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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)

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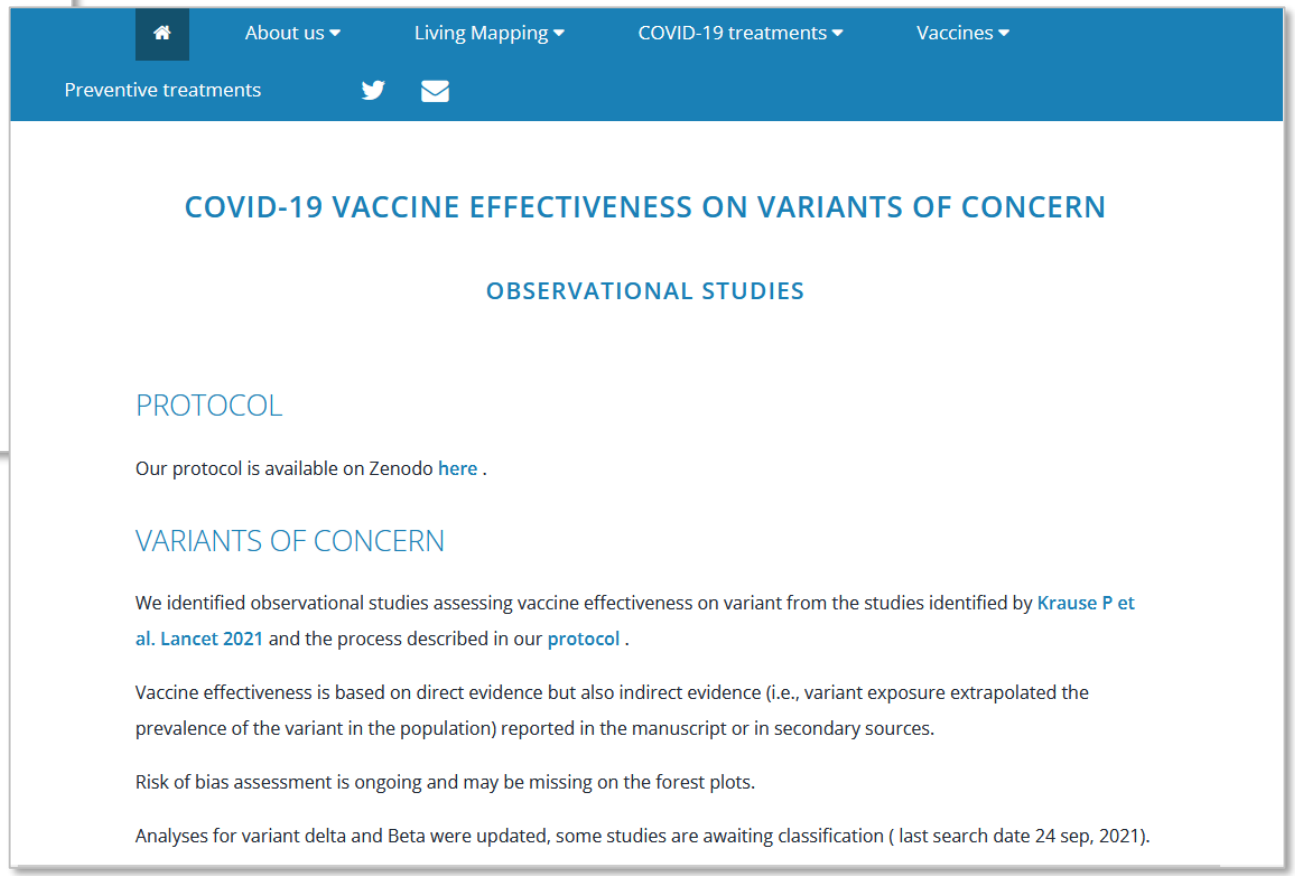

Protocol

- 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

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Trial	Design	Variant	Participants	Type	Int
Bajema K, MMWR, 2021 Full text Commentary	Test-negative	Delta	U.S. veterans hospitalized at five Veterans Affairs Medical Centers (VAMCs) in USA.	RNA based vaccine	n
				RNA based vaccine	
				RNA based vaccine	Bl n
Bar-On Y, N Engl J Med, 2021 Full text Commentary	Cohort	Delta	Israel residents 60 years of age or older who had been fully vaccinated at least 5 months earlier	RNA based vaccine	
				RNA based vaccine	n

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 ViiV Healthcare. No other potential conflicts of interest were disclosed.)

