Observational evidence on vaccine effectiveness against delta variant – latest results and risk of bias considerations

Julian Higgins
Professor of Evidence Synthesis, University of Bristol

Joint work led by
• University of Paris (led by Isabelle Boutron)
with
• Cochrane Response (led by Nicholas Henschke and Gemma Villanueva)
• University of Bristol (led by Julian Higgins)
• WHO (particularly Fatema Kazi)
COVID-NMA is an international research initiative supported by the WHO and Cochrane.

We provide a living mapping of COVID-19 trials. We are also conducting living evidence synthesis on preventive interventions, treatments and vaccines for COVID-19 to assist decision makers.

See the description of our model here and our living review protocol here.

COVID-19 VACCINE EFFECTIVENESS ON VARIANTS OF CONCERN

OBSERVATIONAL STUDIES

PROTOCOL

Our protocol is available on Zenodo here.

VARIANTS OF CONCERN

We identified observational studies assessing vaccine effectiveness on variant from the studies identified by Krause P et al. Lancet 2021 and the process described in our protocol.

Vaccine effectiveness is based on direct evidence but also indirect evidence (i.e., variant exposure extrapolated the prevalence of the variant in the population) reported in the manuscript or in secondary sources.

Risk of bias assessment is ongoing and may be missing on the forest plots.

Analyses for variant delta and Beta were updated; some studies are awaiting classification (last search date 24 Sep, 2021).
• We look for:
  • comparative observational studies in any population
    • must account for at least some confounders in the design or analysis
  • involving any COVID-19 vaccine or vaccine schedule
  • that report severe disease, infection (after 1 or 2 doses), symptomatic disease (after 1 or 2 doses), mortality or long COVID
<table>
<thead>
<tr>
<th>Type</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA based vaccine</td>
<td>U.S. veterans hospitalized at five Veterans Affairs Medical Centers (VAMCs) in USA.</td>
</tr>
</tbody>
</table>

**Study registration:**

**Publication** Bajema K, MMWR, 2021  
**Dates:** 2021-07-01 to 2021-08-06  
**Funding:** Not reported/unclear  
**Conflict of interest:** no COI (Vincent C. Marconi reports research grants from Eli Lilly and Co., Gilead Sciences, and ViV Healthcare. No other potential conflicts of interest were disclosed.)

**Study design:** Test-negative  
**Description of participants:** U.S. veterans hospitalized at five Veterans Affairs Medical Centers (VAMCs) in USA.

**Inclusion criteria:**
- Adults aged ≥18 years  
- hospitalized at five VAMCs in Atlanta, Georgia  
- Bronx, New York  
- Houston, Texas  
- Los Angeles, California  
- and Palo Alto, California  
- Patients were eligible for inclusion if they had COVID-19-like illness (e.g., fever, new or worsened cough or shortness of breath, loss of taste or smell, oxygen saturation on room air <94% requirement for noninvasive ventilation or endotracheal intubation with mechanical ventilation, or chest radiograph or computed tomography pulmonary findings consistent with pneumonia) and a molecular test (reverse transcription–polymerase chain reaction (RT–PCR) or isothermal nucleic acid amplification test) for SARS-CoV-2 performed within 14 days before admission or during the first 72 hours of hospitalization.

**Exclusion criteria:**
- Participants who received only 1 dose of an mRNA COVID-19 vaccine, 2 mRNA doses with receipt of the second dose <14 days before the qualifying SARS-CoV-2 test, mixed mRNA vaccine products (i.e., a different product for each dose), or the Janssen (Johnson & Johnson) COVID-19 vaccine

