“Less is More”

Fractionating vaccines to extend supplies

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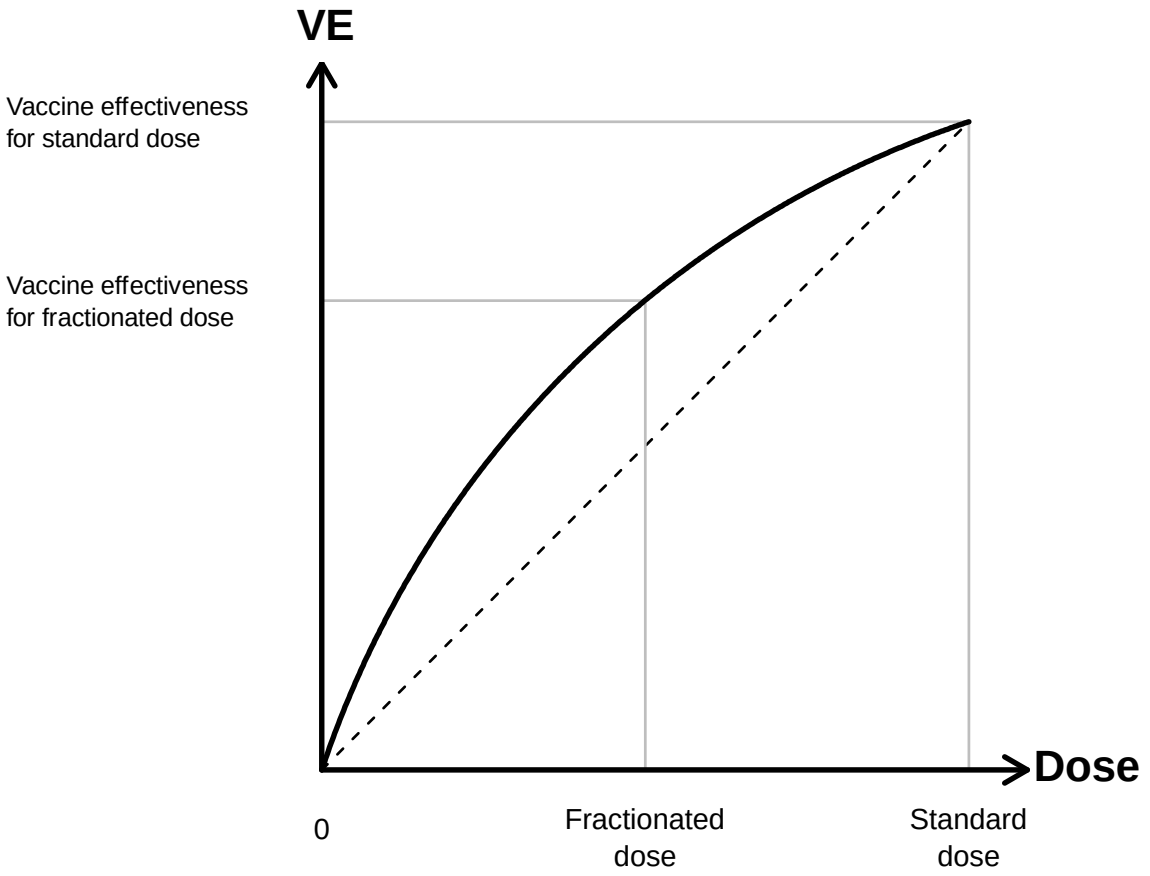
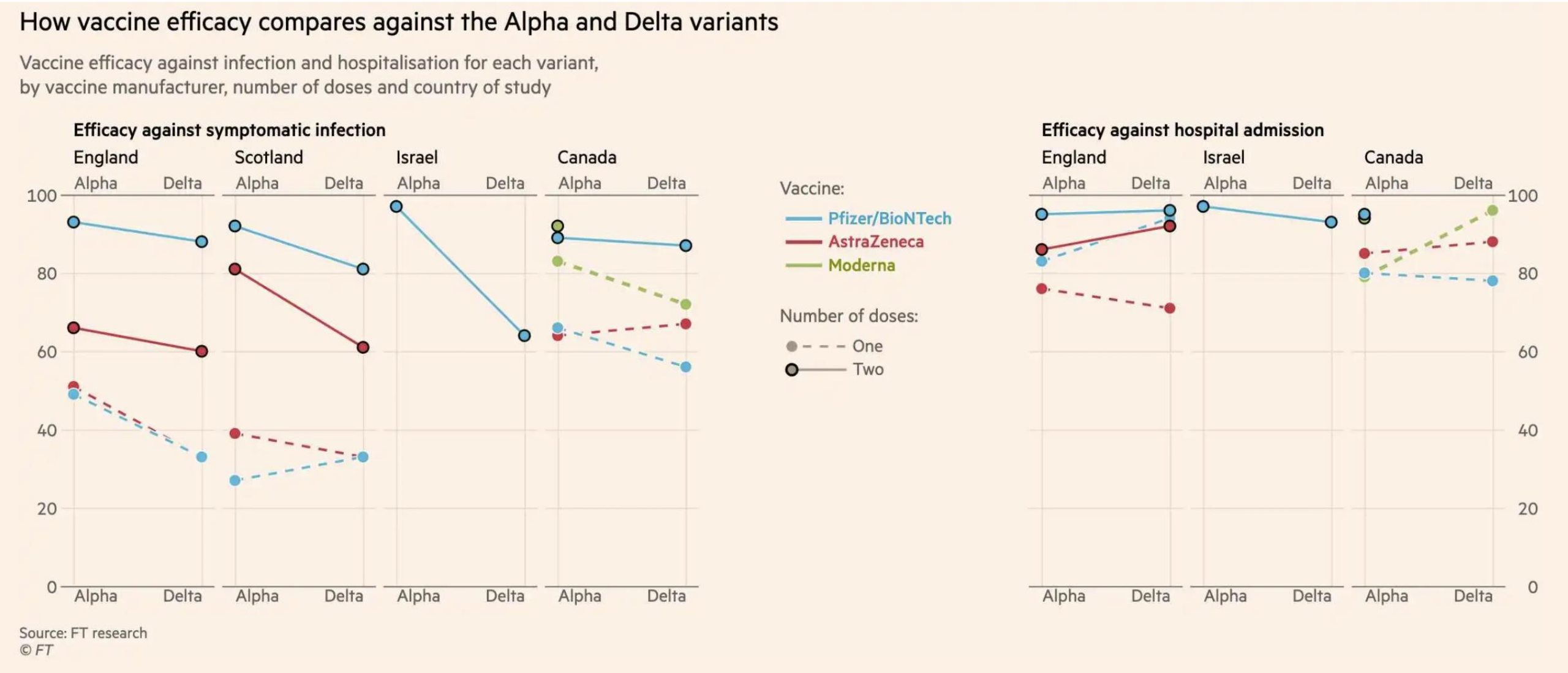
Vaccine fractionation – basic concept

