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 <sup>8</sup>       | Observational | not serious <sup>a</sup> | not serious   | serious <sup>b</sup> | very serious <sup>c,d</sup> | none                 | 14/31 (45.2%)      | 11/33 (33.3%)         | <b>RR 1.35</b> (0.73 to 2.52) | <b>117 more per 1,000</b> (from 90 fewer to 507 more) | VERY LOW<br>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

- 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
- 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.
- The 95% CI includes the potential for possible harms, as well as possible benefit.
- Few events reported do not meet optimal information size and suggest fragility in the estimate.

# **Outcome 6a: Transmissibility of vaccine virus (Surrogate: vaccine virus dissemination)**

**Assessed with: Detection of rVSV in blood/plasma by RT-PCR**

# Outcome 6a: Detection of rVSV in blood/plasma by RT-PCR

## Summary of Findings , n=8

- **Summary:** Longest recorded positive in blood/plasma was day 14 post vaccination [Heppner, 2017]<sup>a</sup>
  - True estimate of duration of viremia is unknown because daily collection not performed
- One study performed viral isolation on selected blood specimens, all negative [Agnandji, 2016]<sup>c</sup>

| Study                      | Limit of detection (copies/mL RNA) | RT-PCR + Day 7 / n (%) | RT-PCR + Day 14 / n (%) |
|----------------------------|------------------------------------|------------------------|-------------------------|
| ElSherif 2017              | NR                                 | 0/30 (0%)              | 0/30 (0%)               |
| Heppner 2017 <sup>a</sup>  | 62.5                               | 2/406 (0.5%)           | 1/403 (0.2%)            |
| Regules 2017               | NR                                 | 12/60 (20%)            | 0/30 (0%)               |
| Agnandji 2016 <sup>b</sup> | < 100                              | 5/40 (12.5%)           | No testing after day 7  |
| Huttner 2015               | < 100                              | 2/95 (2%)              | No testing after day 7  |
| Agnandji 2017              | < 100                              | 5/30 (17%)             | No testing after day 7  |
| Dahlke 2017                | < 200                              | 0/30 (0%)              | 0/30 (0%)               |
| Kennedy 2017 <sup>c</sup>  | NR                                 | No testing on day 7    | 0/8 (0%)                |
| <b>Total</b>               | --                                 | <b>26/691 (3.7%)</b>   | <b>1/501 (0.2%)</b>     |

a. Heppner 2017 also collected at d28 0/38 were positive

b. Agnandji 2016: Data presented only include Kilifi study site, as the other three sites (Geneva, Lamberene, Hamburg) are presented in Huttner, Agnandji 2017, and Dahlke, respectively

c. Kennedy 2017: Plasma from vaccinees tested by RT-PCR on day 3, 10, and 14; 2/8 positive on day 3, and 1/8 positive on day 10. 0/8 positive on day 14

# 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 |
|-----------------------------|------------------------------------|----------------------|---------------|---------------------------|-------------|----------------------|--|-------------------------------|------------|
| No of studies               | Study design                       | Risk of bias         | Inconsistency | Indirectness              | Imprecision | Other considerations |  |                               |            |
| 8<br>2,3,5,6,7,10,<br>11,13 | Observational studies <sup>a</sup> | serious <sup>b</sup> | not serious   | very serious <sup>c</sup> | 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<br>(Evidence type 4) | CRITICAL   |

## Explanations

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

# **Outcome 6b: Transmissibility of vaccine virus (Surrogate: vaccine virus dissemination)**

**Assessed with: Detection of rVSV in saliva and urine by RT-PCR**

# Outcome 6b: Detection of rVSV in saliva and urine by RT-PCR

## Summary of Findings, n= 4

- Summary:** Longest recorded positive RT-PCR in saliva is 14 days and urine is 7 days post vaccination; however, true estimate of duration of shedding is unknown because daily collection not performed

