Covid-19 Vaccine Effectiveness (VE): Updates from HQ

EMRO COVID-19 VE Capacity Building workshop

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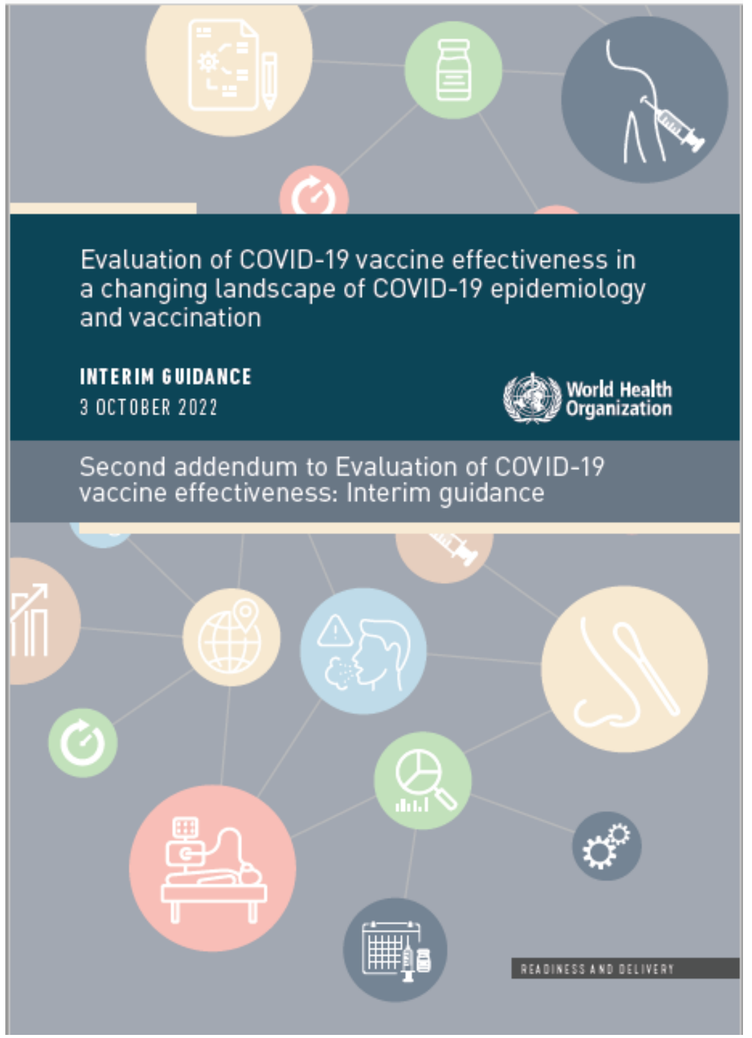
IVB

Global Guidance Update

Global Guidance

- March 2021: Global guidance on conducting COVID-19 VE studies
- July 2021: 1st addendum expanding on key components related to VOCs
- October 2022: 2nd addendum
  - Why a 2nd addendum?
    - Lessons learnt from >2000 studies that have highlighted several methodological concerns that either were not addressed in the initial guidance or are in need of modification.
    - Waning VE is prominent
    - Omicron causing immune evasion
    - High vaccination rate in some settings→unvaccinated dissimilar to vaccinated leading to bias
    - Complex vaccination landscape with multiple vaccines used at different periods targeting specific groups of individuals, heterologous schemes for primary series and booster vaccines, and new vaccines targeting VOCs that will soon add further complexity.
    - Hybrid immunity common in many settings→makes interpretation of VE evaluations more challenging



Second Addendum: Topics Covered

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- Study design
  - Severe case definition of hospitalization is suboptimal due to high burden of infection from Omicron
  - Given the high burden of infection with Omicron, cannot assume those who are not tested in cohorts are negative→need to conduct regular testing (issue mostly for database studies)
  - What is the proper comparison group?
    - Absolute VE. Unvaccinated become different from vaccinated
    - Relative VE: compare different # of vaccine doses (e.g. 1st booster compared to primary series)
    - Comparison to time frames post vaccination
      - E.g compare to 6-9 months after primary series due to waning

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- Hybrid immunity: Recommendations on how to evaluate
- Variant specific estimates: Defining predominant periods/including a wash-out period
- Biases—in addition to biases in original guidance
  - Negative VE→mostly due to unaccounted for confounders
  - Changes in testing practices need to be considered when conducting VE studies
  - Should not use persons testing positive for influenza and negative for COVID-19 as controls in TND studies
  - Duration of protection
    - Depletions of susceptibles
    - Early vaccinee bias

Current Policy Questions in which VE data is relevant

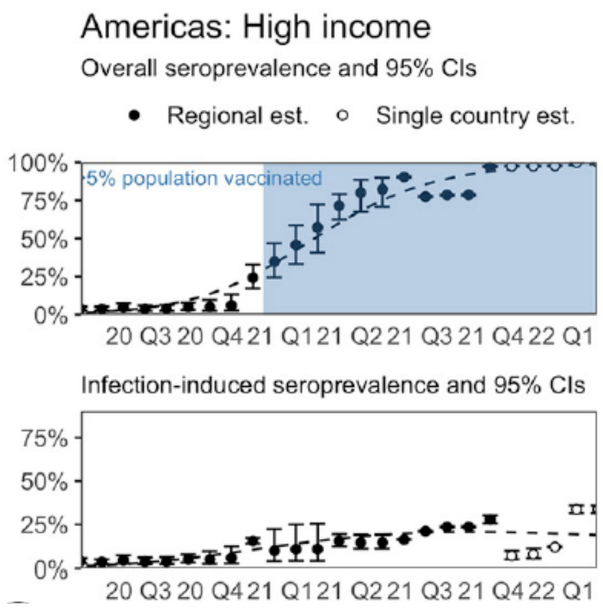
- What is the optimal number and timing of booster doses after receiving the primary series?
  - High risk or all groups
  - Severe disease vs. infection prevention
- Should vaccine products and schedules should be amended in the setting of high population immunity (hybrid immunity)?
- How to optimize VE evaluations in the setting of future variants with immune evasion?
- Are variant-containing vaccines more beneficial than the original ancestral vaccines?

