WHO protocols and guidance for evaluation of COVID-19 vaccine effectiveness: Recent revisions and current recommendations

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Technical Consultation Meeting for the EM Regional COVID-19 Vaccine Effectiveness Studies

12–13 November 2023 | Cairo, Egypt

Nothing beats an RCT

Why need VE studies for Covid-19 vaccines?

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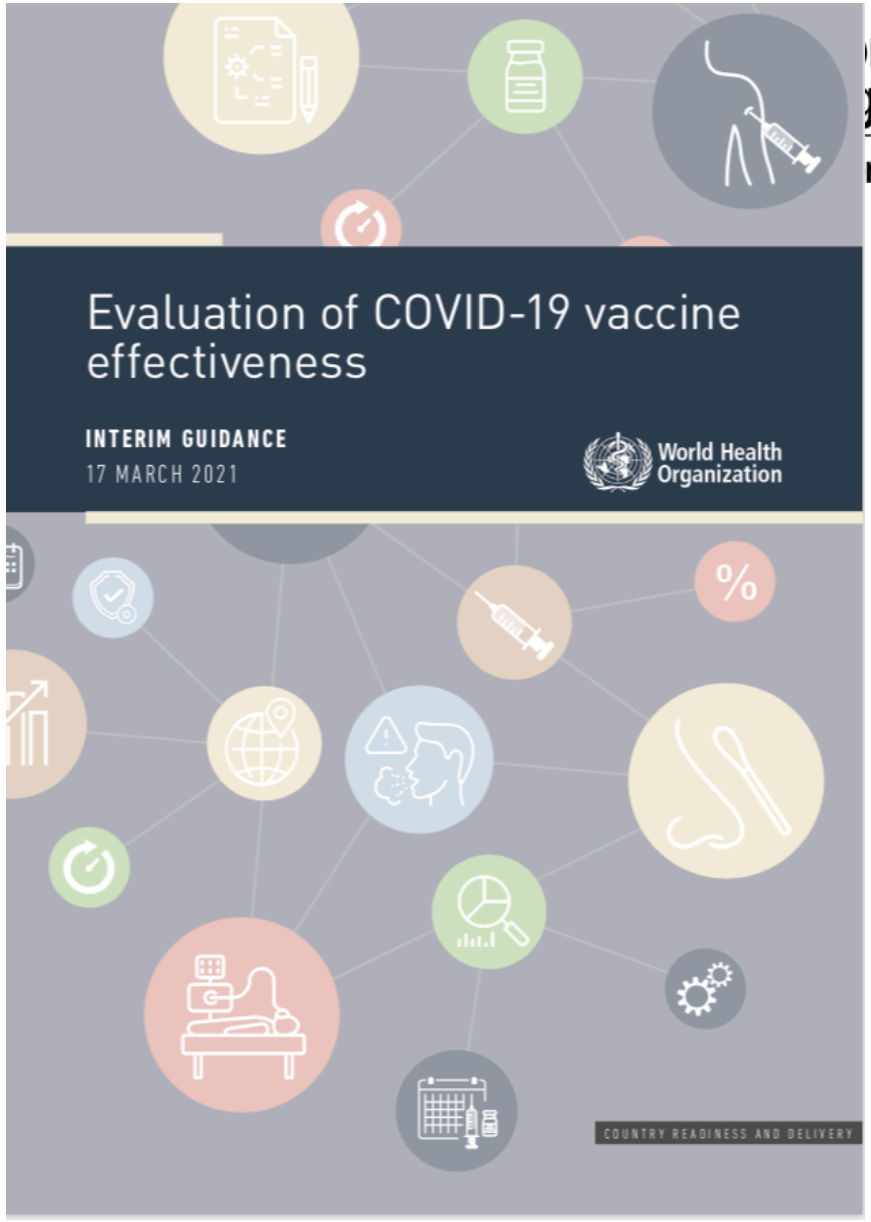
- Randomized clinical trials (RCTs) can only tell us how the vaccines work under ideal conditions
- Real world is messier, and there are unanswered questions
  - Program delivery issues
  - Implementation differences
  - People not studied in RCT might have different immune responses
  - Some outcomes might not have been studied in the RCT
  - Pathogen evolution
  - Duration of protection
  - Impact of co-administration with other routine vaccines
- Provide input into models that estimate impact
- Provide post-authorization confirmation for regulatory bodies and for those authorized by immunobridging studies