| Study                        | Limit of detection (copies/mL RNA) | Saliva                 |                         | Urine                  |                         |
|------------------------------|------------------------------------|------------------------|-------------------------|------------------------|-------------------------|
|                              |                                    | RT-PCR + Day 7 / n (%) | RT-PCR + Day 14 / n (%) | RT-PCR + Day 7 / n (%) | RT-PCR + Day 14 / n (%) |
| Agnandji, 2016 <sup>a</sup>  | < 100;<br>< 200 Hamburg site       | 0/130 (0%)             | No testing after day 7  | 0/129 (0%)             | No testing after day 7  |
| ElSherif, 2017 <sup>b</sup>  | NR                                 | 0/30 (0%)              | 0/30 (0%)               | 0/30 (0%)              | 0/30 (0%)               |
| Heppner, 2017 <sup>c</sup>   | < 31.25                            | 0/38 (0%)              | 0/38 (0%)               | 1/38 (2.6%)            | 0/38 (0%)               |
| Regules, 2017 <sup>d,e</sup> | NR                                 | 6/59 (%)               | 1/30 (%)                | 1/49 (%)               | 0/30 (0%)               |
| <b>Total</b>                 | --                                 | <b>6/257 (2.3%)</b>    | <b>1/98 (1.0%)</b>      | <b>2/246 (0.8%)</b>    | <b>0/98 (0%)</b>        |

- Agnandji 2016: These data combine across 4 study sites (Geneva, Lamberene, Kilifi, Hamburg); limit of detection <100 refers to Geneva, Lamberene, Kilifi sites; in Geneva site samples were collected on day 7 +/- 2; did not test after day 7
- ElSherif 2017: Virus in urine and saliva were only tested if viremia was detected at or above the level of quantification.
- Heppner 2017: 0/38 positive on day 28
- Regules 2017: No further testing of saliva beyond day 14 was reported, although the paper mentions the cycle-threshold values for the day 14 sample was “near the lower-limit for detection”.
- Regules 2017: Not all who received the vaccine were tested. 30/60 were tested on day 1, 48/60 were tested on day 3, 59/60 were tested on day 7, and 30/60 were tested on day 14.

# 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 |
|-----------------------|------------------------------------|----------------------|---------------|---------------------------|-------------|----------------------|--|-------------------------------|------------|
| No of studies         | Study design                       | Risk of bias         | Inconsistency | Indirectness              | Imprecision | Other considerations |  |                               |            |
| 4 <sup>3,5,7,11</sup> | Observational studies <sup>a</sup> | serious <sup>b</sup> | not serious   | very serious <sup>c</sup> | not serious | none                 | <p>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.</p> <p>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.</p> | VERY LOW<br>(Evidence type 4) | CRITICAL   |

## Explanations

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

# **Outcome 7: Vaccine-related serious adverse events**

# Outcome 7: Vaccine-related Serious Adverse Events

## Summary of findings, n=12

- Across 12 studies, out of 19,184 people that received the vaccine, **3 SAEs** judged to be 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]
- **Summary: vaccine-related SAEs are rare**

# Evidence Table: Vaccine-related serious adverse events

Summary: Vaccine-related SAEs are an uncommon occurrence

| No of studies                                   | Study design                       | Certainty assessment |               |              |             |                      | Summary of Findings   | Certainty                | Importance |
|---|------------------------------------|----------------------|---------------|--------------|-------------|----------------------|---|--------------------------|------------|
|   |                                    | Risk of bias         | Inconsistency | Indirectness | Imprecision | Other considerations |   |                          |            |
| 12<br>1,3,4,5,6<br>,7,10,11,<br>12,13,14<br>,15 | Observational studies <sup>a</sup> | not serious          | not serious   | not serious  | not serious | none                 | Across 12 studies, 3/19,184 (0.02%) vaccinees were judged to have an SAE related to or possibly related to vaccination. | LOW<br>(Evidence type 3) | CRITICAL   |

## Explanations

- Outcome data was only collected from the vaccinated study arm from these studies; therefore they were considered observational for these outcomes
- 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 \(NRS, without comparator\)](#)

# Thank you

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