Hybrid immunity

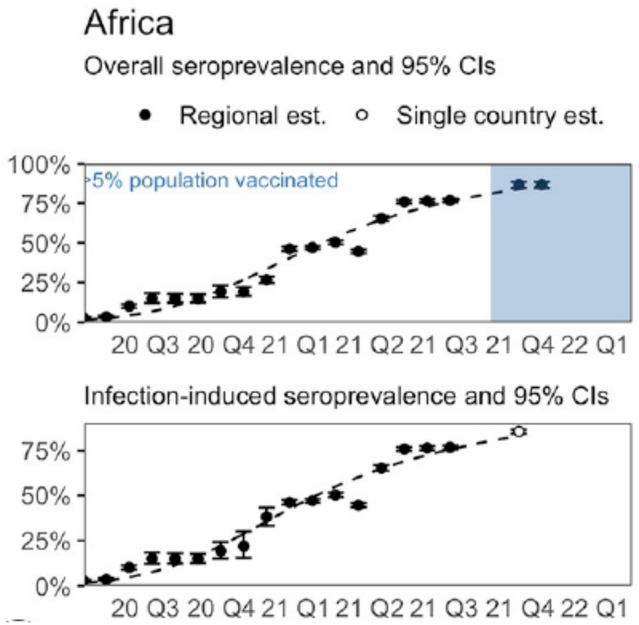
Hybrid Immunity

- Infection-induced immunity: Protection afforded by SARS-CoV-2 infection (alone)
- Vaccine-induced immunity: Protection afforded by vaccination (alone)
- Hybrid immunity: Protection afforded by vaccination plus SARS-CoV-2 infection (in any order)

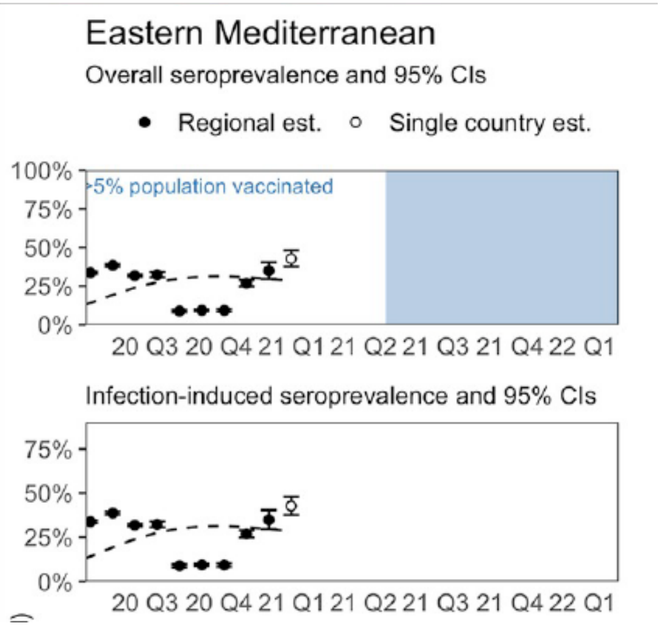
Much of the world's population has been infected by now



