Randomized evidence on COVID-19 vaccines and variants

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WHO consultation on COVID-19 vaccines research
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Outline

- Living systematic review process
- RCT evidence on variants
- Methodological issues on data for variants
- RCT evidence on heterologous prime-boost
- RCT evidence on long-term vaccine efficacy
- RCT evidence on booster doses
- Conclusions

Living systematic review

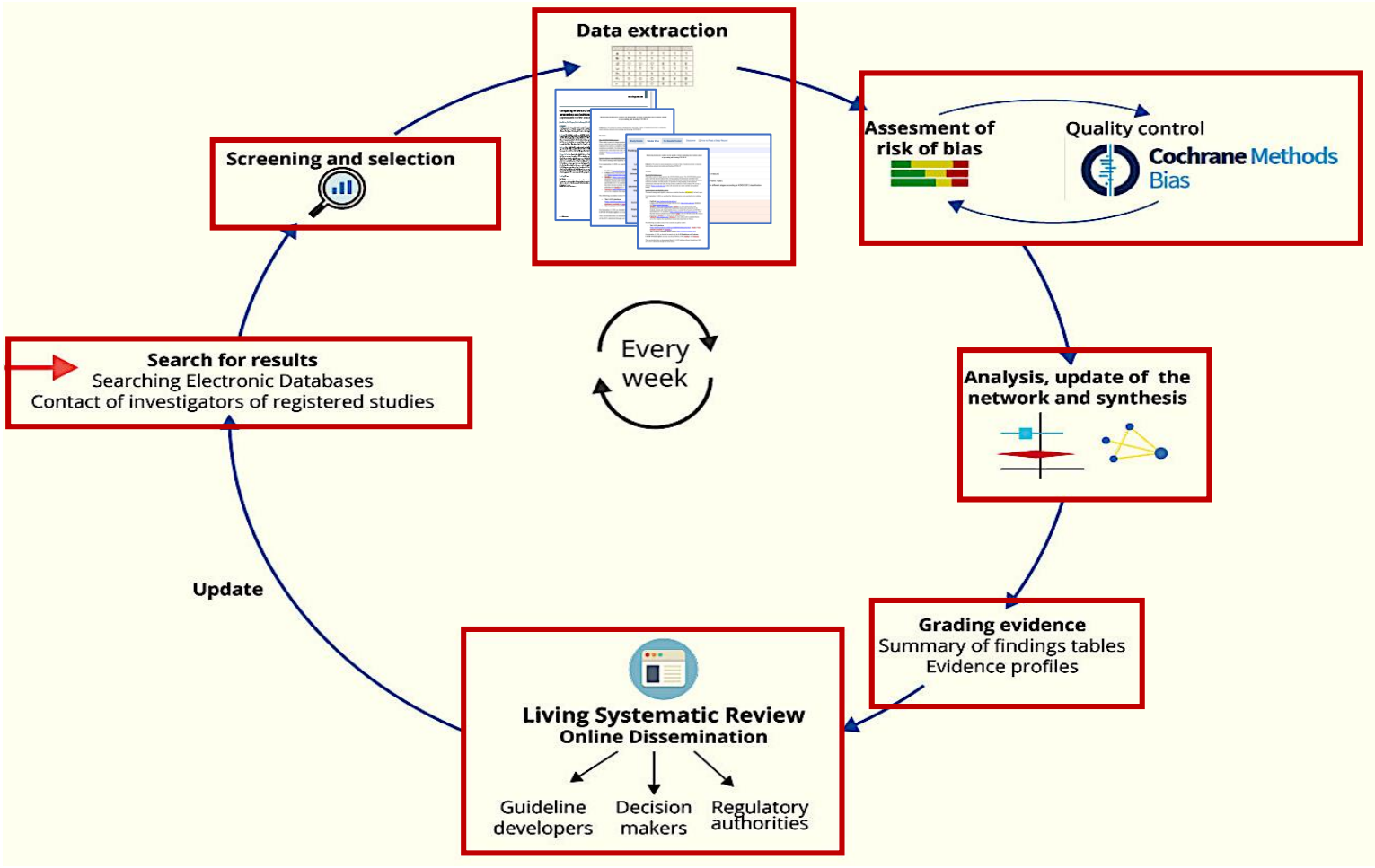
296 registered
RCTs on vaccines
(120 recruiting)

55 published
RCTs on vaccines

Cochrane COVID-19 Study Register
Trusted evidence. Informed decisions. Better health.