- If you have two million doses of a COVID-19 vaccine, you can give two doses to 1 million people
- For COVID-19 we could consider the idea of giving two half-doses (for example) to 2 million people
  - Individual protection could be lower, but this strategy is likely to improve population protection and save more lives



Cowling et al. 2021 Nat Med

Vaccine effectiveness vs different outcomes



https://www.ft.com/content/5a24d39a-a702-40d2-876d-b12a524dc9a5

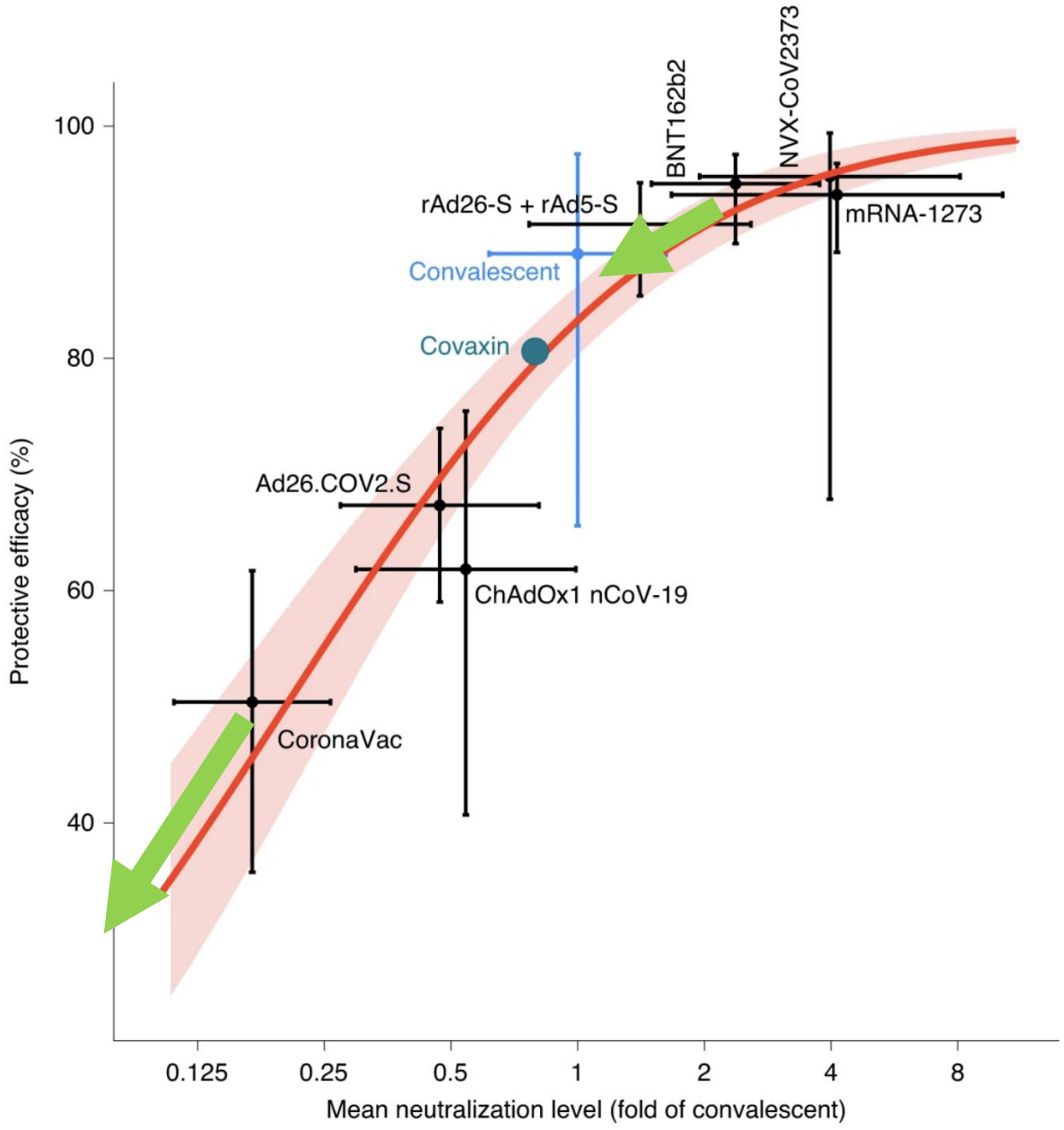
Correlates of protection

Khoury et al. discussed the potential for neutralizing antibody titers to be a ”correlate of protection” against symptomatic infection

Higher titers following mRNA vaccination are shown in top right, with high efficacy