Mostly vaccine-induced immunity



Mostly infection-induced immunity



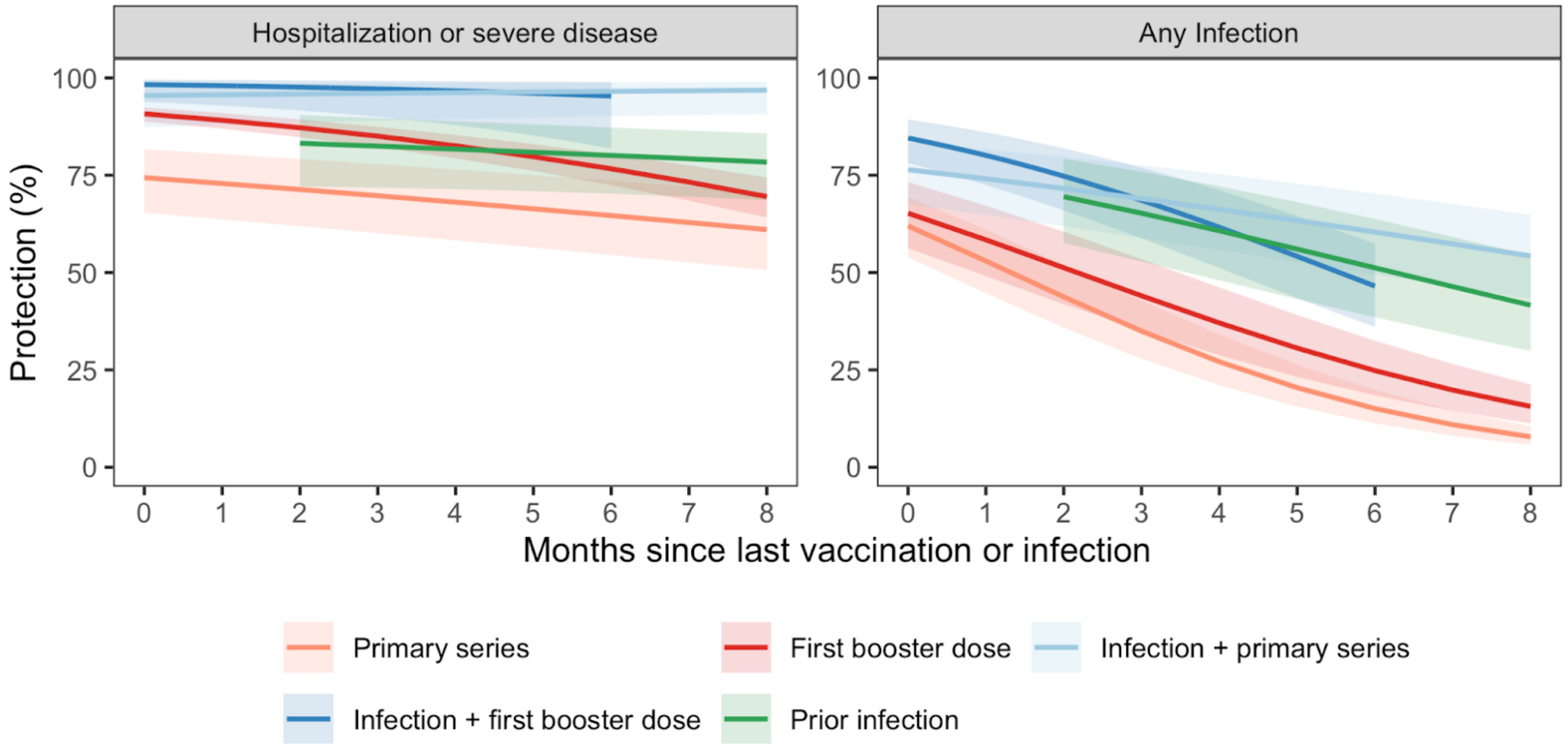
Mostly infection-induced immunity

Most serosurveys were done before omicron. Infection-induced immunity and hybrid immunity now likely much higher

From Bergeri I, et al. PlosMed. https://doi.org/10.1371/journal.pmed.1004107

Hybrid immunity – Infection plus vaccination

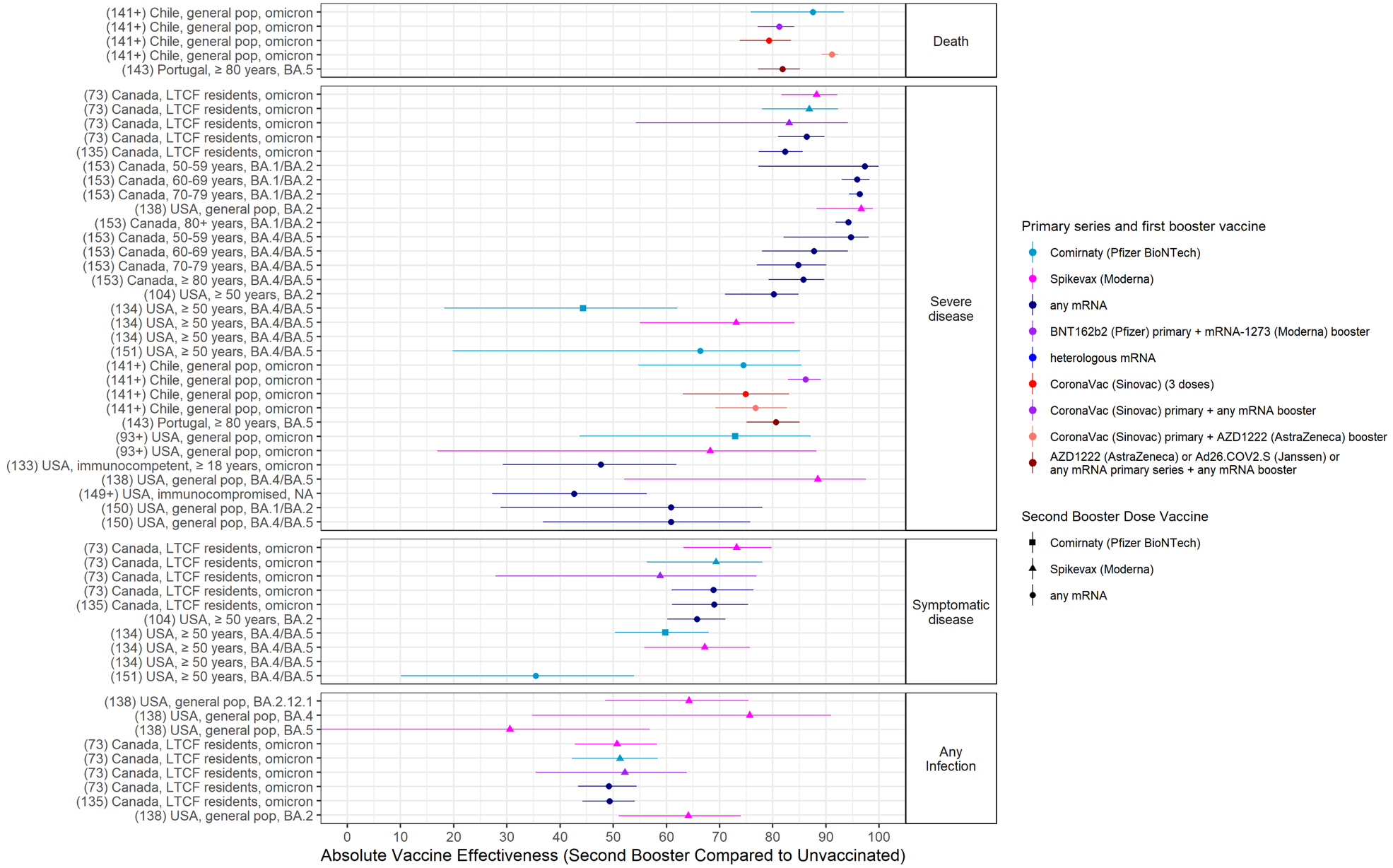
Hybrid immunity confers higher and more sustained effectiveness than vaccination or infection alone