Methods

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 (i.e., 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

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Results for **RNA-based** vaccines against Delta variant:

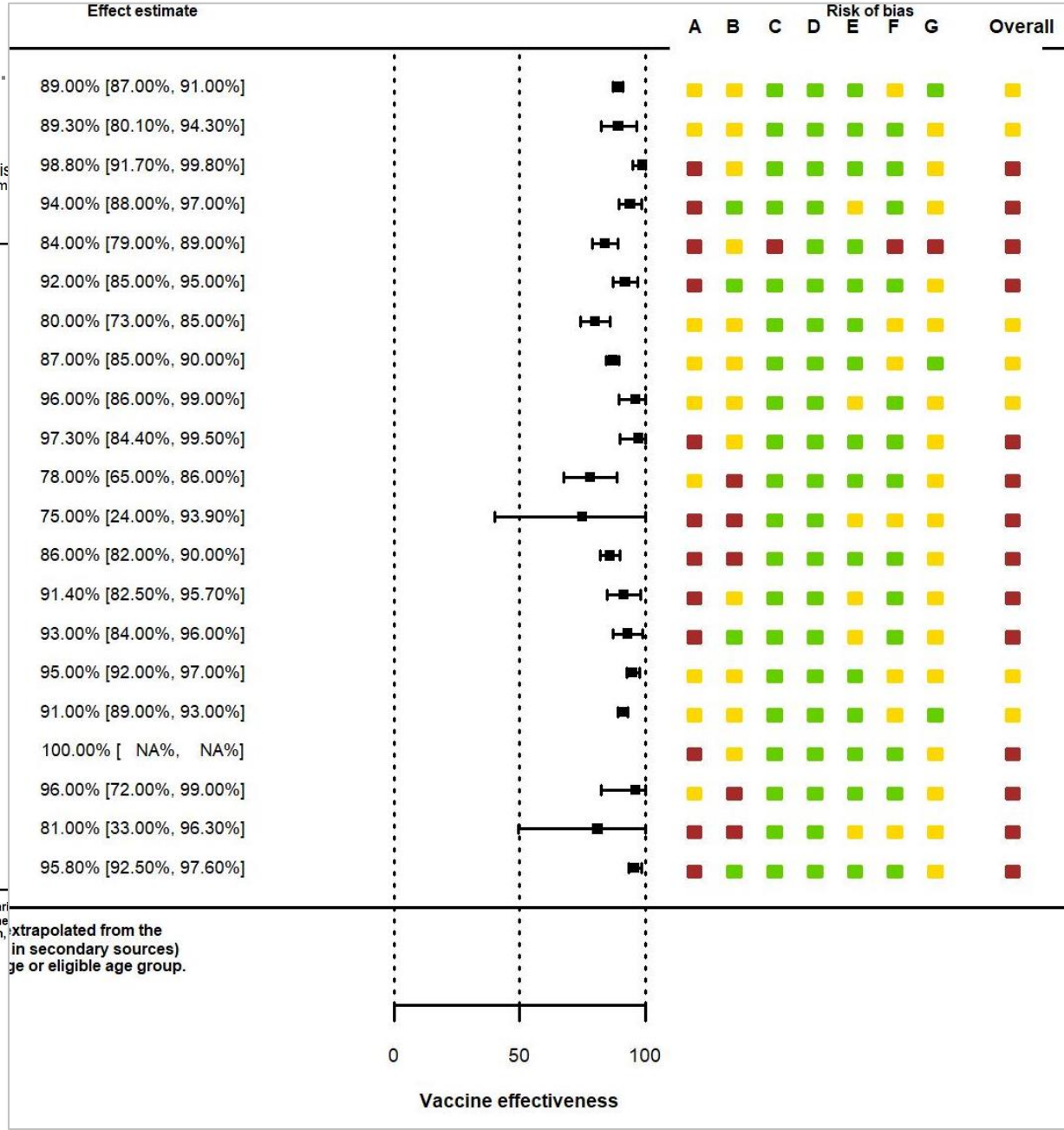
Severe COVID-19 dis
Type of vaccine platform

Study	Study design	Age	Follow-up months	Countries	Effect size
Pfizer/BioNTech or ModernaTX					
Thompson M,2021*.3	Test-negative	74	5.77	USA	Vaccine effectiveness
Baiema K,2021	Test-negative	(18+)	1.2	USA	Vaccine effectiveness
Tang P,2021.3	Test-negative	31	7	Qatar	Vaccine effectiveness
Nunes B,2021*	Cohort	71	4.47	Portugal	Vaccine effectiveness
Tenforde M,2021*	Cohort	59	7	USA	Vaccine effectiveness
McKeigue P,2021*	Case-control		8.5	Scotland	Vaccine effectiveness
Pfizer/BioNTech					
Grannis S,2021*.2	Test-negative	65	7.17	USA	Vaccine effectiveness
Thompson M,2021*.2	Test-negative	74	5.77	USA	Vaccine effectiveness
Stowe J,2021	Test-negative		1.77	UK	Vaccine effectiveness
Tang P,2021.2	Test-negative	31	7	Qatar	Vaccine effectiveness
Nasreen S,2021*.2	Test-negative	(16+)	6.1	Canada	Vaccine effectiveness
Puranik A,2021*.2	Cohort	18+	1	USA	Vaccine effectiveness
Goldberg Y,2021*	Cohort	60+	7	Israel	Vaccine effectiveness
Israeli Ministry of Health,2021*	Cohort	16+	6.93	Israel	Vaccine effectiveness
Tartof S,2021	Cohort	45	7.9	USA	Vaccine effectiveness
ModernaTX					
Grannis S,2021*.1	Test-negative	65	7.17	USA	Vaccine effectiveness
Thompson M,2021*.1	Test-negative	74	5.77	USA	Vaccine effectiveness
Tang P,2021.1	Test-negative	31	7	Qatar	Vaccine effectiveness
Nasreen S,2021*.1	Test-negative	(16+)	6.1	Canada	Vaccine effectiveness
Puranik A,2021*.1	Cohort	18+	1	USA	Vaccine effectiveness
Bruxvoort K,2021*	Cohort	65	6.47	USA	Vaccine effectiveness