VARIANTS

Initial WHO guidance. March 2021

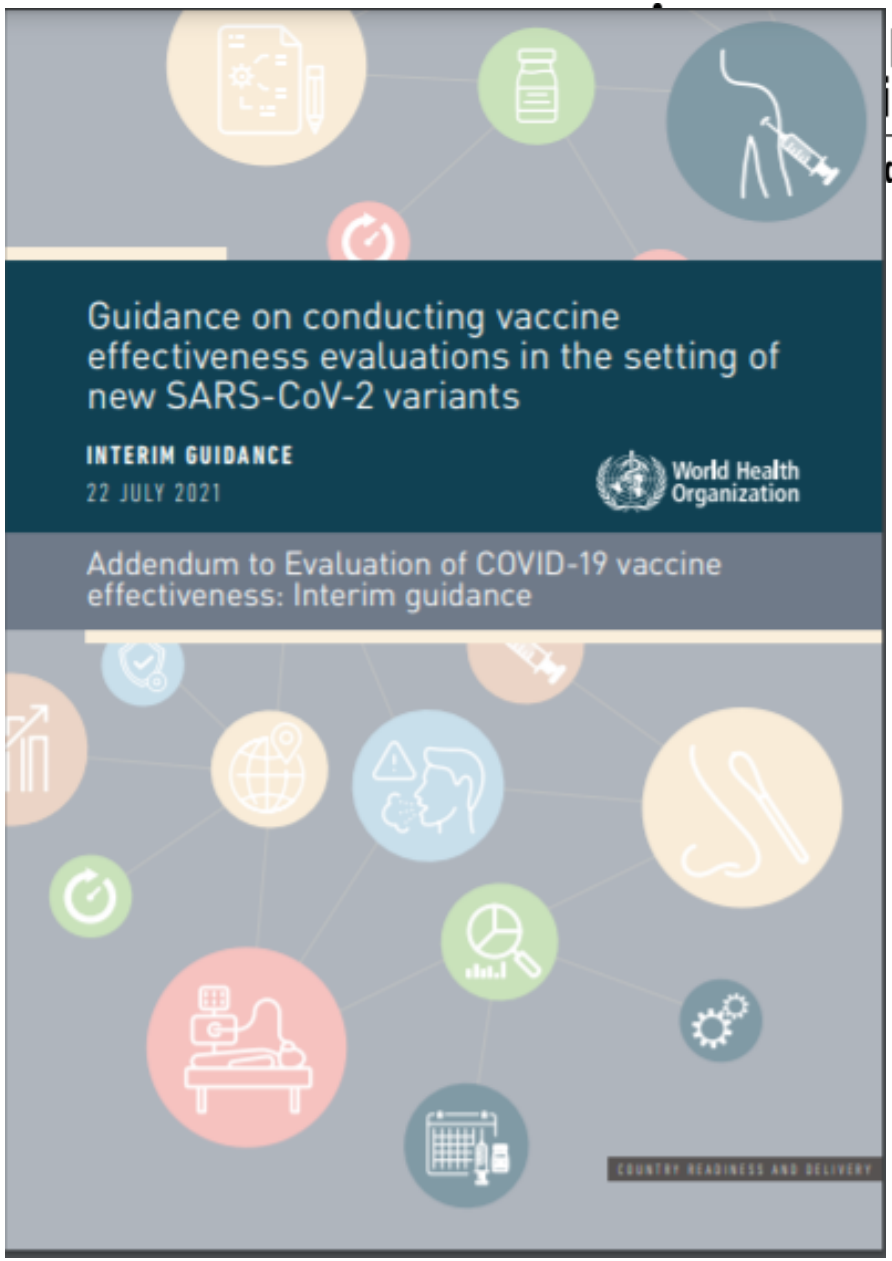
- VE methods working group October 2020
- Target audience LMICs
- Multiple designs possible – test-negative design most practical/'easiest' in most settings
- Every participant should have PCR-based outcome
- Rapid antigen tests too low sensitivity and specificity
- Covariates to collect
- Vaccination history should be documented, not just reported
- Biases will always exist→need to carefully consider in study design (bias) and analysis (confounding)
- Updated STROBE reporting requirements (e.g. report on VOC in study population)
- EMRO collaborators involved



https://www.who.int/teams/immunization-vaccines-and-biologicals/immunization-analysis-and-insights/surveillance/covid-19-vaccine-effectiveness-and-impact

VE guidance Addendum 1. July 2021

- VE in the setting of VOCs
- Early triggers of reduced vaccine effectiveness against new variants
  -Screening method
- Case only analysis
  Comparison of variant prevalence in unvaccinated/vaccinated
  Sieve analysis (like influenza clade analysis)
- “Traditional” methods
  -Genomic characterization of all/some of cases
  -S gene target failure in Taq-Path PCR
- Analytic considerations, e.g., representative characterization
- Biases, e.g., variant changes ability to be detected by RT-PCR or results in different clinical spectrum