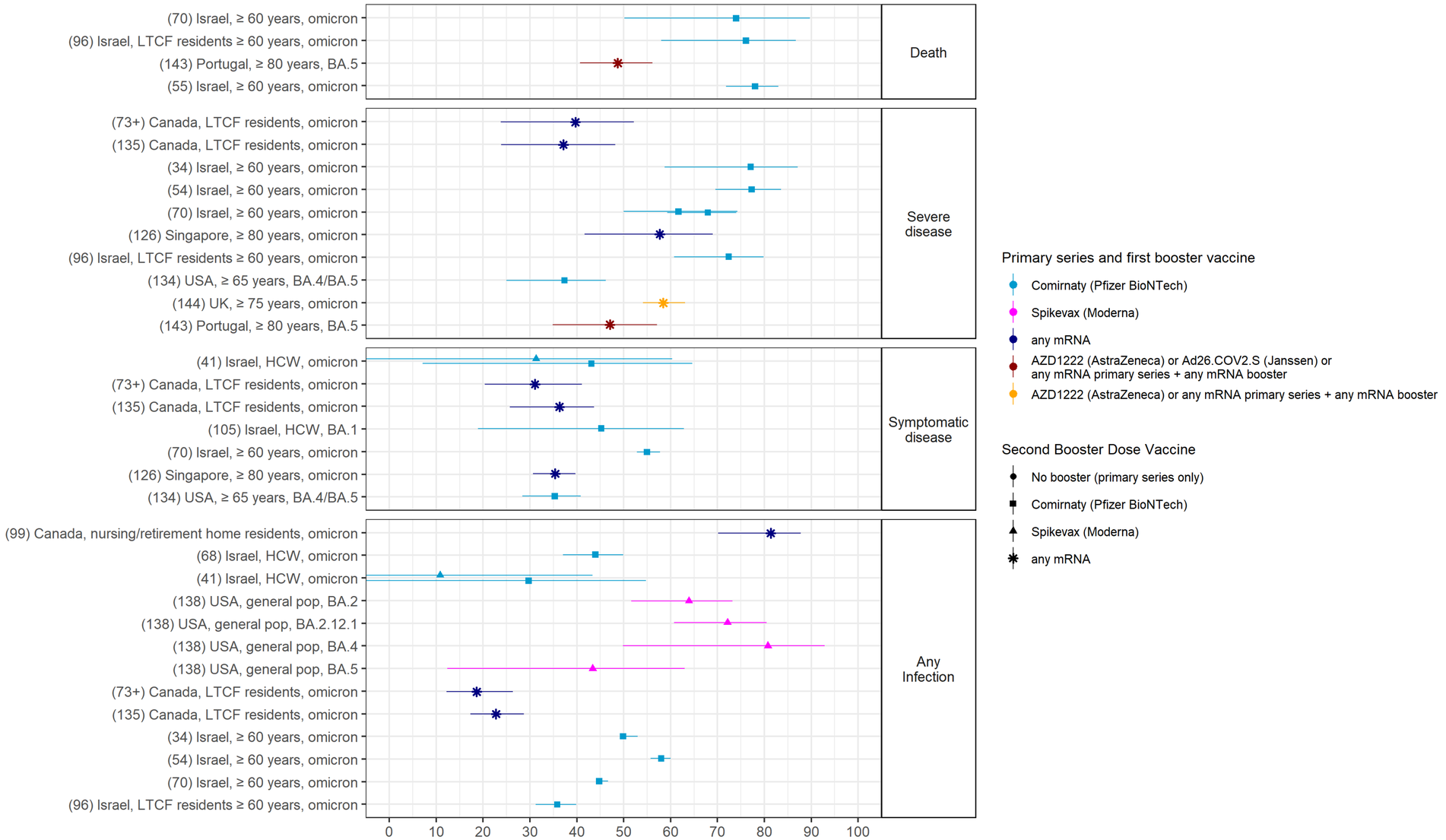
Bobrovitz, N et al, in press

VE of a second booster dose?