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

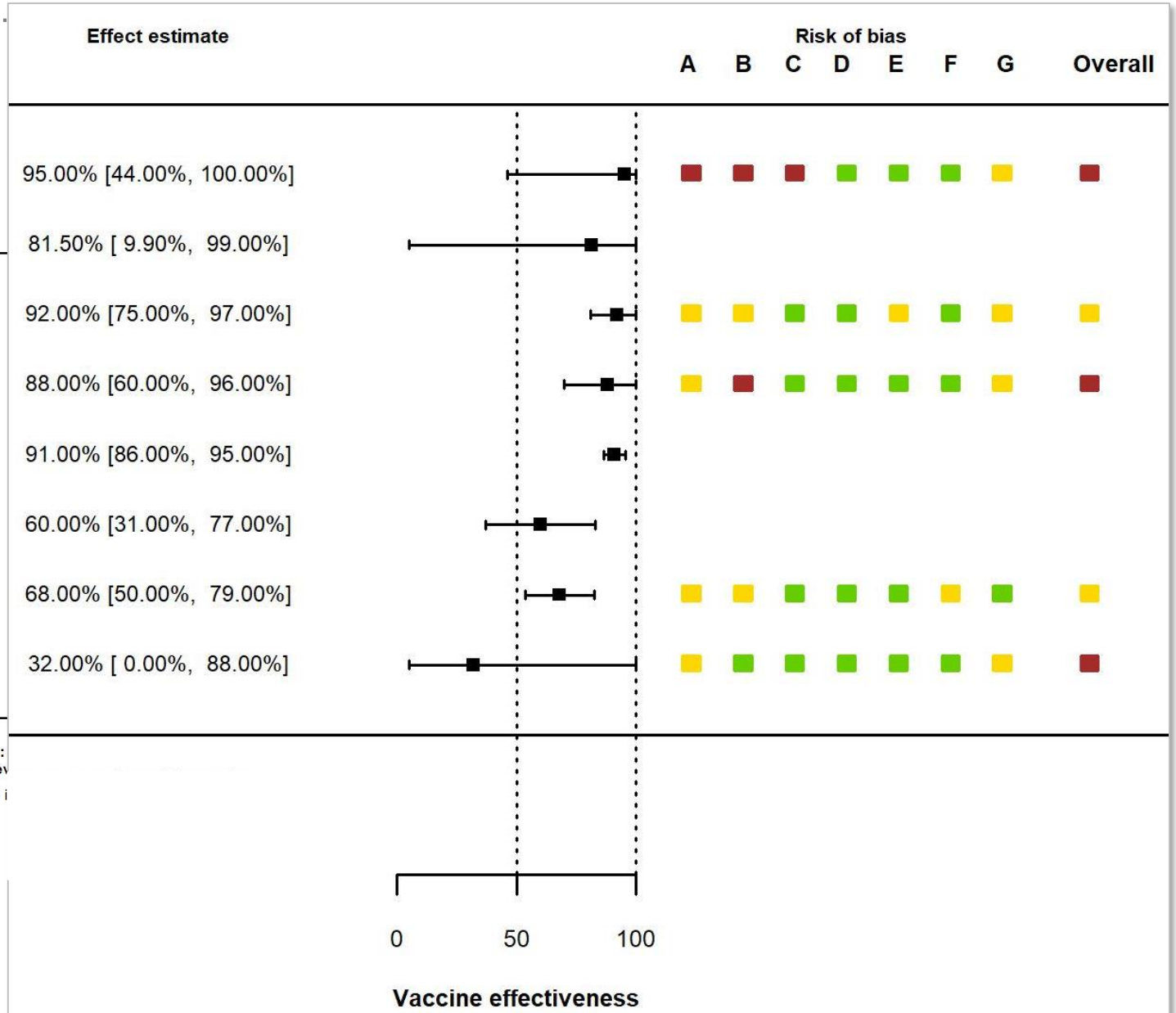
Risk of Bias Domains:
- A: Bias due to confounding
- B: Bias in selection of participants into the study
- C: Bias in classification of interventions
- D: Bias due to deviations from intended interventions
- E: Bias due to missing data
- F: Bias due to measurement of outcomes
- G: Bias due to selection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

*: Indirect evidence (vari
prevalence reported in the
Age is reported as median,



Results for **non-replicating viral vector** vaccines against Delta variant: **Severe disease**