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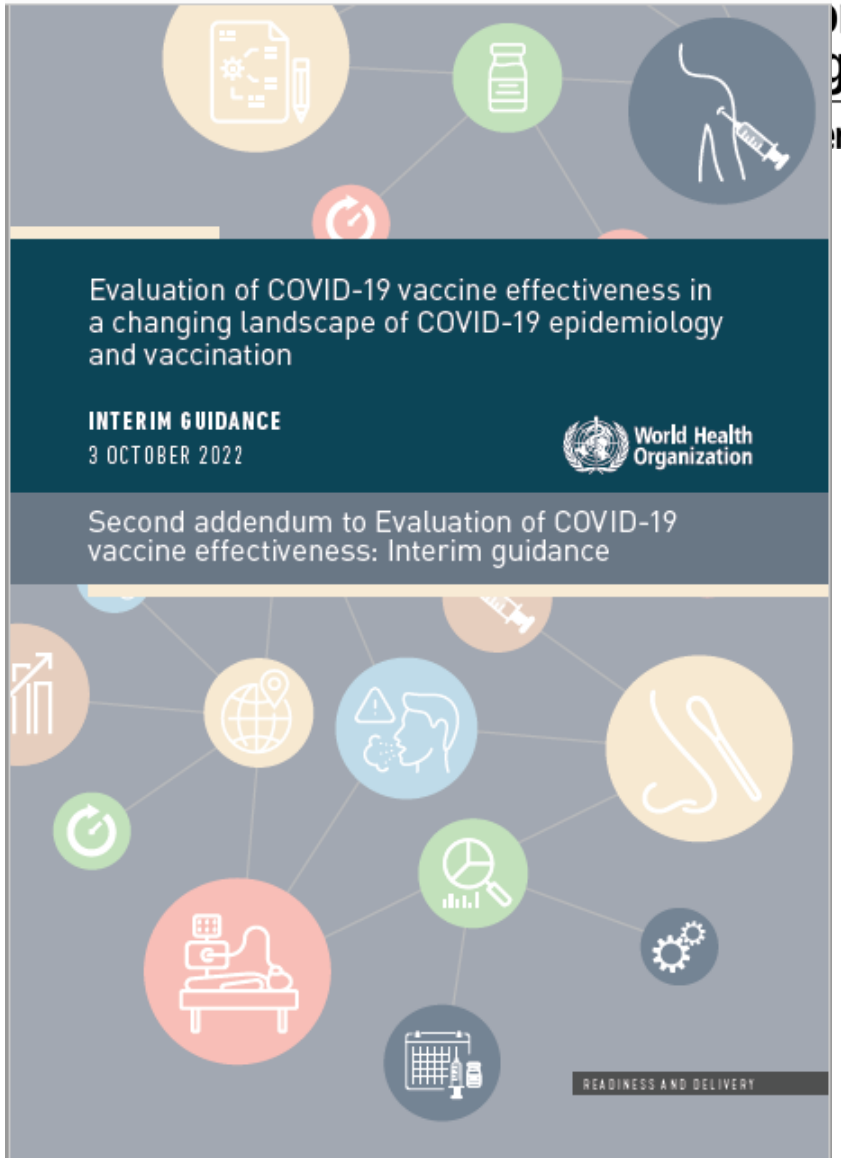
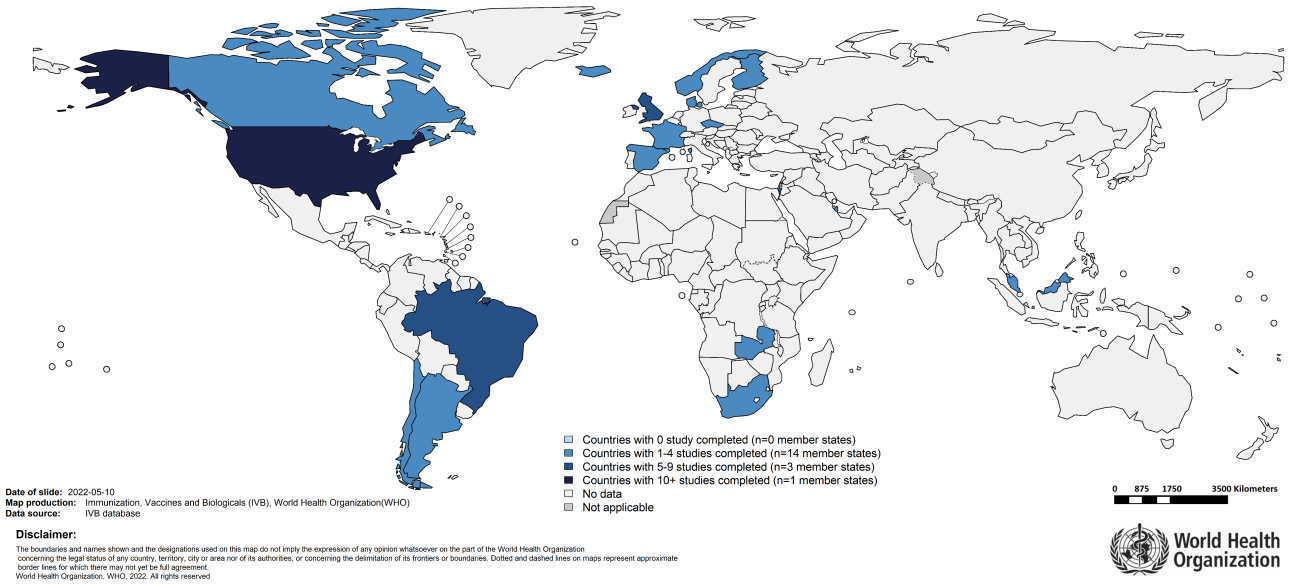
VE Guidance Addendum 2. October 2022

- VE in the setting of Omicron, waning VE, booster doses
- Infection-induced immunity
- Relative VE
- Defining severe disease
- Selection of controls more challenging
- Vaccinated Comparison group
- Hybrid immunity
- Biases



VE Stakeholders meeting

Number of completed studies by country



Date of slide: 2022-05-10
Map production: Immunization, Vaccines and Biologicals (IVB), World Health Organization(WHO)
Data source: IVB database

Disclaimer:

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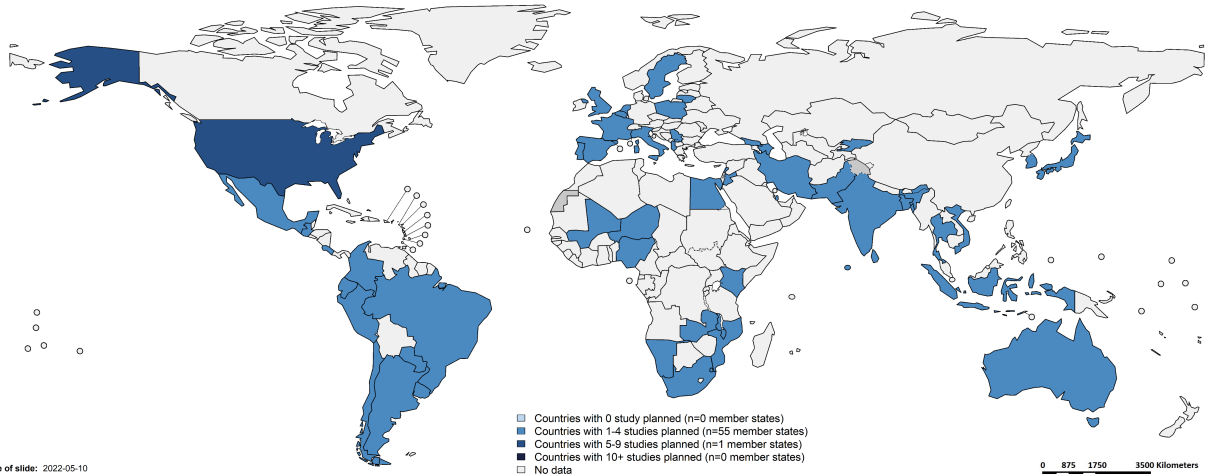
Number of planned studies by country



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Vaccine Effectiveness Studies Over Time as of November 2, 2023