COVID-19
Search in this L·OVE
By PICO

Living mapping of RCTs



Key characteristics:

- A living protocol scalable to stakeholders' evolving needs
- Strong quality control process
- Regular requests of missing data

https://covid-nma.com

PICO

Objective: To assess the effectiveness and safety of COVID-19 vaccines

- **Participants**: children or adults with no restriction in age and comorbidities
- **Interventions**: any COVID-19 vaccines
- **Comparator**: placebo, no vaccine or another COVID-19 vaccine
- **Outcomes** (clinical-primary):
  - Confirmed SARS-CoV-2 infection after complete vaccination
  - Confirmed symptomatic COVID-19 after complete vaccination
  - Severe or critical COVID-19 disease
  - All-cause mortality
  - Systemic adverse events
  - Any adverse events
  - Serious adverse events

Variants of concern - Alpha

Vaccines

Incidence of symptomatic COVID-19 confirmed with positive test for SARS-CoV-2 infection

Type of variant: Alpha (B.1.1.7)

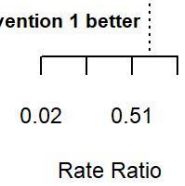
Study (Developer)	N-days after dose (days-dose)	Follow-up months	Intervention 1	Intervention 2	r1/N1	r2/N2	Risk of bias A B C D E Overall	Vaccine Efficacy [95% CI]	Rate ratio [95% CI]
University of Oxford/AstraZeneca									
Emary K, 2021, DE*	14-D2	3.49	ChAdOx1 nCoV-19	MenACWY	12/4244	40/4290		70.40% [43.60%,84.50%]	0.30 [0.16, 0.56]
Novavax									
Heath P, 2021, DE*	7-D2	4	NVX-CoV2373	Placebo	8/7020	58/7019		86.30% [71.30%,93.50%]	0.14 [0.07, 0.29]

Risk of bias ratings:
- Low Risk of Bias
- Some Concerns
- High Risk of Bias

Risk of Bias Domains:
- A: Bias due to randomization
- B: Bias due to deviation from intended intervention
- C: Bias due to missing data
- D: Bias due to outcome measurement
- E: Bias due to selection of reported result

(* Post-hoc analysis)