Lower titers following inactivated vaccines are shown in the lower left

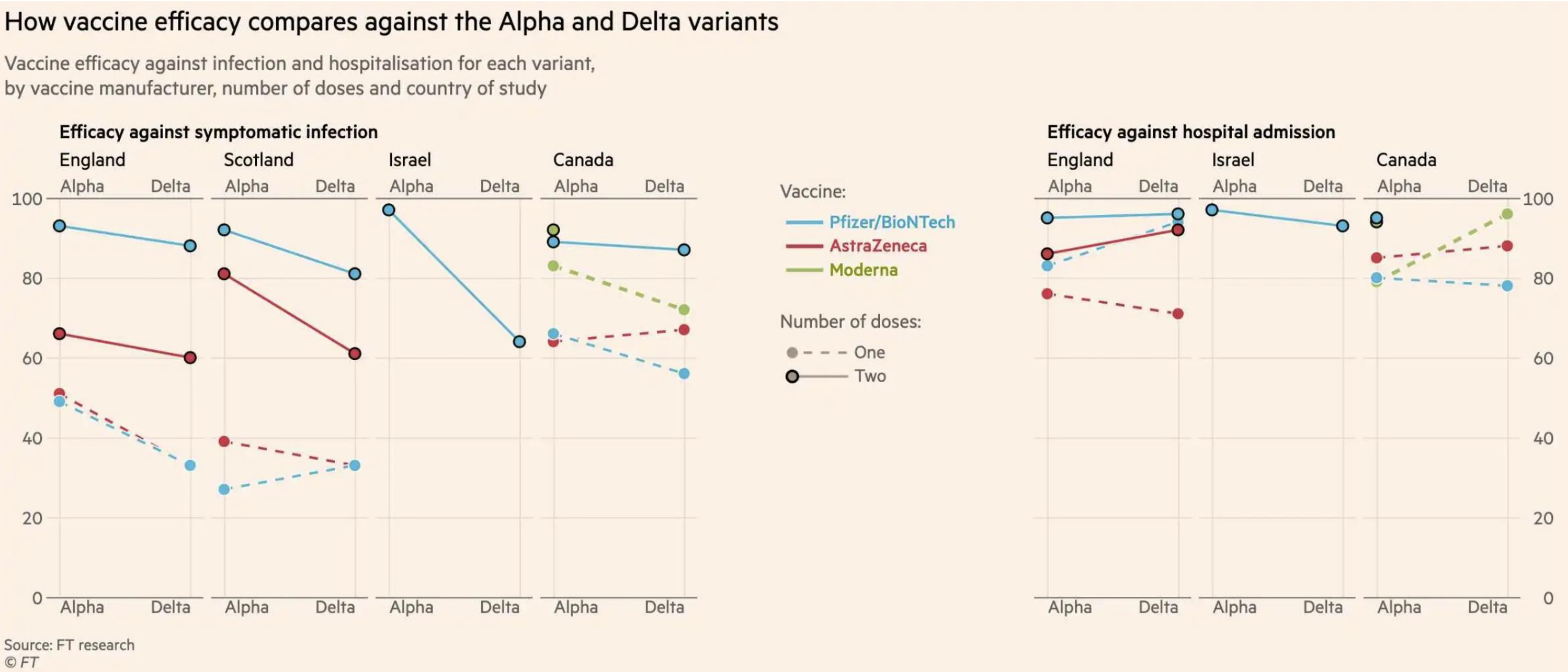
Note that a drop in antibody titer by half would reduce mRNA vaccine efficacy by 5%-10% but would reduce inactivated vaccine efficacy by >20%



Khoury et al. 2021 Nat Med

If neutralizing antibodies correlate with protection against symptomatic infection (as per previous slide) …

… is there an immune correlate for protection against severe COVID?