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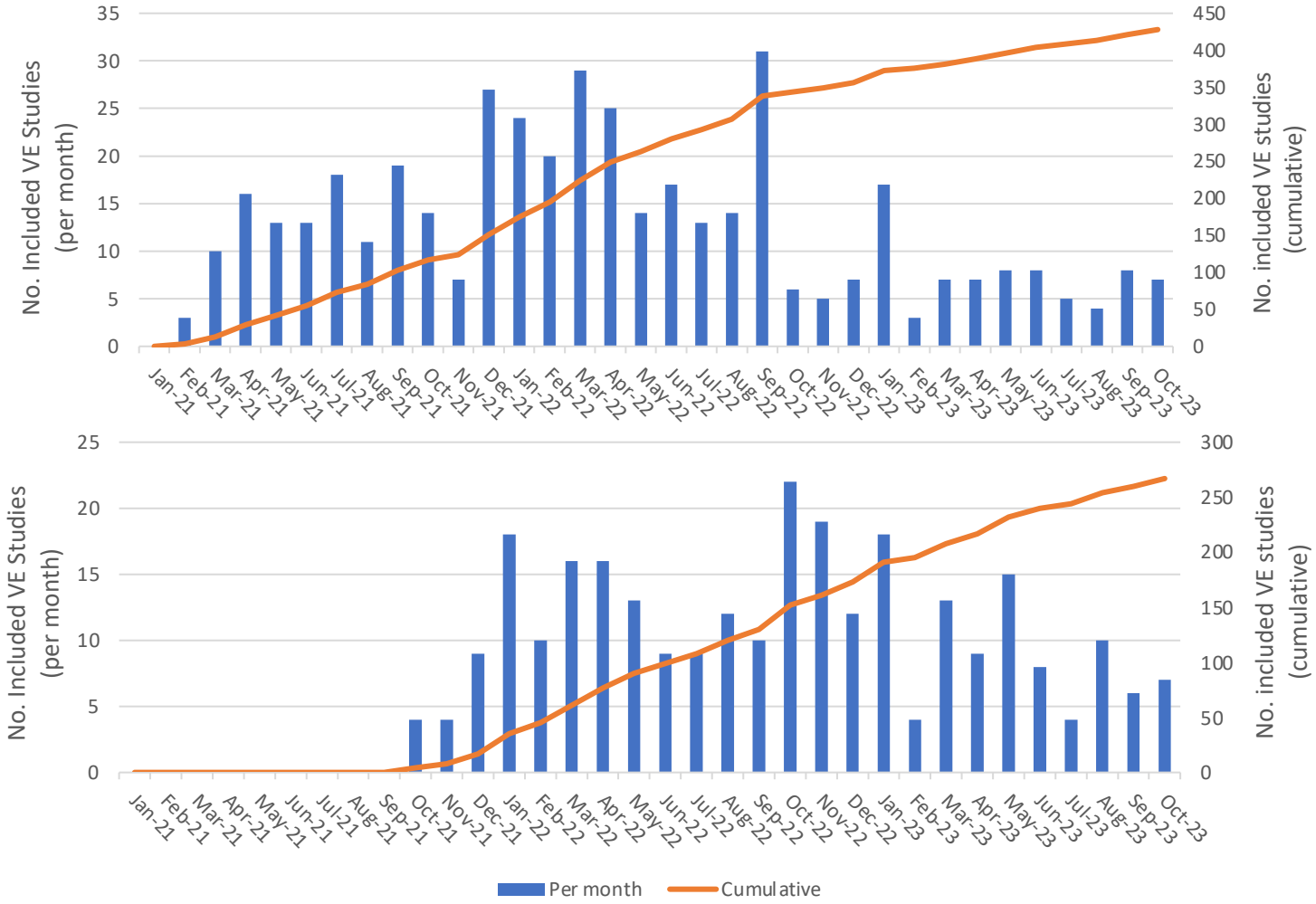
Total Studies: 522