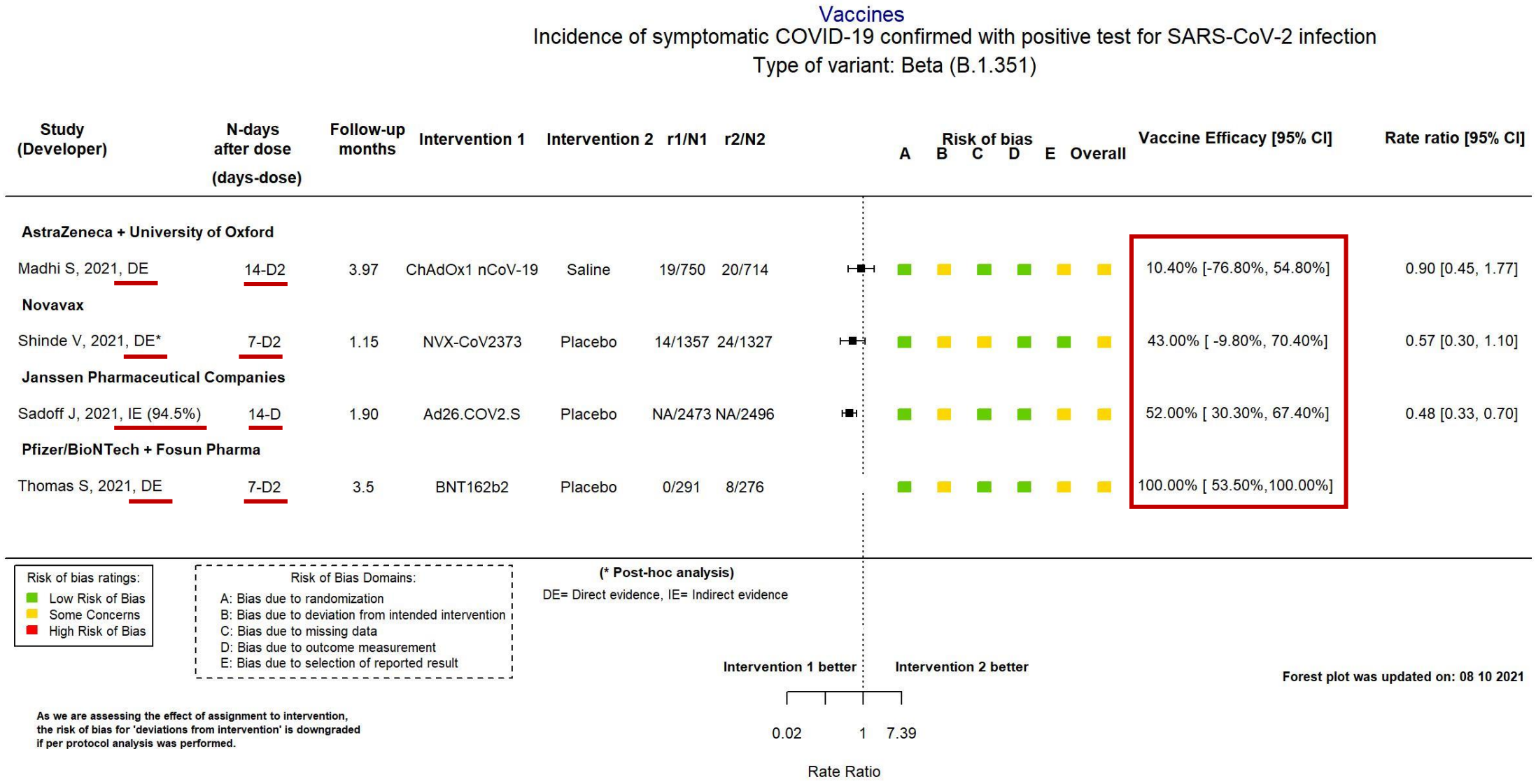
DE= Direct evidence, IE= Indirect evidence