Study	Study design	Age	Follow-up months	Countries
University of Oxford/AstraZeneca				
Pramod S,2021*	Test-negative	34	4.5	India
Thiruvengadam R,2021*	Test-negative		4.5	India
Stowe J,2021	Test-negative		1.77	UK
Nasreen S,2021*	Test-negative	(16+)	6.1	Canada
McKeigue P,2021*	Case-control		8.5	Scotland
Janssen Biotech, Inc.				
Grannis S,2021*	Test-negative	65	7.17	USA
Thompson M,2021*	Test-negative	74	5.77	USA
Corchado-Garcia J,2021*	Cohort	(18+)	1.6	USA



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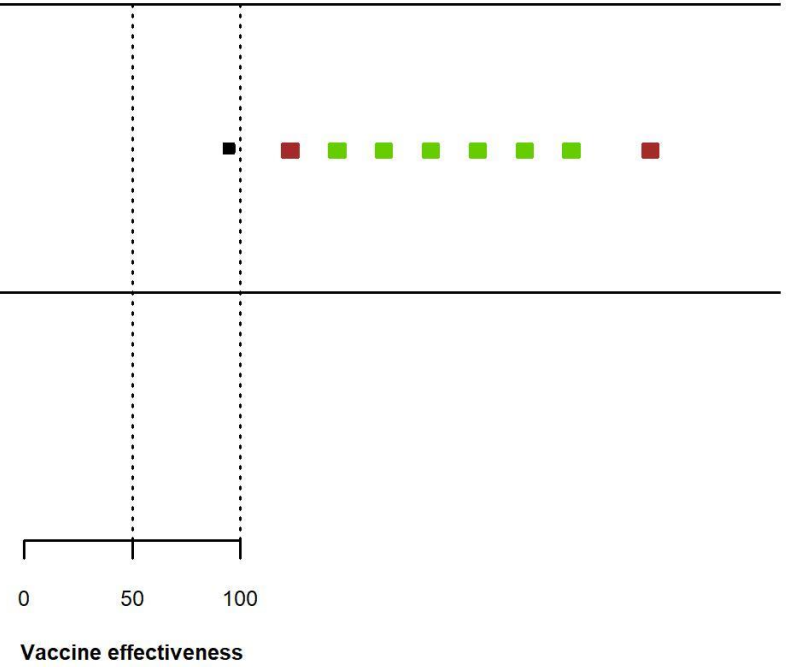
*:
prev
Age i

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

Severe COVID-19 disease, Variant: Delta

Study	Study design	Age	Follow-up months	Countries	Effect size	Effect estimate	Risk of bias A	B	C	D	E	F	G	Overall
Pfizer/BioNTech(BNT162b2 booster vs BNT162b2)														
Bar-On Y,2021*	Cohort	(60+)	0.88	Israel	Vaccine effectiveness	94.87% [92.25%, 96.61%]								



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

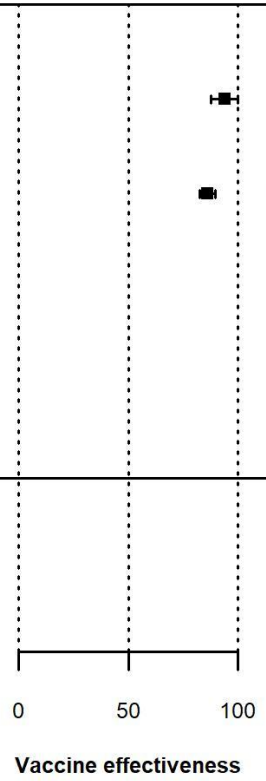
Age is reported as median, mean, age range or eligible age group.

Results for **various** vaccines (inseparable) against Delta variant: **Severe disease**

Severe COVID-19 disease, Variant: Delta

Type of vaccine platform: Any COVID-19 vaccine

Study	Study design	Age	Follow-up months	Countries	Effect size	Effect estimate	Risk of bias A	B	C	D	E	F	G	Overall
Pfizer/BioNTech or University of Oxford/AstraZeneca														
Stowe J,2021	Test-negative		1.77	UK	Vaccine effectiveness	94.00% [85.00%, 98.00%]								
Pfizer/BioNTech or ModernaTX or JANSSEN														
Grannis S,2021*	Test-negative	65	7.17	USA	Vaccine effectiveness	86.00% [82.00%, 89.00%]								
Griffin J,2021*	Cohort	16+	7.87	USA	Vaccine effectiveness	96.60% [NA%, NA%]								
Rosenberg E,2021*	Cohort	18+	7.87	USA	Vaccine effectiveness	93.60% [NA%, NA%]								



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Quality of the evidence: assessing **risk of bias** in each result