Absolute VE of 4th dose compared to unvaccinated

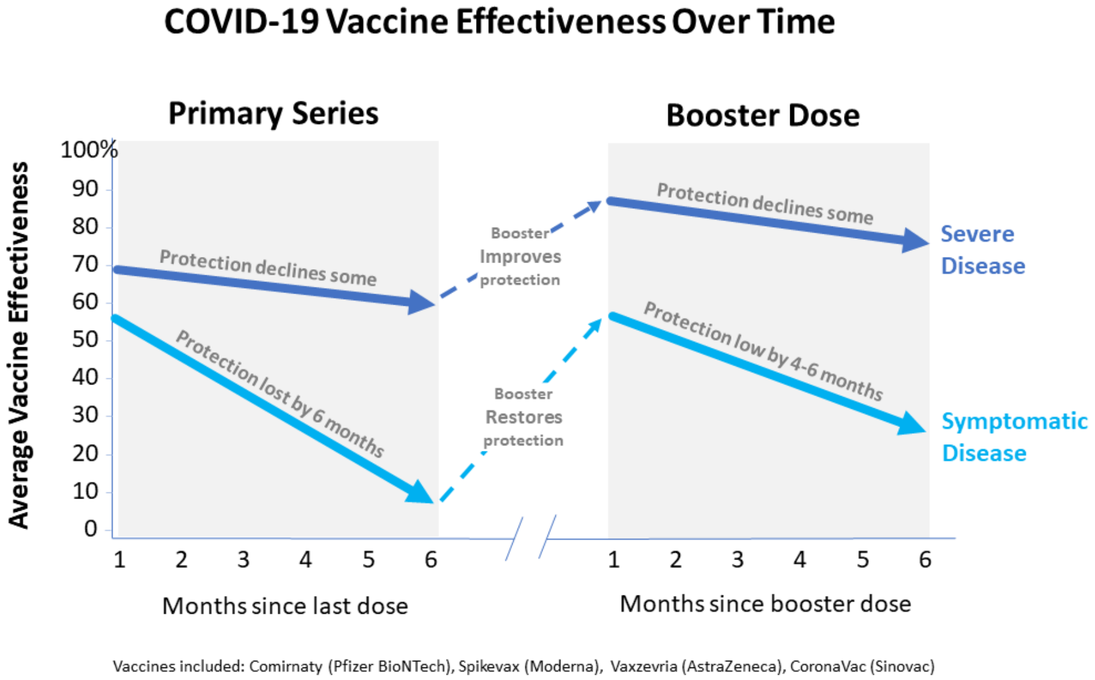


Relative VE of 4th dose compared to 3rd dose

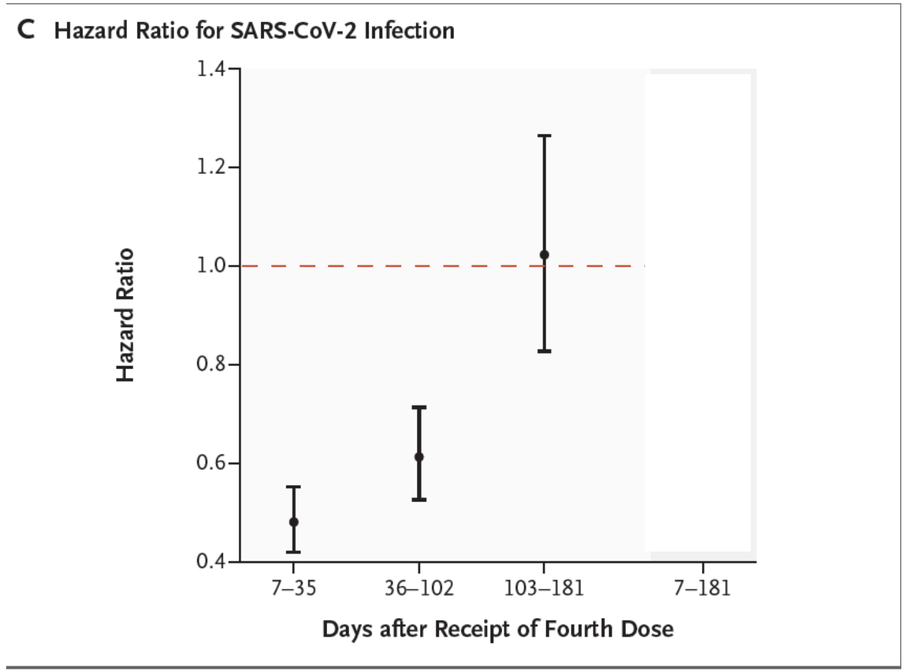


*All values shown estimate VE of a 2nd booster dose relative to 3 doses.
+Indicates follow-up period extends beyond 4 months post receipt of final dose.

Waning after 4th dose seems similar to after 3rd dose



Hazards ratio for infection after 4th dose in HCWs, Israel

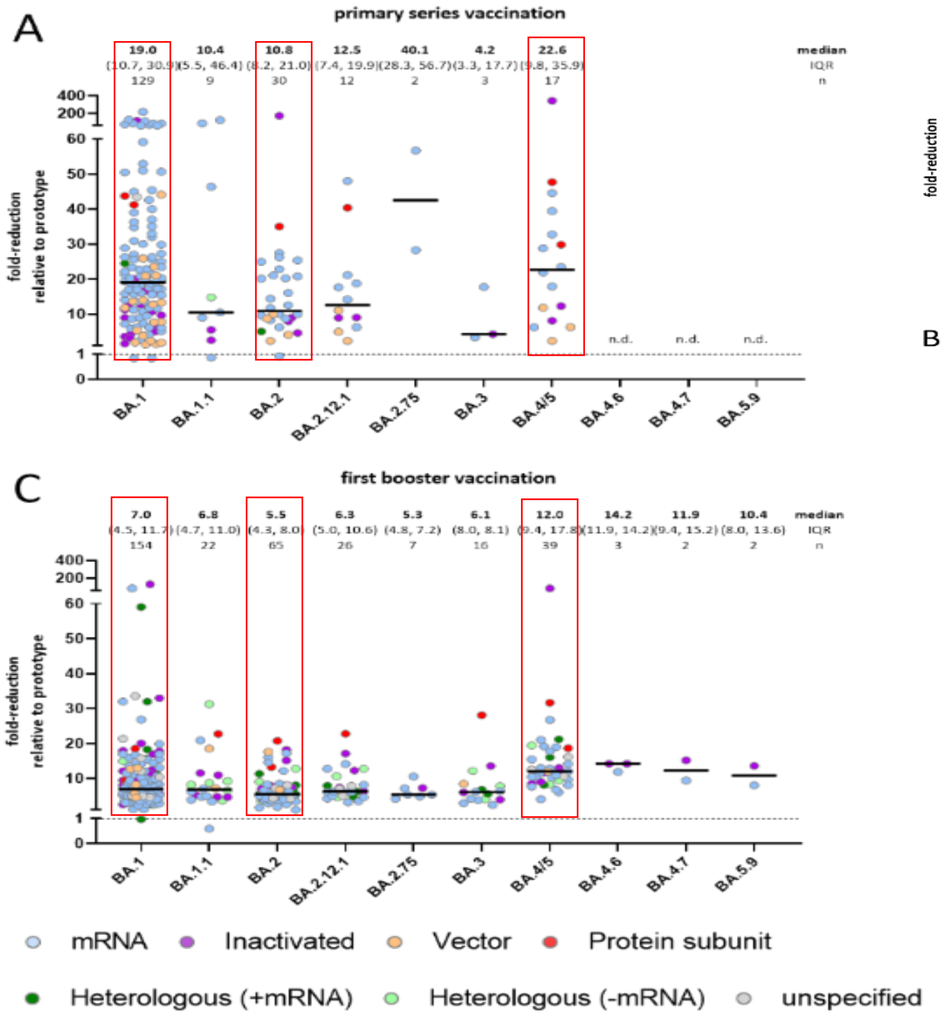


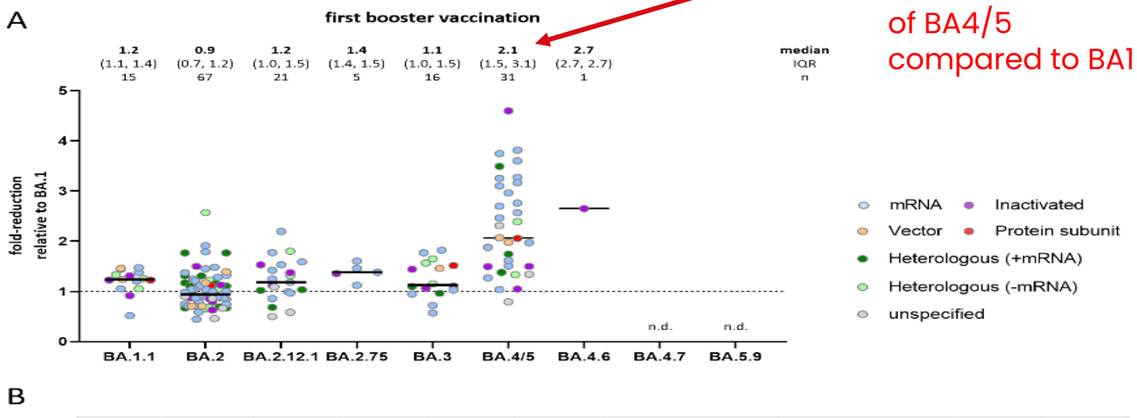
From Canetti M, et al, NEJM

- Early data available only, need more time to accumulate more duration of VE data after 4th dose