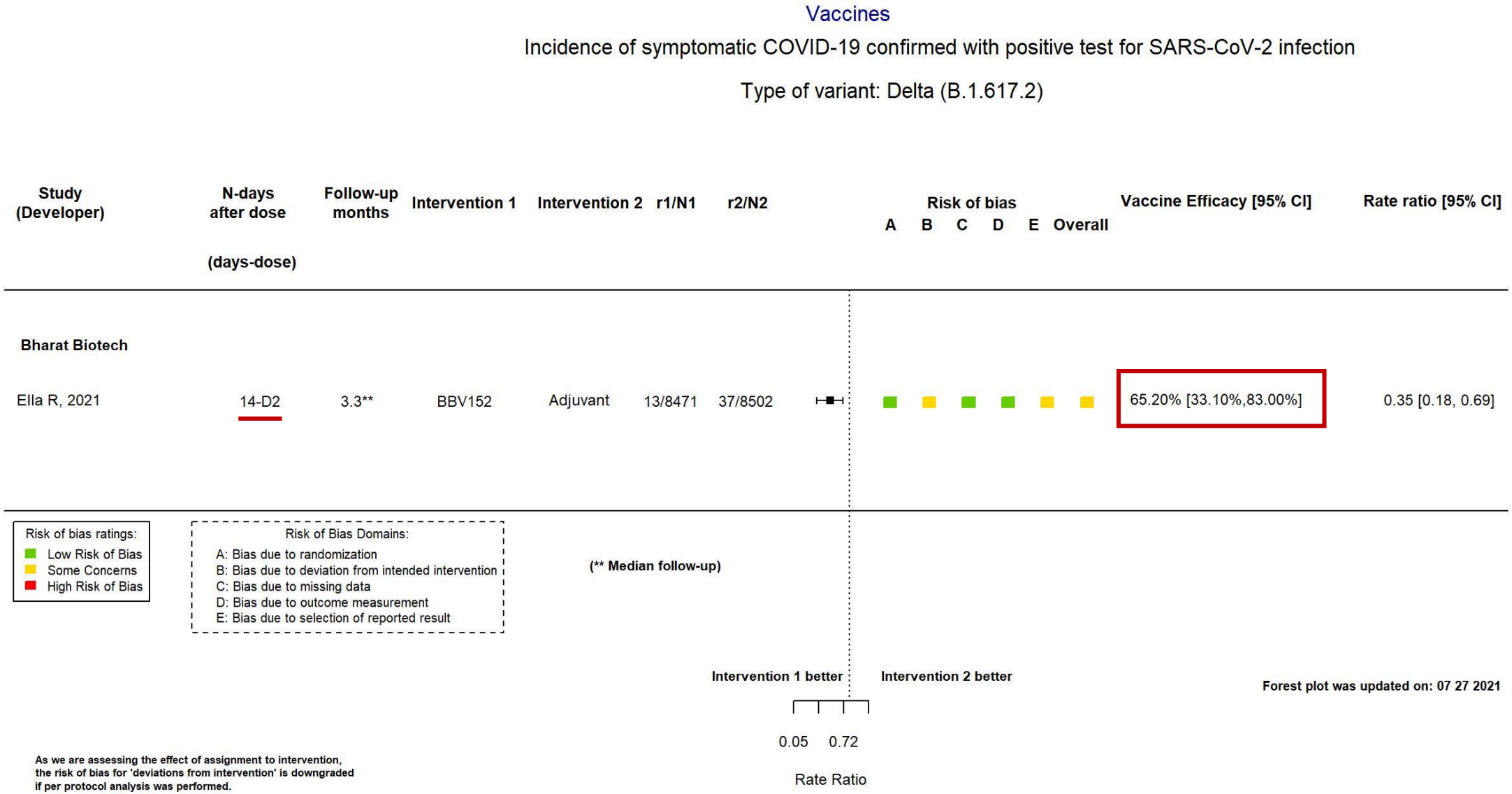
Forest plot was updated on: 07 10 2021

As we are assessing the effect of assignment to intervention, the risk of bias for 'deviations from intervention' is downgraded if per protocol analysis was performed.