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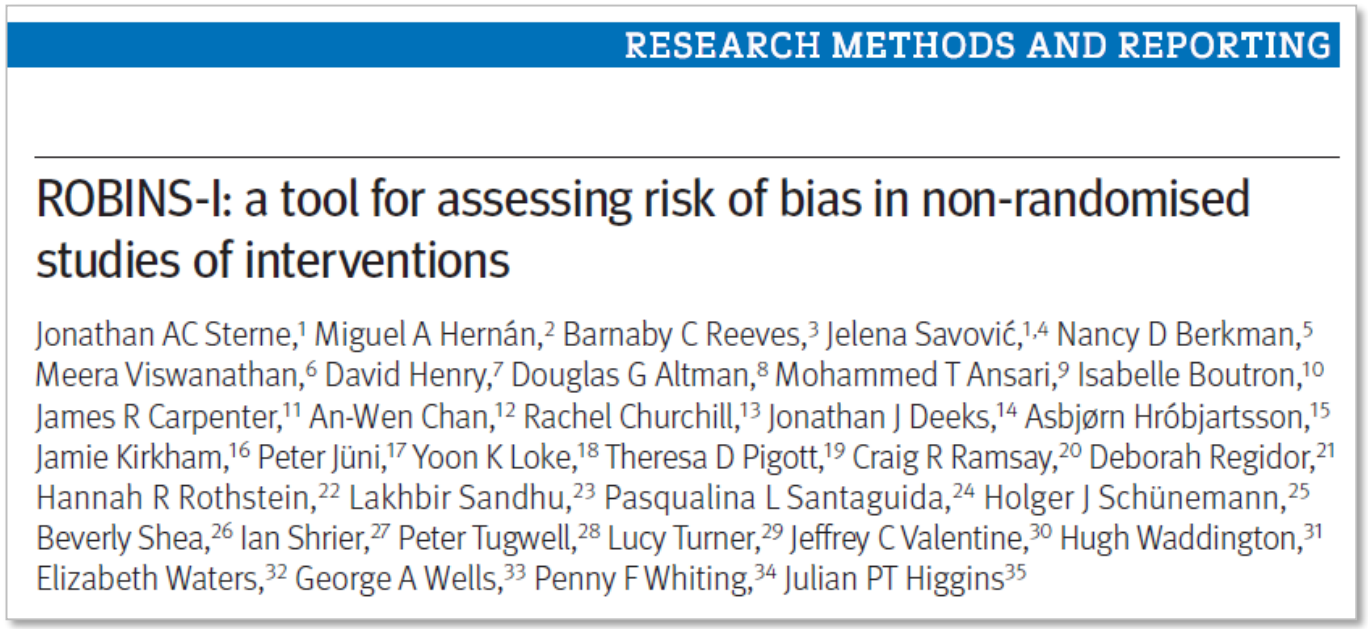
ROBINS-I



RESEARCH METHODS AND REPORTING

ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions

Jonathan AC Sterne,[1] Miguel A Hernán,[2] Barnaby C Reeves,[3] Jelena Savović,[1,4] Nancy D Berkman,[5] Meera Viswanathan,[6] David Henry,[7] Douglas G Altman,[8] Mohammed T Ansari,[9] Isabelle Boutron,[10] James R Carpenter,[11] An-Wen Chan,[12] Rachel Churchill,[13] Jonathan J Deeks,[14] Asbjørn Hróbjartsson,[15] Jamie Kirkham,[16] Peter Jüni,[17] Yoon K Loke,[18] Theresa D Pigott,[19] Craig R Ramsay,[20] Deborah Regidor,[21] Hannah R Rothstein,[22] Lakhbir Sandhu,[23] Pasqualina L Santaguida,[24] Holger J Schünemann,[25] Beverly Shea,[26] Ian Shrier,[27] Peter Tugwell,[28] Lucy Turner,[29] Jeffrey C Valentine,[30] Hugh Waddington,[31] Elizabeth Waters,[32] George A Wells,[33] Penny F Whiting,[34] Julian PT Higgins[35]

BMJ 2016
(undergoing update 2021)

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

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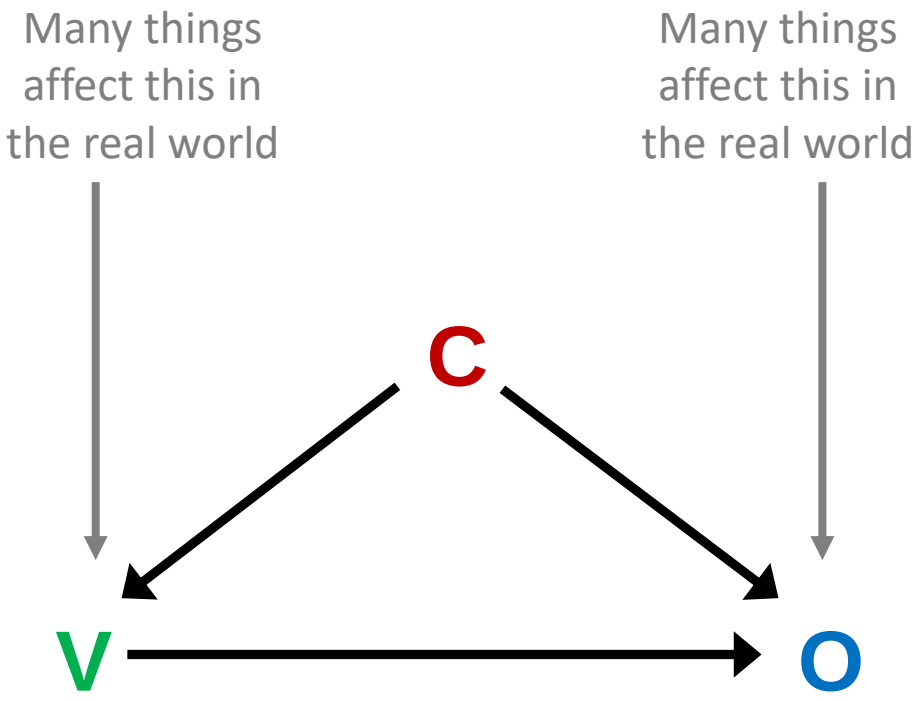
Confounding