VE of Omicron BA4/5

Neutralization for BA4/5 slightly lower than other omicron sub-variants





2.1 fold reduction in neutralization of BA4/5 compared to BA1

Fold-reduction in neutralization titers, median (IQR)

From Jacobsen H, et al. Vaccines, in press.

South Africa: VE against Hospitalization

- Pfizer VE among persons in Discovery Healthy (private insurance) from a TND study
- No difference between BA4/5 and BA1/2 wave VE by time
- Waning seen more steeply than other studies against hospitalization

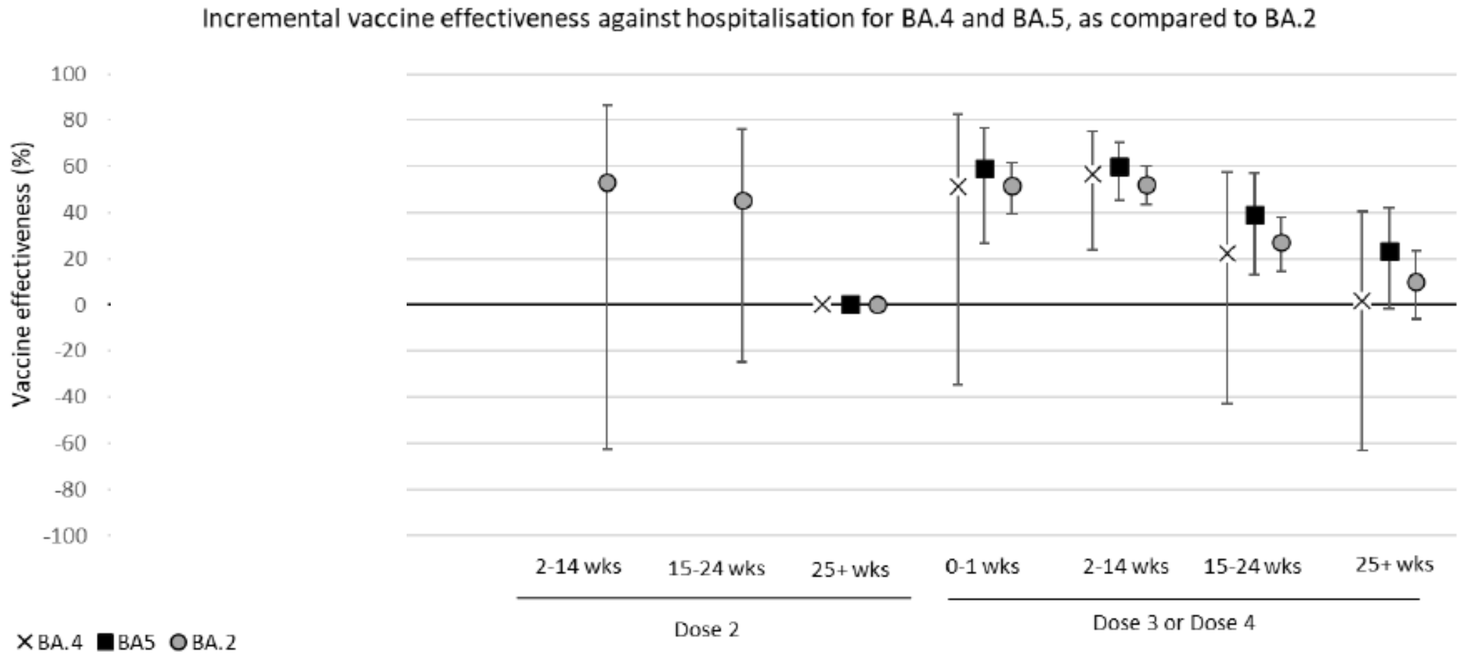
Table 1. BNT162b2 Vaccine Effectiveness against Hospitalization for Covid-19 in South Africa, According to the Dominant Omicron Sublineage.*

Time since Most Recent Vaccine Dose	VE of Dose 2		VE of Dose 3	
	BA.1–BA.2 Omicron Wave	BA.4–BA.5 Omicron Wave	BA.1–BA.2 Omicron Wave	BA.4–BA.5 Omicron Wave
	percent (95% CI)			
0–13 days	66.7 (38.3–82.0)	—	—	—
14–27 days	80.3 (62.8–89.5)	—	81.6 (68.1–89.4)	—
1–2 mo	61.3 (54.7–66.9)	—	66.4 (53.7–75.6)	68.8 (59.5–76.0)
3–4 mo	56.3 (51.6–60.5)	47.4 (19.9–65.5)	50.0 (4.4–73.9)	46.8 (35.3–56.2)
5–6 mo	45.6 (39.3–51.3)	26.3 (7.1–41.6)	—	—
7–8 mo	38.4 (16.9–54.4)	23.6 (11.1–34.3)	—	—
≥9 mo	—	19.3 (6.3–30.5)	—	—

Collie, S., Nayager, J., Bamford, L., Bekker, L.-G., Zylstra, M., & Gray, G. (2022). Effectiveness and Durability of the BNT162b2 Vaccine against Omicron Sublineages in South Africa. *New England Journal of Medicine*. https://doi.org/10.1056/NEJMc2210093