Variants of concern - Beta



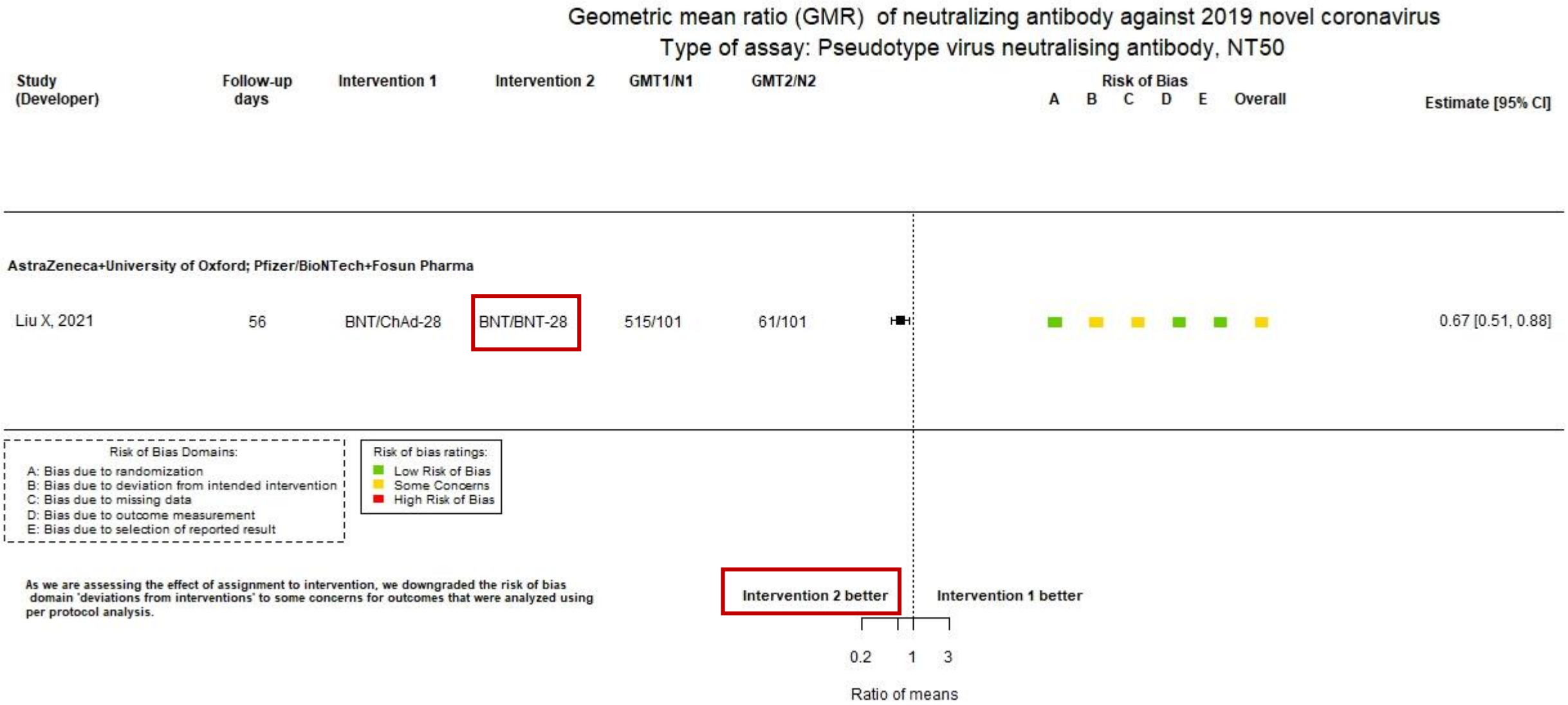
Variants of concern - Delta



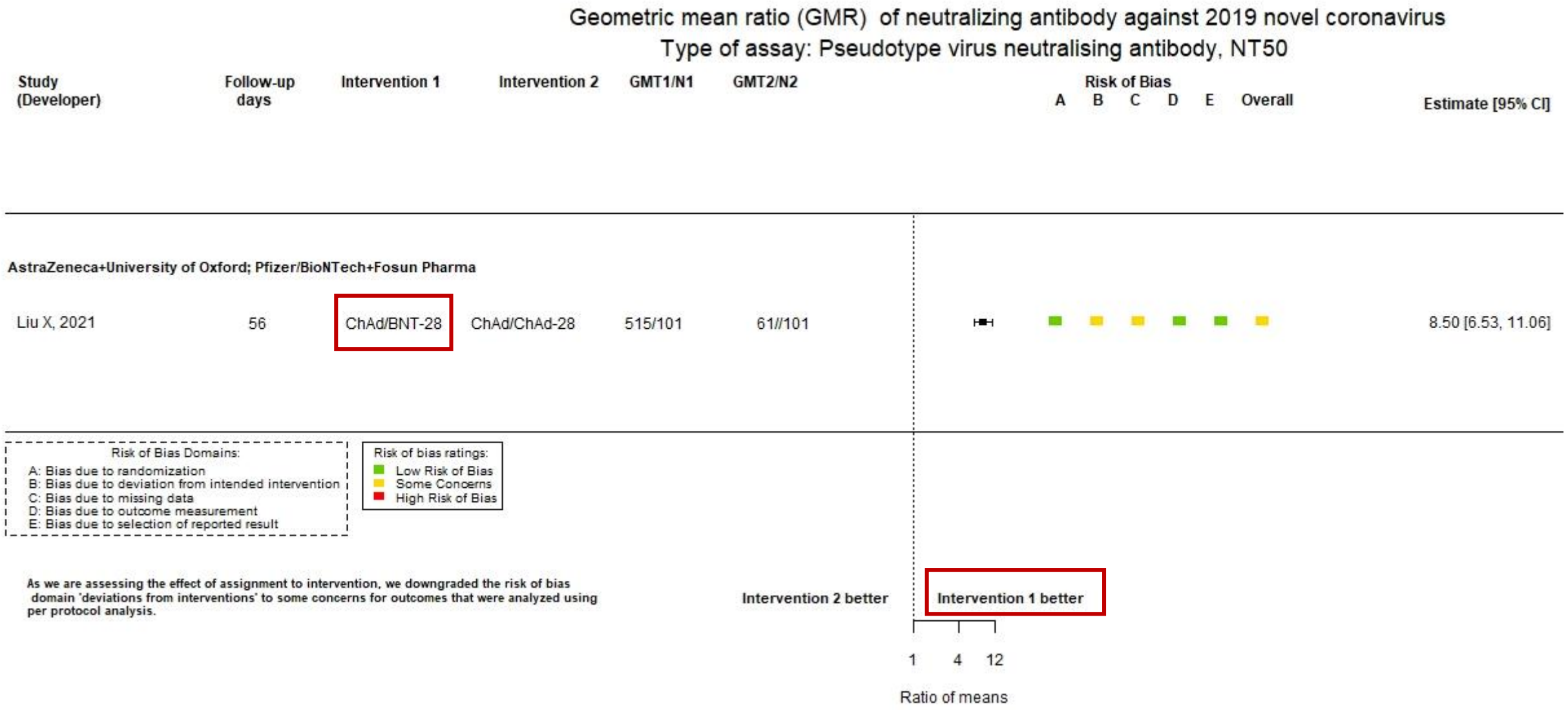
Methodological issues on variant data

- **Post-hoc analyses**
  - Post-hoc sequencing of samples
- **Lack of power**
  - Trials were not planned to assess vaccine efficacy on COVID-19 by variants
  - Very imprecise results
- **Missing outcome data**
  - No sequencing results available/no sequence performed
- **Heterogenous measurements of outcome**
  - Direct/indirect evidence
  - Timepoint after vaccination

Heterologous prime-boost - BNT/ChAd-28 vs BNT/BNT-28



Heterologous prime-boost - ChAd/BNT-28 vs ChAd/ChAd-28



BNT vaccine efficacy and safety after 6 months

Ongoing RCTs on booster doses

1. **The Cov-Boost study (https://www.covboost.org.uk/about)**
   - Comparison of 7 different COVID-19 vaccines compared to a control group (vaccine against the meningococcal bacteria)
   - Objective: to evaluate the immune response after the booster dose and whether it provides extra protection against COVID-19 virus infections and disease
   - Adults aged ≥30 who received their first dose of COVID-19 vaccination in December 2020, January or February 2021 and are 84 days post second vaccination
   - New vaccines can be added