Confounding occurs when there is a common cause (C) of BOTH

whether someone is vaccinated (V)

AND

whether someone has an outcome event (O)



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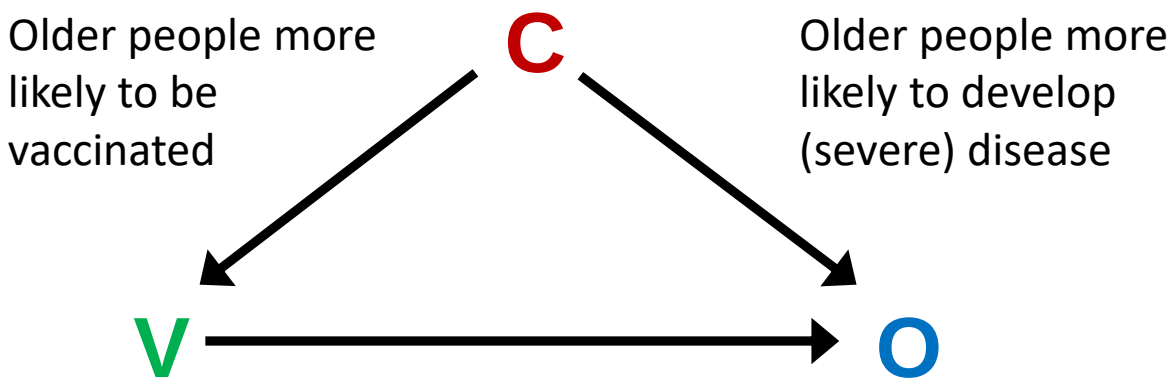
Confounding: age



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

We can address this by *adjusting for age*

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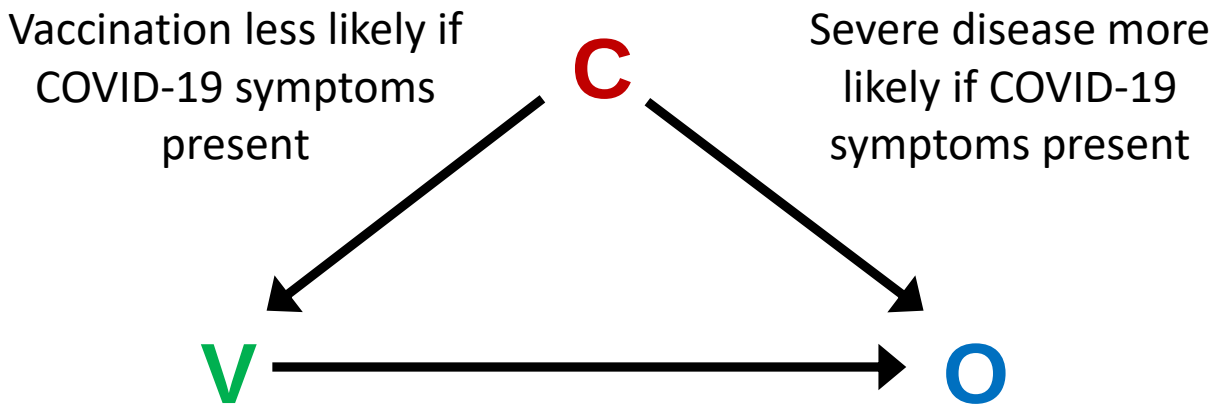
We examine a fixed list of potential confounding factors

- 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)