UK HSA: relative VE of BA4/5 vs BA2 cases

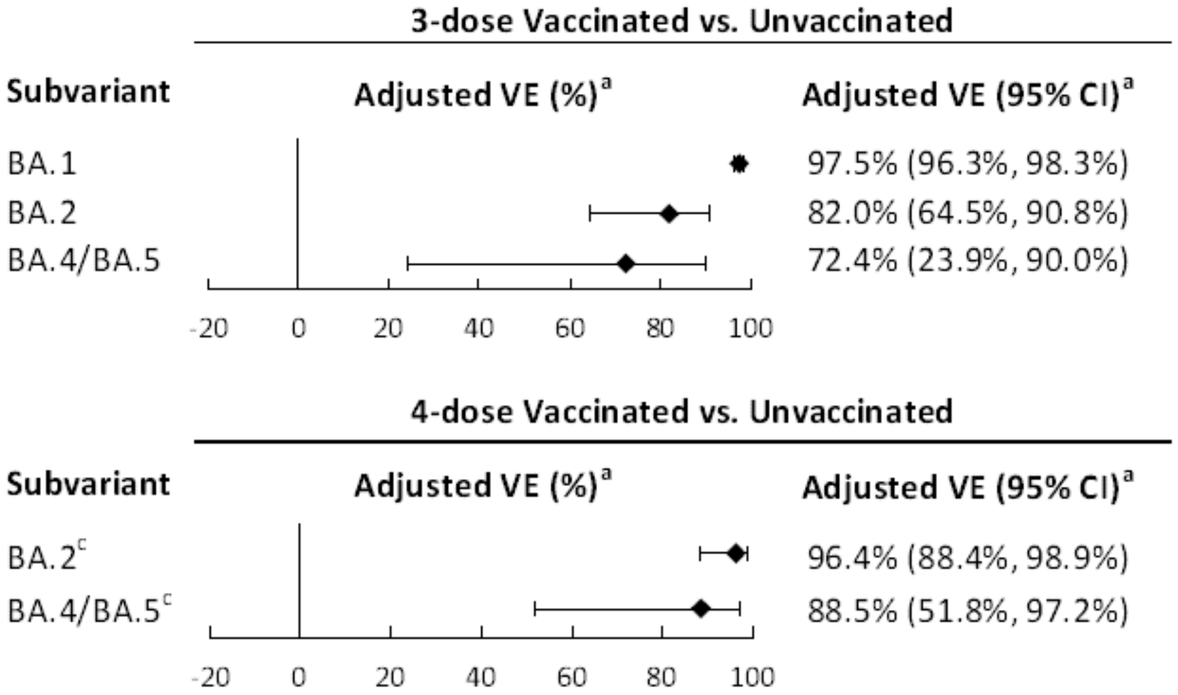
- TND case control among hospitalized patients comparing BA4/5 vs BA2 cases, April-July 2022
- Relative (incremental) VE using 25+ weeks post-dose 2 as comparison to booster doses
- Combined boosters with Pfizer or Moderna; combined primary of Pfizer, Moderna, AZ
- No difference in VE BA4/5 compared to BA2



Kirsebom F et al, MedRxIv. https://www.medrxiv.org/content/10.1101/2022.08.31.22279444v1

USA: VE against severe disease

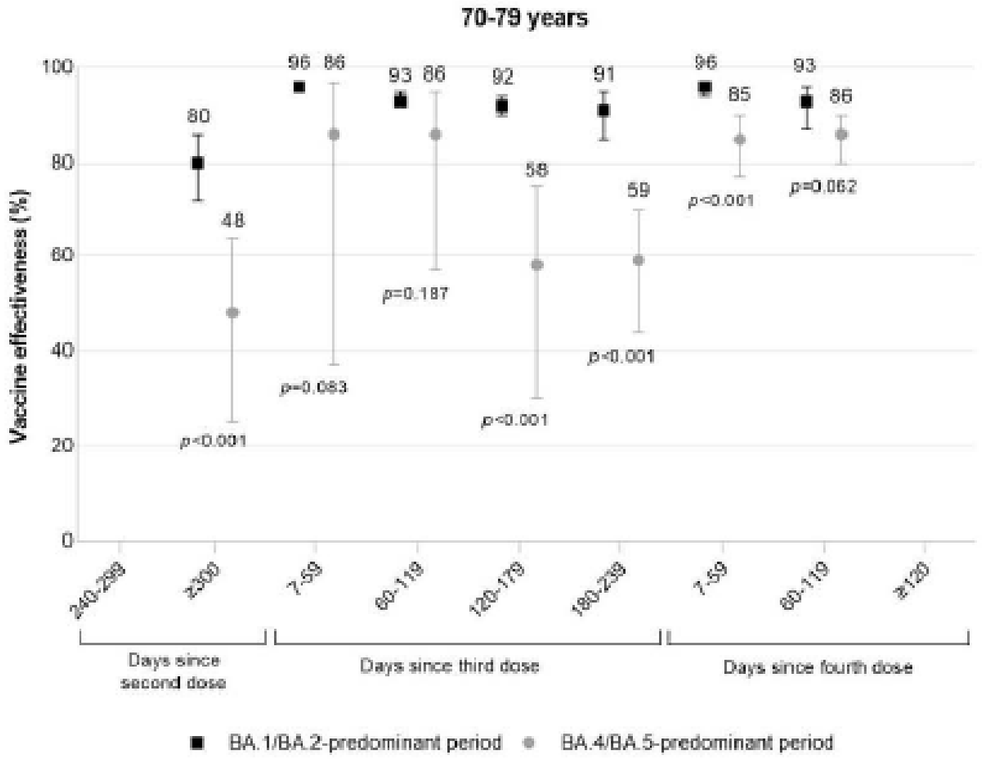
- TND study evaluating Moderna VE against different Omicron subvariants
- VE BA.4/5 lower than BA.1; similar to BA.2