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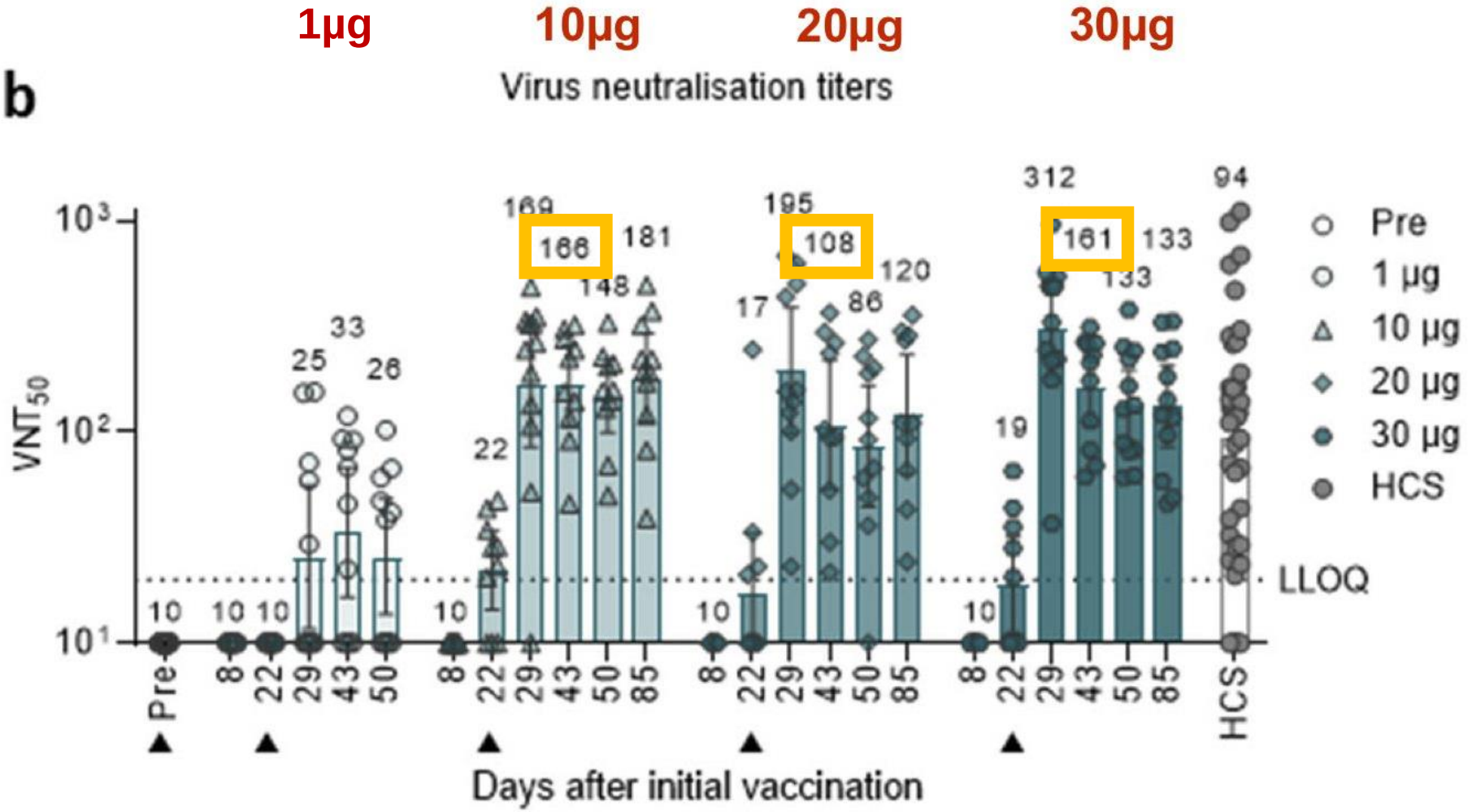
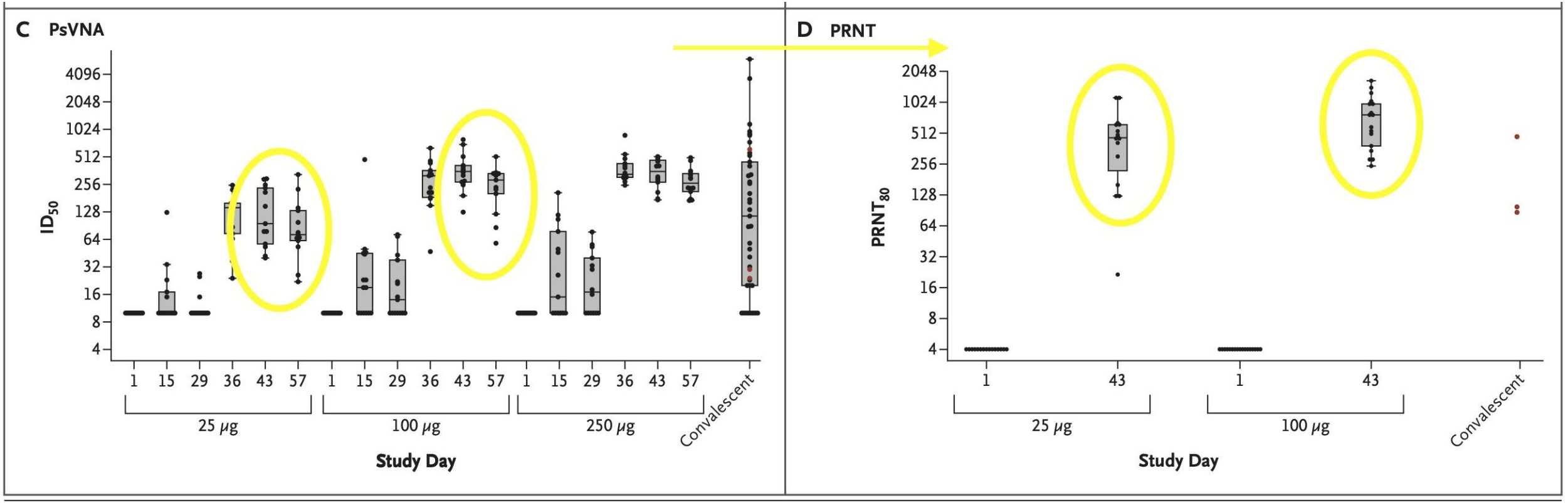
Antibody responses for reduced doses – BNT