Primary Series Studies: 428

Booster Dose Studies: 267

ViewHub.org

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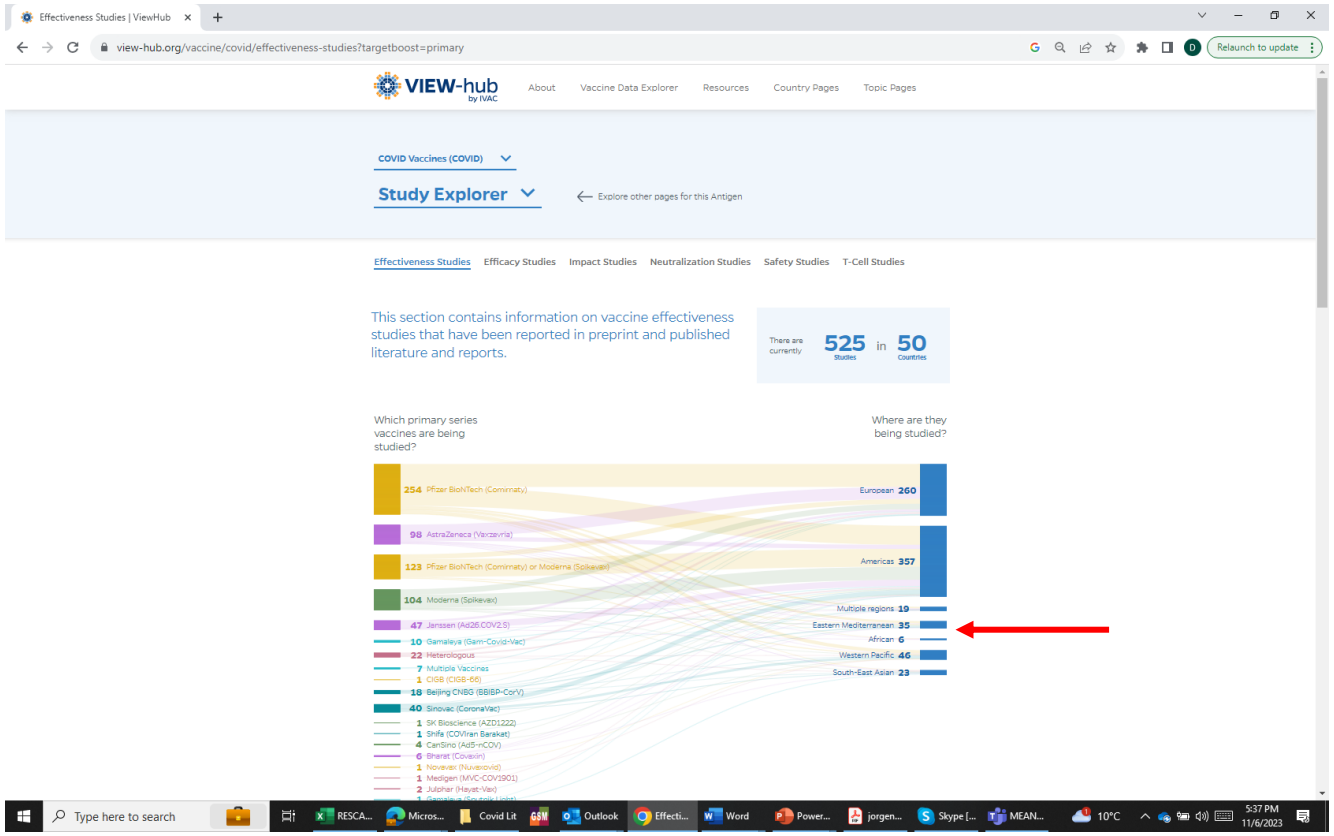
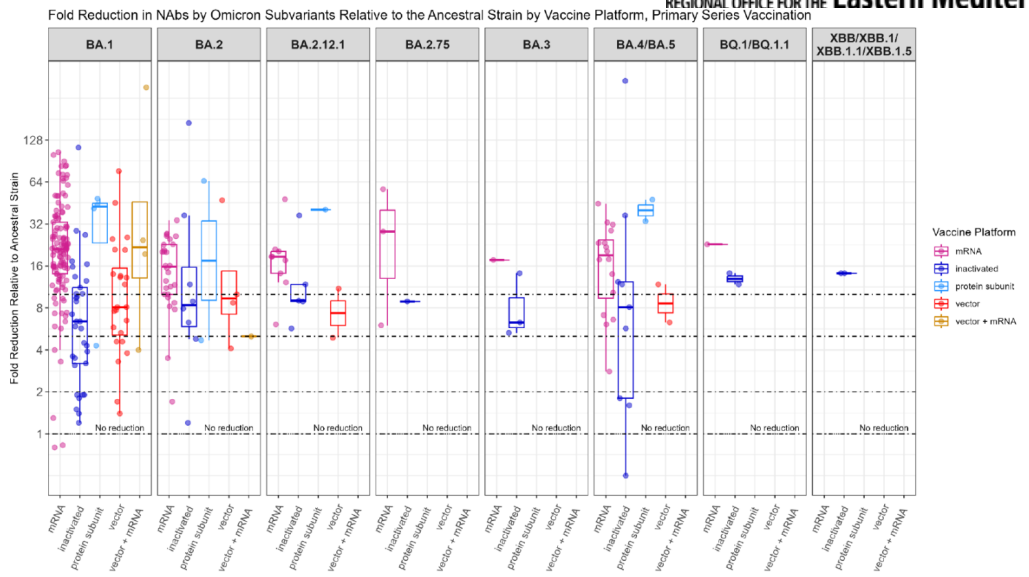
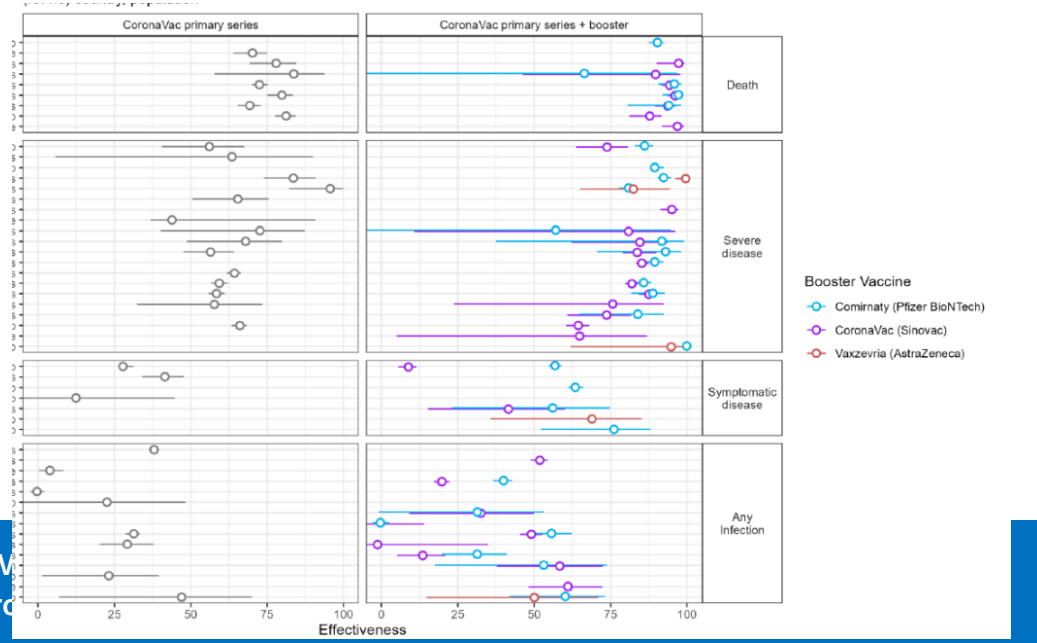






Current issues in Covid VE studies

- Vaccinated comparator group / Relative VE
- Definitions of severe disease
- Infection induced immunity