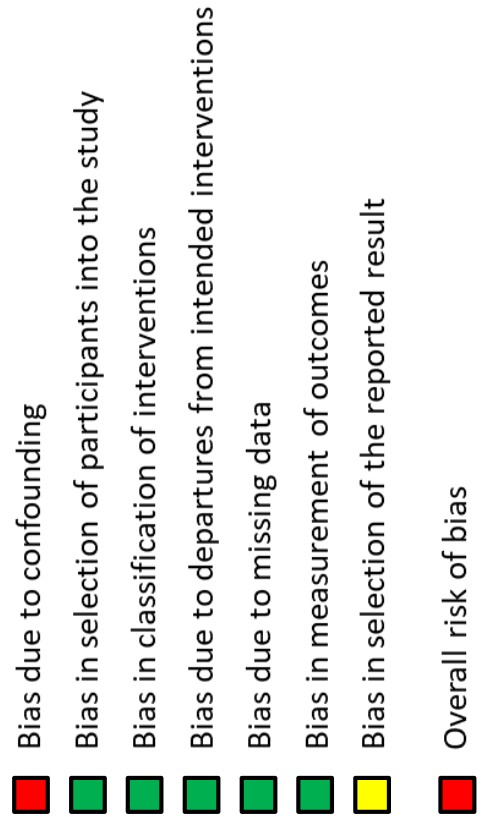
Confounding: COVID-19 symptoms



More difficult to address

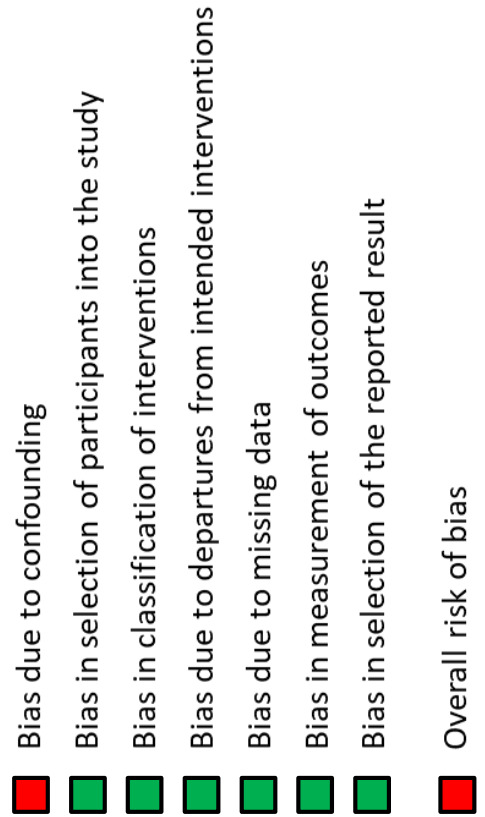
Example 1: Bruxvoort et al (Kaiser Permanente, Southern California)

- 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



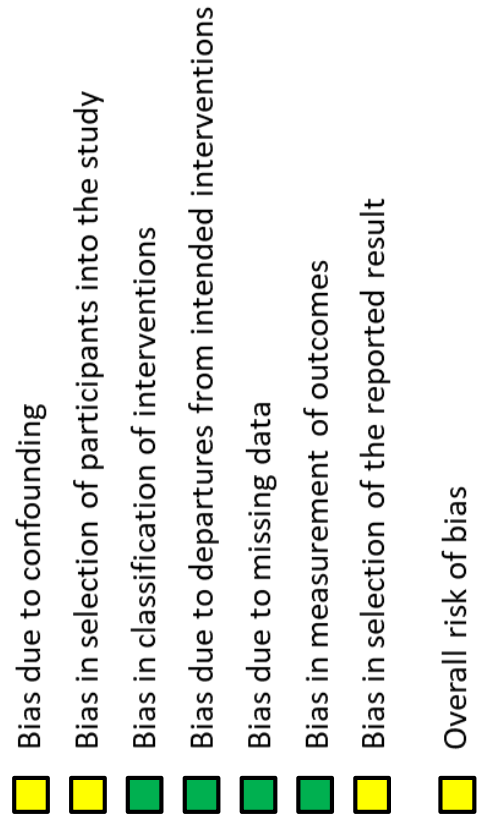
Example 2: Bar-On et al (Israel)

- 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**

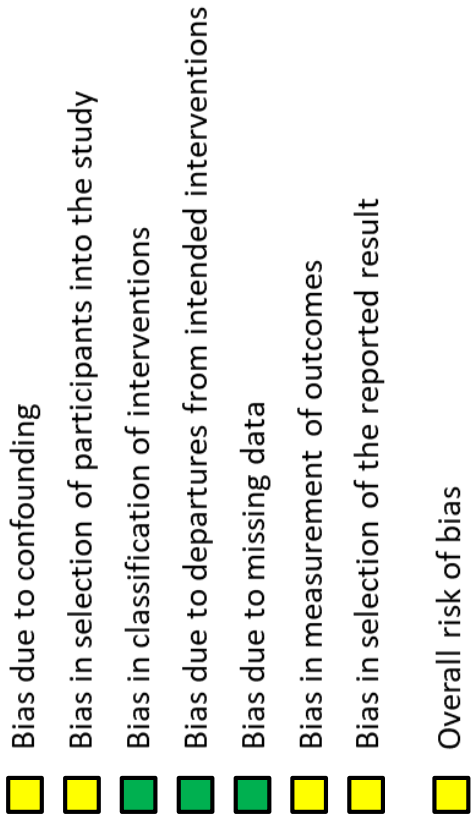


- Pfizer or Moderna, VE 89.3% (95% CI 80.1% to 94.3%)

Example 4: Grannis et al (multiple USA sites)