Tseng, H. F., Ackerson, B. K., Bruxvoort, K. J., Sy, L. S., Tubert, J. E., Lee, G. S., Ku, J. H., Florea, A., Luo, Y., Qiu, S., Choi, S. K., Takhar, H. S., Aragones, M., Paila, Y. D., Chavers, S., & Qian, L. (2022). Effectiveness of mRNA-1273 against infection and COVID-19 hospitalization with SARS-CoV-2 Omicron subvariants: BA.1, BA.2, BA.2.12.1, BA.4, and BA.5. *MedRxiv*, 2022.09.30.22280573. https://doi.org/10.1101/2022.09.30.22280573

VE BA1/2 vs. BA4/5 severe outcomes, Ontario, Canada

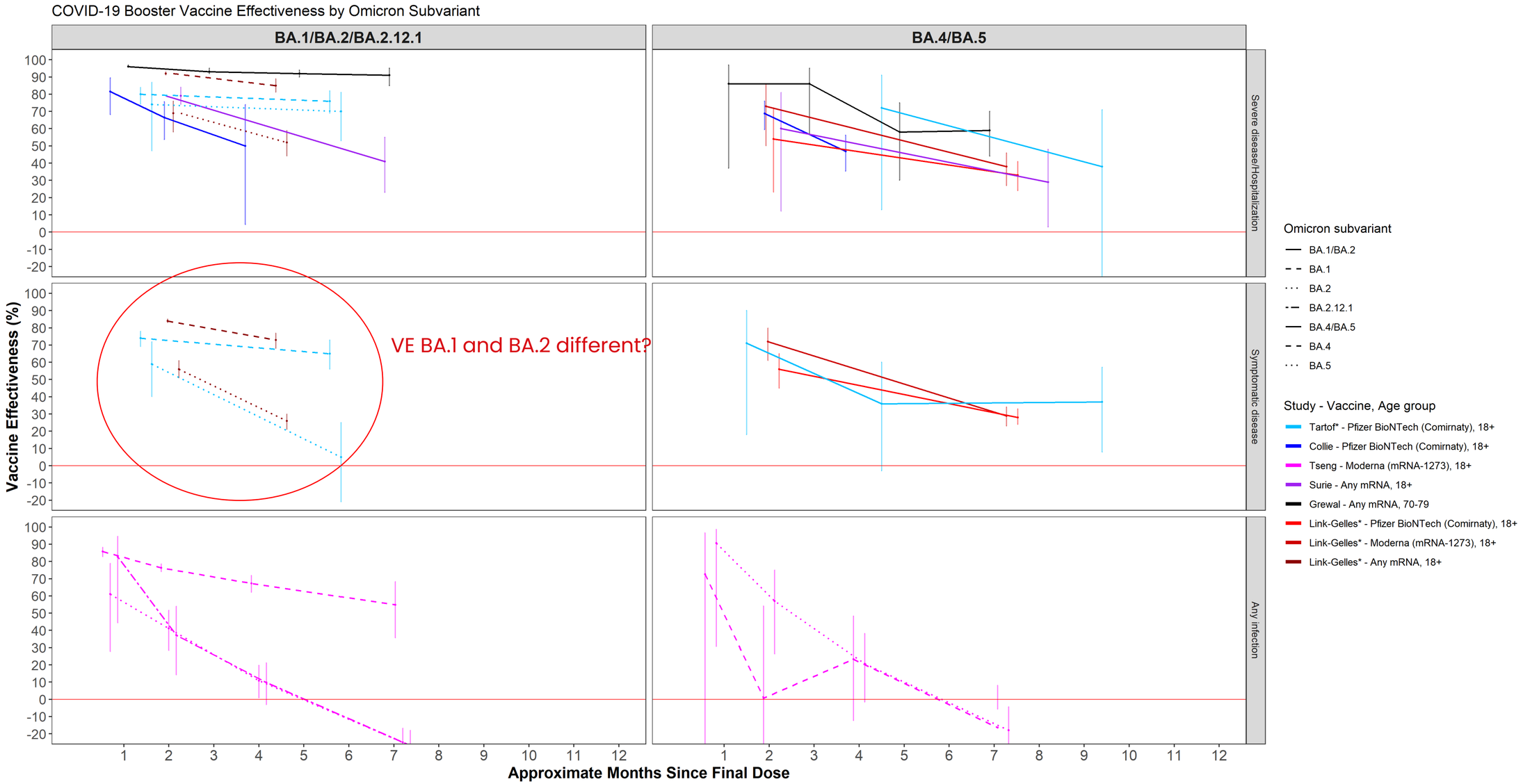
- Monovalent mRNA vaccines
- VE lower for BA.4/5 than BA.1/2 predominant periods



*Similar results for other age groups

From Grewal R, et al. MedRxiv. https://www.medrxiv.org/content/10.1101/2022.10.31.22281766v1

Duration of VE comparing BA1/2 with BA4/5



*BA.1/BA.2/BA.2.12.1 and BA.4/BA.5 assessed in separate publications.

Slide courtesy of Melissa Higdon, IVAC, JHSPH

Summary of VE severe disease against BA4/5 vs. VE 1/2

VE similar BA4/5 vs. BA1/2	VE lower BA4/5 vs. BA1/2
US (Kaiser/Lewnard)	Portugal (Kislaya)
S. Africa (Discovery Health, Collie)	US* (Vision, Links-Gelles)
UK (UKHSA, Kirsebom)	US* (Kaiser S. Calif., Tseng)
US (IVY, Surie)	Canada (Ontario province, Grewal)

*VE BA5 lower than BA1, but similar to BA2

Possible reasons for lower VE for BA4/5 compared to BA 1/2

1. More time elapsed since last dose, more waning (methodological)
2. More infection induced immunity in unvaccinated, depletion of susceptibles (methodological)
3. Greater immune evasion (immunological, real)

Conclusions vaccine effectiveness against BA 4/5

- Waning occurs against BA4/5, especially infection
- Boosters restore VE BA4/5
- Vaccines protect against infection (few months) and severe disease (many months)
- Neutralization shows slight decrease compared to BA1
- Data suggests similar or some decrease in VE for BA4/5, compared to BA1
  - How much is real vs. methodological not clear.

Thank you

World Health Organization