Absolute vs. Relative VE

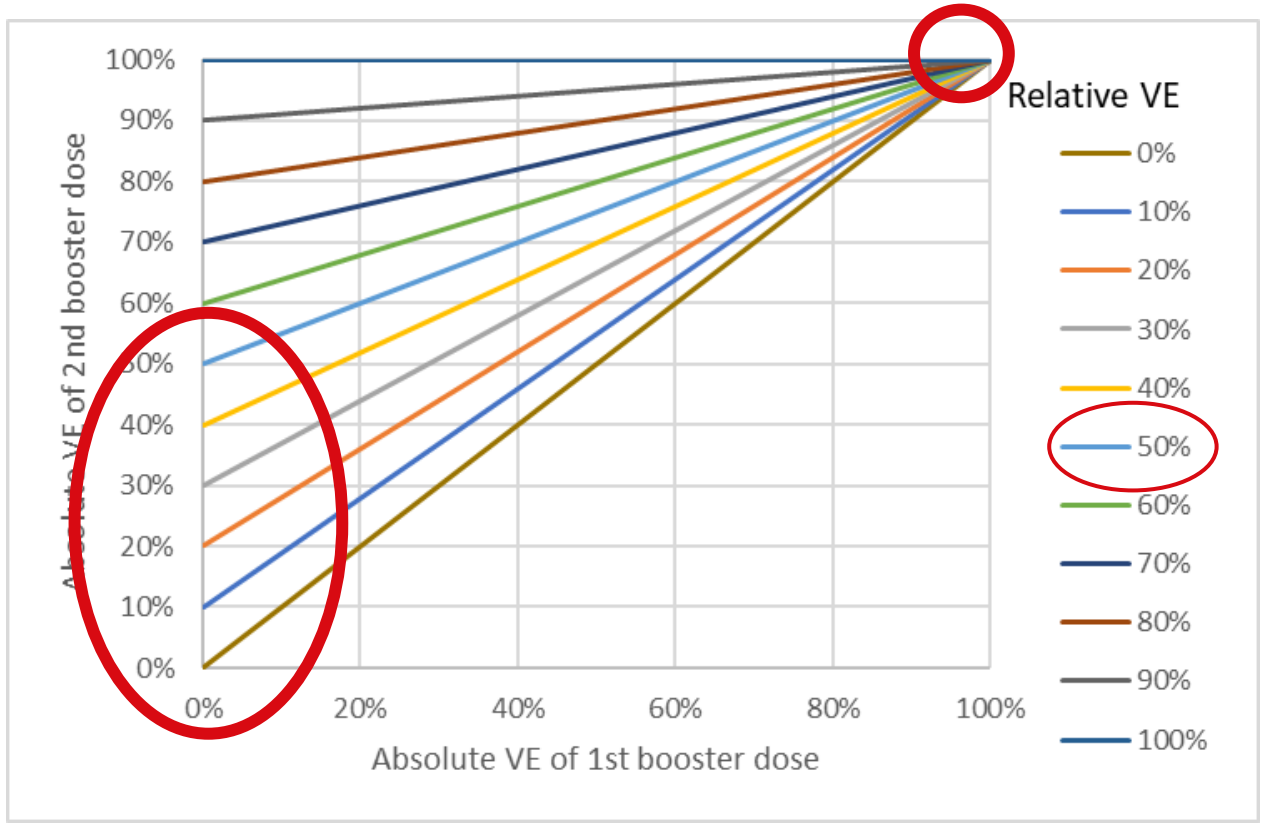
- Most recent VE studies use a vaccinated comparator group
- Absolute VE compares vaccinated people to *unvaccinated* people
- Relative VE compares vaccinated people to other vaccinated people, who have had fewer doses (e.g., 1st booster vs. primary series, 2nd booster to 1st booster, etc)
- Also called incremental VE or marginal VE
- Why Relative VE?
  - Few unvaccinated persons in many settings.
  - 2+ years since vaccine first introduced, unvaccinated people choose to be unvaccinated, and have many confounders

Absolute versus Relative VE

$$rVE = \frac{aVE_{2nd\ booster} - aVE_{1st\ booster\ dose}}{1 - aVE_{1st\ booster\ dose}}\ x\ 100\%$$

- Marginal increase in aVEs between two vaccinated groups
- Comparison group may have residual aVE
- rVE is < or = to aVE (few exceptions)

Absolute VE 1st booster dose	Absolute VE 2nd booster dose	Absolute gain in VE	Relative VE 2nd booster dose
0%	50%	50%	50%
90%	95%	5%	50%



- Relative VEs cannot be compared between studies as contingent upon residual immunity in comparator population