   - Half dose for 3 vaccines to assess efficacy and reduction of side effects (→ increase in supply)

2. **Sequential Immunization of Inactivated COVID-19 Vaccine and Recombinant COVID-19 Vaccine (https://clinicaltrials.gov/ct2/show/NCT04952727?cond=boost+covid&draw=2)**
   - primed with two doses of inactive SARS-CoV-2 vaccine + booster vaccine after 3-6 months:
     recombinant SARS-CoV-2 Ad5 vectored booster **vs** inactive SARS-CoV-2 vaccine booster

Preliminary results on booster doses

Li et al. medRxiv, posted August 8, 2021
(https://www.medrxiv.org/content/10.1101/2021.08.03.21261544v1.full)

- third dose of CoronaVac (Sinovac) given 8 months after the second dose
- significantly increased neutralizing antibody levels on day 7
- 3 doses tested: 1.5 µg, 3 µg, **6 µg**
- GMTs increased from 4.1 (3.2-5.2) six months after the second dose to 418.8 (295.6-593.3) seven days after the third dose

To add safety

Conclusions

- Limited evidence available on variants
- Interpretation of results with caution due to methodological issues
- Heterologous prime-boost seem to perform well on immunogenicity outcomes
- Efficacy of BNT vaccine after 6 months…
- Preliminary results on booster doses suggest an important increase in neutralizing antibody levels…