**Follow-up duration (months):** 1.2
Results for RNA-based vaccines against Delta variant:

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Age</th>
<th>Follow-up months</th>
<th>Countries</th>
<th>Effect size</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech</td>
<td>Test-negative</td>
<td>74</td>
<td>5.77</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Bocera M.2021</td>
<td>Test-negative</td>
<td>(18+)</td>
<td>1.2</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Moderate Risk of bias</td>
</tr>
<tr>
<td>Tanaka P.2021</td>
<td>Test-negative</td>
<td>31</td>
<td>7</td>
<td>Qatar</td>
<td>Vaccine effectiveness</td>
<td>Serious Risk of bias</td>
</tr>
<tr>
<td>Nunes B.2021</td>
<td>Cohort</td>
<td>71</td>
<td>4.47</td>
<td>Portugal</td>
<td>Vaccine effectiveness</td>
<td>Critical Risk of bias</td>
</tr>
<tr>
<td>Tantalese M.2021</td>
<td>Cohort</td>
<td>59</td>
<td>7</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Critical Risk of bias</td>
</tr>
<tr>
<td>McLaughlin P.2021</td>
<td>Case-control</td>
<td>65</td>
<td>8.5</td>
<td>Scotland</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Grenn S.2021</td>
<td>Test-negative</td>
<td>74</td>
<td>5.77</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Stove J.2021</td>
<td>Test-negative</td>
<td>1.77</td>
<td>1</td>
<td>UK</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Tanaka P.2021</td>
<td>Test-negative</td>
<td>31</td>
<td>7</td>
<td>Qatar</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Naseem S.2021</td>
<td>Test-negative</td>
<td>6.1</td>
<td>1</td>
<td>Canada</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Purak K.2021</td>
<td>Cohort</td>
<td>16+</td>
<td>1</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Moderate Risk of bias</td>
</tr>
<tr>
<td>Goldberg Y.2021</td>
<td>Cohort</td>
<td>60+</td>
<td>7</td>
<td>Israel</td>
<td>Vaccine effectiveness</td>
<td>Serious Risk of bias</td>
</tr>
<tr>
<td>Israel Ministry of Health 2021</td>
<td>Cohort</td>
<td>16+</td>
<td>6.93</td>
<td>Israel</td>
<td>Vaccine effectiveness</td>
<td>Serious Risk of bias</td>
</tr>
<tr>
<td>Tantalese S.2021</td>
<td>Cohort</td>
<td>45</td>
<td>7.6</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Moderna TX</td>
<td>Test-negative</td>
<td>65</td>
<td>7.17</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Thompson M.2021</td>
<td>Test-negative</td>
<td>74</td>
<td>5.77</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Tanaka P.2021</td>
<td>Test-negative</td>
<td>31</td>
<td>7</td>
<td>Qatar</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Naseem S.2021</td>
<td>Test-negative</td>
<td>6.1</td>
<td>1</td>
<td>Canada</td>
<td>Vaccine effectiveness</td>
<td>Low Risk of bias</td>
</tr>
<tr>
<td>Purak K.2021</td>
<td>Cohort</td>
<td>16+</td>
<td>1</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Moderate Risk of bias</td>
</tr>
<tr>
<td>Brusso D.2021</td>
<td>Cohort</td>
<td>61</td>
<td>6.1</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>Moderate Risk of bias</td>
</tr>
</tbody>
</table>

**Risk of Bias Ratings:**
- Low Risk of Bias
- Moderate Risk of Bias
- Serious Risk of Bias
- Critical Risk of Bias
- No Information

**Risk of Bias Domains:**
A: Bias due to confounding
B: Bias in selection of participants into the study
C: Bias in classification of interventions
D: Bias due to deviations from intended interventions
E: Bias due to missing data
F: Bias due to measurement of outcomes
G: Bias due to selection of the reported result

Vaccine effectiveness: 89.00% [87.00%, 91.00%]
Results for **non-replicating viral vector** vaccines against Delta variant:

**Severe disease**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Age</th>
<th>Follow-up months</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Oxford/AstraZeneca</td>
<td>Test-negative</td>
<td>34</td>
<td>4.5</td>
<td>India</td>
</tr>
<tr>
<td>Pramod S.2021*</td>
<td>Test-negative</td>
<td></td>
<td>4.5</td>
<td>India</td>
</tr>
<tr>
<td>Thiruvengadam R.2021*</td>
<td>Test-negative</td>
<td></td>
<td>4.5</td>
<td>India</td>
</tr>
<tr>
<td>Stowe J.2021</td>
<td>Test-negative</td>
<td>1.77</td>
<td></td>
<td>UK</td>
</tr>
<tr>
<td>Nasreen S.2021*</td>
<td>Test-negative</td>
<td>(16+)</td>
<td>6.1</td>
<td>Canada</td>
</tr>
<tr>
<td>McKelgue P.2021*</td>
<td>Case-control</td>
<td></td>
<td>8.5</td>
<td>Scotland</td>
</tr>
<tr>
<td>Grannis S.2021*</td>
<td>Test-negative</td>
<td>65</td>
<td>7.17</td>
<td>USA</td>
</tr>
<tr>
<td>Thompson M.2021*</td>
<td>Test-negative</td>
<td>74</td>
<td>5.77</td>
<td>USA</td>
</tr>
<tr>
<td>Corchado-Garcia J.2021*</td>
<td>Cohort</td>
<td>(18+)</td>
<td>1.6</td>
<td>USA</td>
</tr>
</tbody>
</table>

**Risk of bias ratings:**
- Low Risk of Bias
- Moderate Risk of Bias
- Serious Risk of Bias
- Critical Risk of bias
- ? = No information

**Risk of Bias Domains:**
- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias due to selection of the reported result

**Effect estimate**

- **University of Oxford/AstraZeneca**
  - Test-negative: 95.00% [44.00%, 100.00%]

- **Thiruvengadam R.2021**
  - Test-negative: 81.50% [9.90%, 99.00%]

- **Stowe J.2021**
  - Test-negative: 92.00% [75.00%, 97.00%]

- **Nasreen S.2021**
  - Test-negative: 88.00% [60.00%, 96.00%]

- **McKelgue P.2021**
  - Case-control: 91.00% [86.00%, 95.00%]

- **Grannis S.2021**
  - Test-negative: 60.00% [31.00%, 77.00%]

- **Thompson M.2021**
  - Test-negative: 68.00% [50.00%, 79.00%]

- **Corchado-Garcia J.2021**
  - Cohort: 32.00% [0.00%, 88.00%]

**Vaccine effectiveness**

---

University of Bristol
Results for **booster dose** of RNA-based vaccine against Delta variant: **Severe disease**

Severe COVID-19 disease, Variant: Delta

<table>
<thead>
<tr>
<th>Study design</th>
<th>Age</th>
<th>Follow-up months</th>
<th>Countries</th>
<th>Effect size</th>
<th>Effect estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech (BNT162b2 booster vs BNT162b2)</td>
<td>Cohort</td>
<td>(60+)</td>
<td>0.88</td>
<td>Israel</td>
<td>Vaccine effectiveness 94.87% [92.25%, 96.61%]</td>
</tr>
</tbody>
</table>

### Risk of bias ratings:
- Low Risk of Bias
- Moderate Risk of Bias
- Serious Risk of Bias
- Critical Risk of bias
- ? = No information

### Risk of Bias Domains:
- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias due to selection of the reported result

*: Indirect evidence (variant exposure extrapolated from the prevalence reported in the manuscript or in secondary sources)

Age is reported as median, mean, age range or eligible age group.

---

Vaccine effectiveness

bristol.ac.uk
### Results for various vaccines (inseparable) against Delta variant:

#### Severe disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Age</th>
<th>Follow-up months</th>
<th>Countries</th>
<th>Effect size</th>
<th>Effect estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech or University of Oxford/AstraZeneca</td>
<td>Test-negative</td>
<td>1.77</td>
<td>UK</td>
<td>Vaccine effectiveness</td>
<td>94.00% [85.00%, 98.00%]</td>
<td></td>
</tr>
<tr>
<td>Pfizer/BioNTech or ModernaTX or JANSSEN</td>
<td>Test-negative</td>
<td>65</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>86.00% [82.00%, 89.00%]</td>
<td></td>
</tr>
<tr>
<td>Grannis S, 2021*</td>
<td>Cohort</td>
<td>16+</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>96.60% [NA%, NA%]</td>
<td></td>
</tr>
<tr>
<td>Rosenberg E, 2021*</td>
<td>Cohort</td>
<td>18+</td>
<td>USA</td>
<td>Vaccine effectiveness</td>
<td>93.60% [NA%, NA%]</td>
<td></td>
</tr>
</tbody>
</table>