Relative VE to assess waning can distort results

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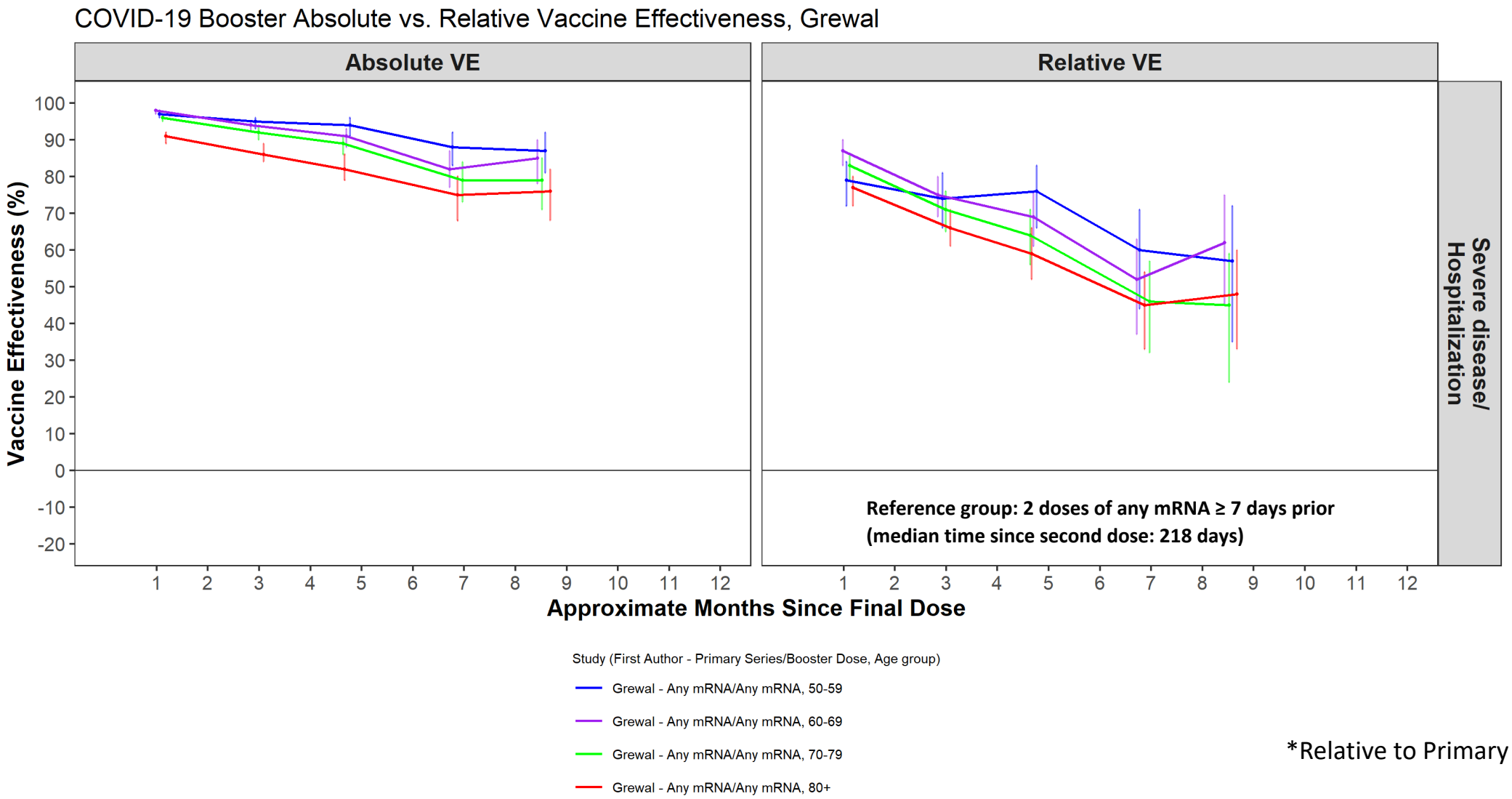
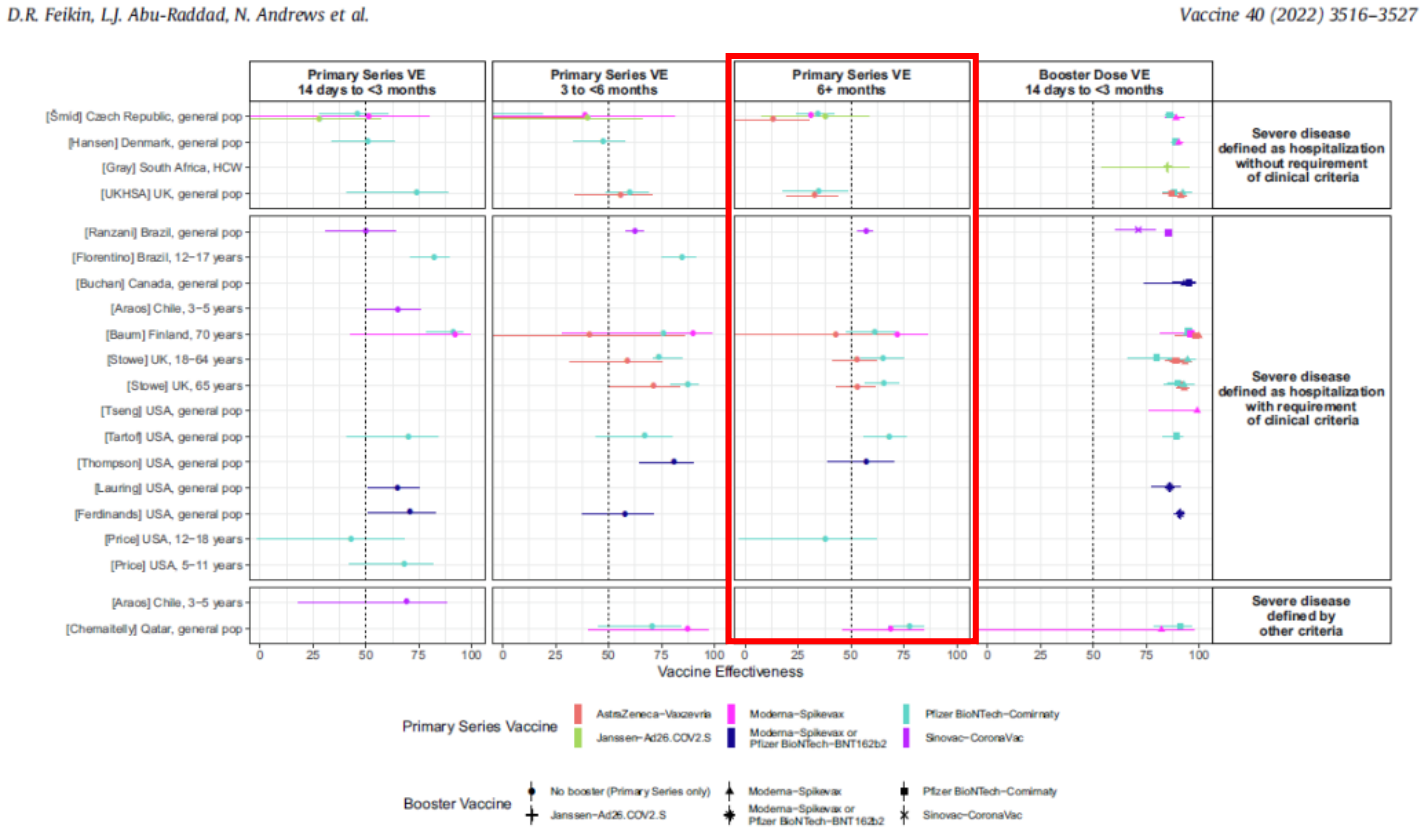