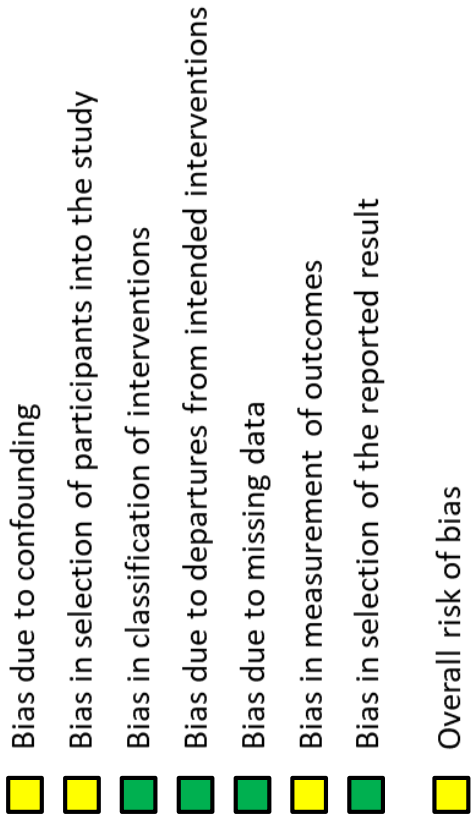
- Another test-negative design

- 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)



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Implications

- 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

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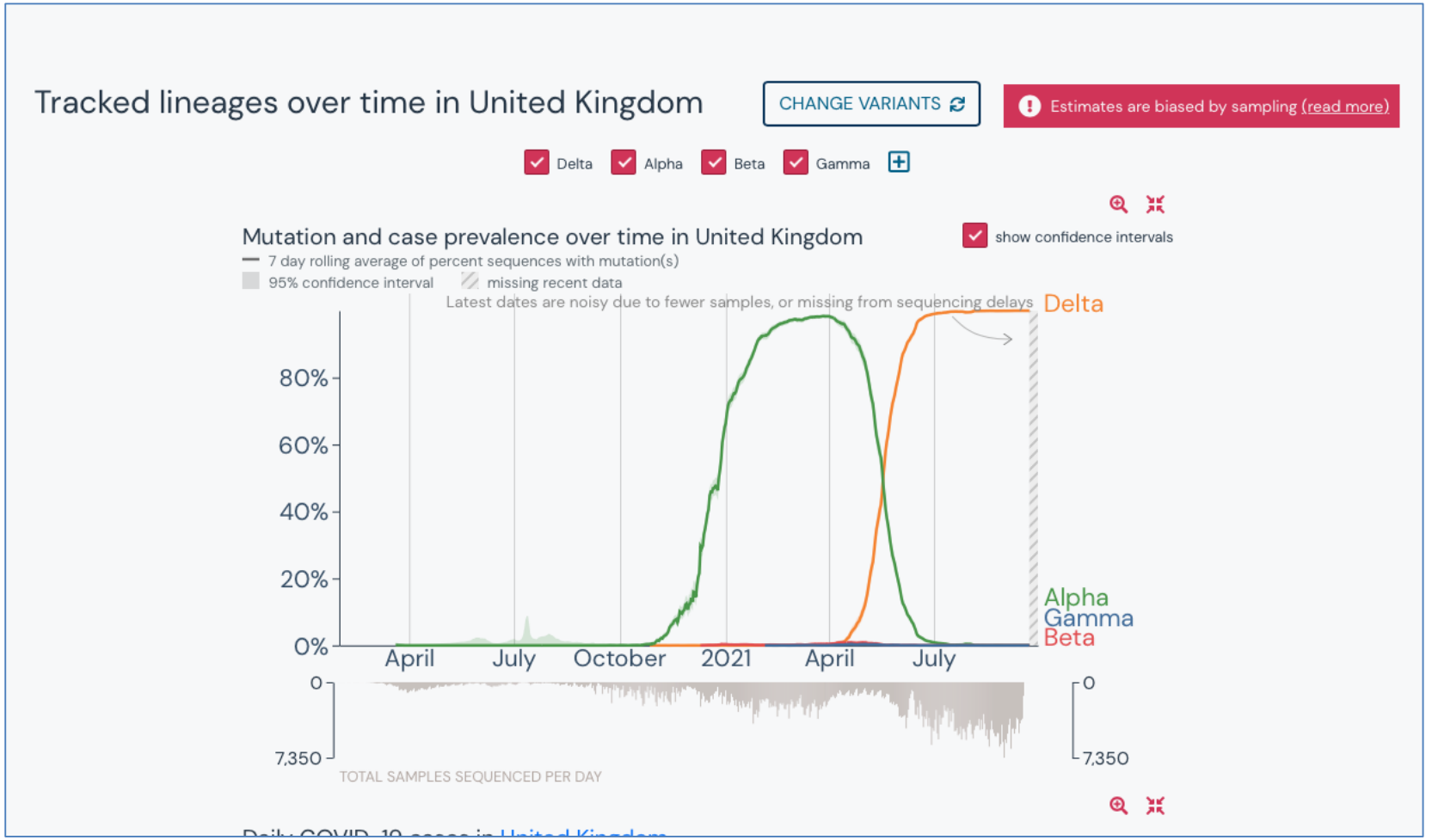
Full results and details of methods are available from covid-nma.com

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