#### Risk of bias ratings:
- **Low Risk of Bias**
- **Moderate Risk of Bias**
- **Serious Risk of Bias**
- **Critical Risk of Bias**
- **Indirect Evidence** (variant exposure extrapolated from the prevalence reported in the manuscript or in secondary sources)
- **No Information**

#### Risk of Bias Domains:
A: Bias due to confounding
B: Bias in selection of participants into the study
C: Bias in classification of interventions
D: Bias due to deviations from intended interventions
E: Bias due to missing data
F: Bias due to measurement of outcomes
G: Bias due to selection of the reported result

Age is reported as median, mean, age range or eligible age group.
Quality of the evidence: assessing risk of bias in each result
ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions


Bias domains

- Bias due to confounding
- Bias in selection of participants into the study
- Bias in classification of interventions
- Bias due to departures from intended interventions
- Bias due to missing data
- Bias in measurement of outcomes
- Bias in selection of the reported result

BMJ 2016 (undergoing update 2021)
**Confounding** occurs when there is a common cause (C) of BOTH whether someone is vaccinated (V) AND whether someone has an outcome event (O).

Many things affect this in the real world.
Confounding: age

Older people more likely to be vaccinated

Older people more likely to develop (severe) disease

Leads to association between vaccination and disease even if the vaccine is ineffective

We can address this by *adjusting for age*
We examine a fixed list of potential confounding factors:

- Age
- Sex
- Socioeconomic status
- Ethnicity
- Comorbidities
- Geographic location
- Specific populations (e.g. healthcare worker/elderly in institution)

- **Calendar time** (to reflect changing incidence of virus)
- Hospitalization and need for health care
- **Symptoms at time of planned vaccination**
- **Health-seeking behaviour** (e.g. frequency of consultation, flu vaccine history)
Confounding: COVID-19 symptoms

Vaccination less likely if COVID-19 symptoms present

Severe disease more likely if COVID-19 symptoms present

More difficult to address
Example 1: Bruxvoort et al (Kaiser Permanente, Southern California)

- Cohort study

- Did not control for symptoms at the time of potential vaccination (judged to be at serious risk of bias due to confounding)

- No evidence of a protocol (very common in these studies) – so possibility of cherry picking of results

- Moderna, VE 95.8% (95% CI 92.5% to 97.6%) against severe disease
Example 2: Bar-On et al (Israel)

- Cohort study

- Did not control for potential confounding due to socioeconomic status, health seeking behaviour, specific populations, comorbidities, calendar time, COVID-19 symptoms at time of planned vaccination

- Otherwise seems quite strong
  - and a protocol is available (unusual for these studies)

- Pfizer booster, VE 94.9% (95% CI 92.5% to 96.6%)
Example 3: Bajema et al (US Veterans)

- Test-negative design
  - restricts the investigation to those who provide a test result
  - compare vaccination history in those who test positive with those who test negative
  - reduces confounding due to health-seeking behaviour
  - but this is not a panacea...
    - there is a risk of introducing spurious associations between vaccination and disease
    - (because these may both cause people to get tested)
    - risk of selection bias

- Pfizer or Moderna, VE 89.3% (95% CI 80.1% to 94.3%)
Example 4: Grannis et al (multiple USA sites)

- Another test-negative design
- In addition, possible bias in determination of severe COVID-19 due to knowledge of vaccination status of hospital patients
Example 5: Thompson et al (multiple USA sites)

• Another test-negative design

• A protocol is available (unusual for these studies)
• There are **risks of bias** in all the studies, although in general we think most large studies have done a good job

• **Magnitudes and directions** of the combined effects of different sources biases of bias are extremely **difficult to predict**

• But we **do not think that the biases are large** in comparison with the observed vaccine effectiveness estimates

• **Conclusion**: there is **robust evidence of high effectiveness**, substantially beyond 50% VE in most cases
Full results and details of methods are available from covid-nma.com
Variants of concern

- **Direct evidence**: effectiveness against variant determined by sequencing all cases

- **Indirect evidence**: study performed while variant of concern was >50% prevalent in the population

https://outbreak.info/location-reports