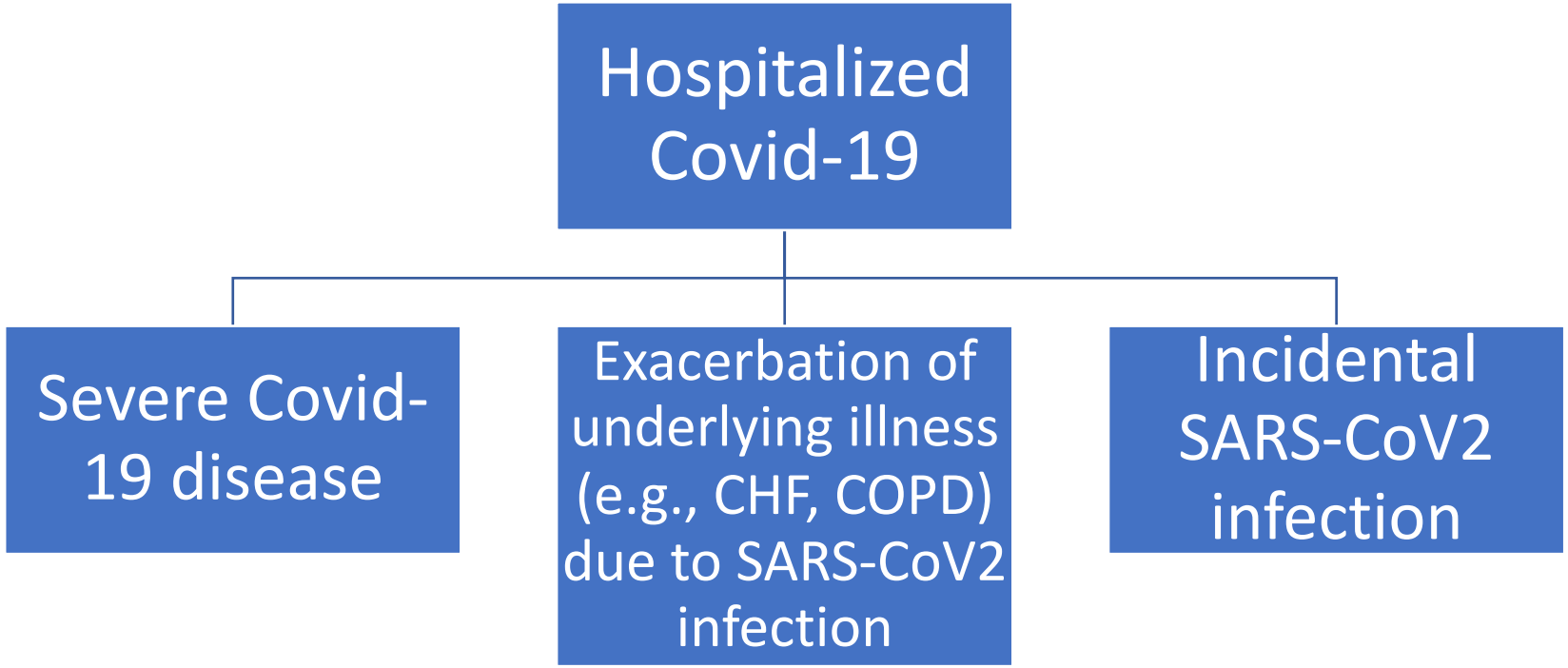
*Relative to Primary series VE

Defining severe disease

- VE against “severe disease” is lower with Omicron
- Hospitalization alone not an adequate definition of severity during Omicron



Defining severe disease during omicron



How to address misclassification of severe disease

- Include symptoms/signs of Covid-19 in case definition
- Use more severe outcomes in case definition (e.g., oxygen requirement, ICU)

High Infection-induced immunity

- High seroprevalence in most adult populations post-omicron
- Multiple reinfections common due to waning immunity against infection
- Absolute VE higher among those with hybrid immunity (vaccination + infection)

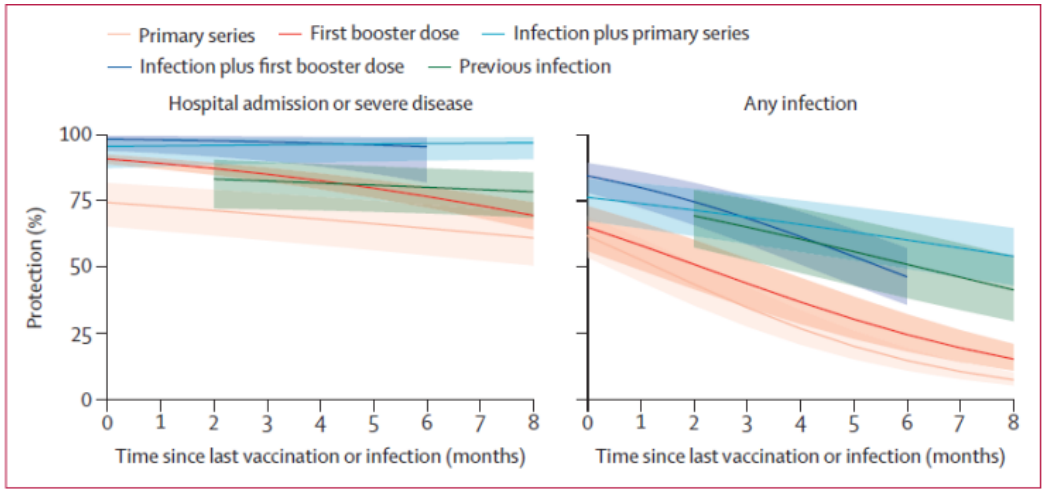


Figure 3: Protection against omicron variant conferred by the primary series vaccine, first booster vaccine, previous infection, and hybrid immunity compared to immune-naive individuals over time
The shaded areas denote 95% CIs. Vaccine effectiveness data were procured from a separate systematic review.

Bobrovitz N et al. Lancet ID
https://doi.org/10.1016/S1473-3099(22)00801-5

High Infection-induced immunity

- “Depletion of susceptibles”
- Recent infection higher in unvaccinated or less vaccinated group
- So the comparator group in VE studies might have more recent infection-induced immunity than vaccinated group
- This leads to spuriously low VE, especially when looking at duration of protection
- In extreme cases, this can result in negative VE

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Thank you

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