Sahin et al. 2020 medRxiv

Antibody responses – Moderna



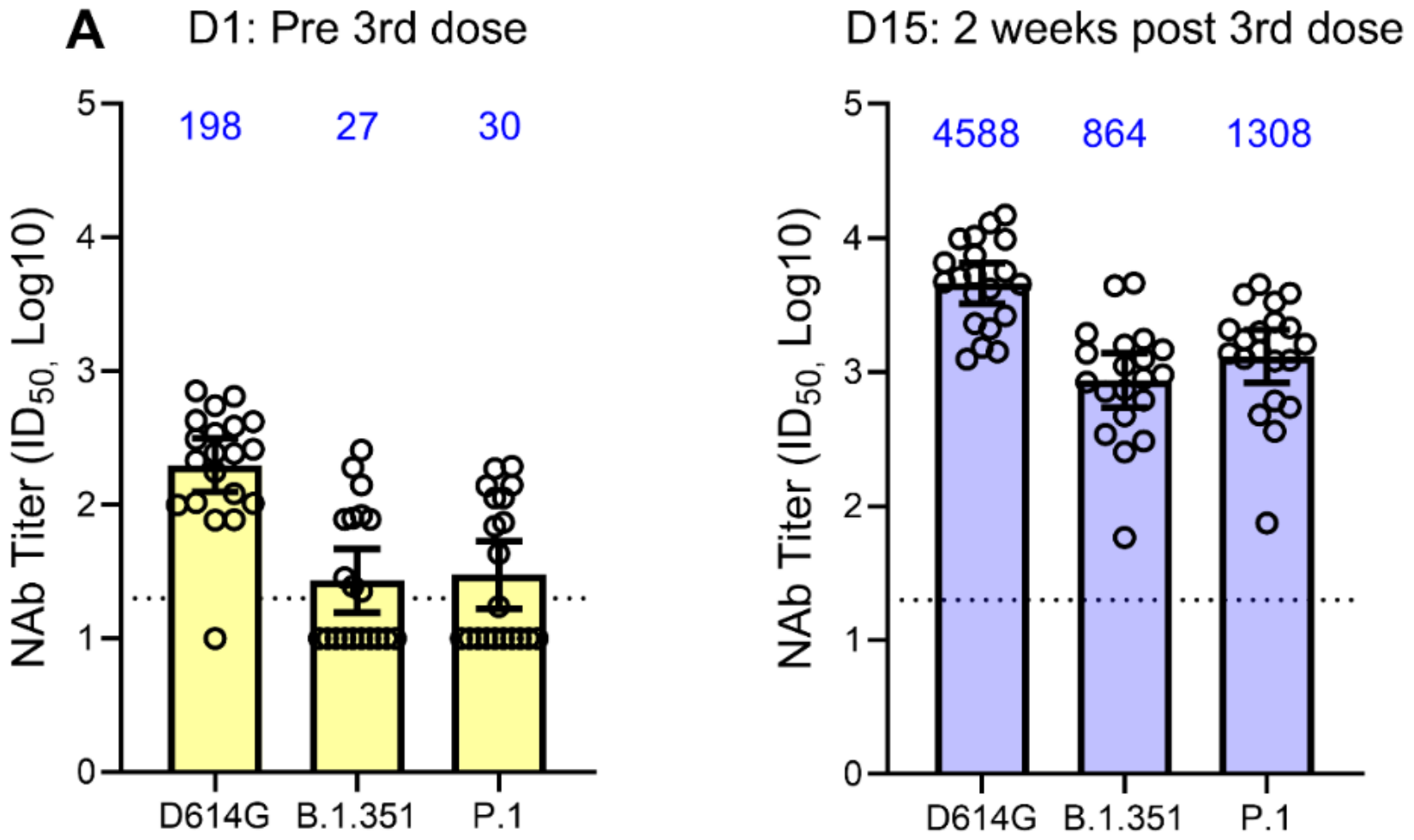
Jackson et al. 2020 NEJM

AstraZeneca – fractional first dose was better!

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)

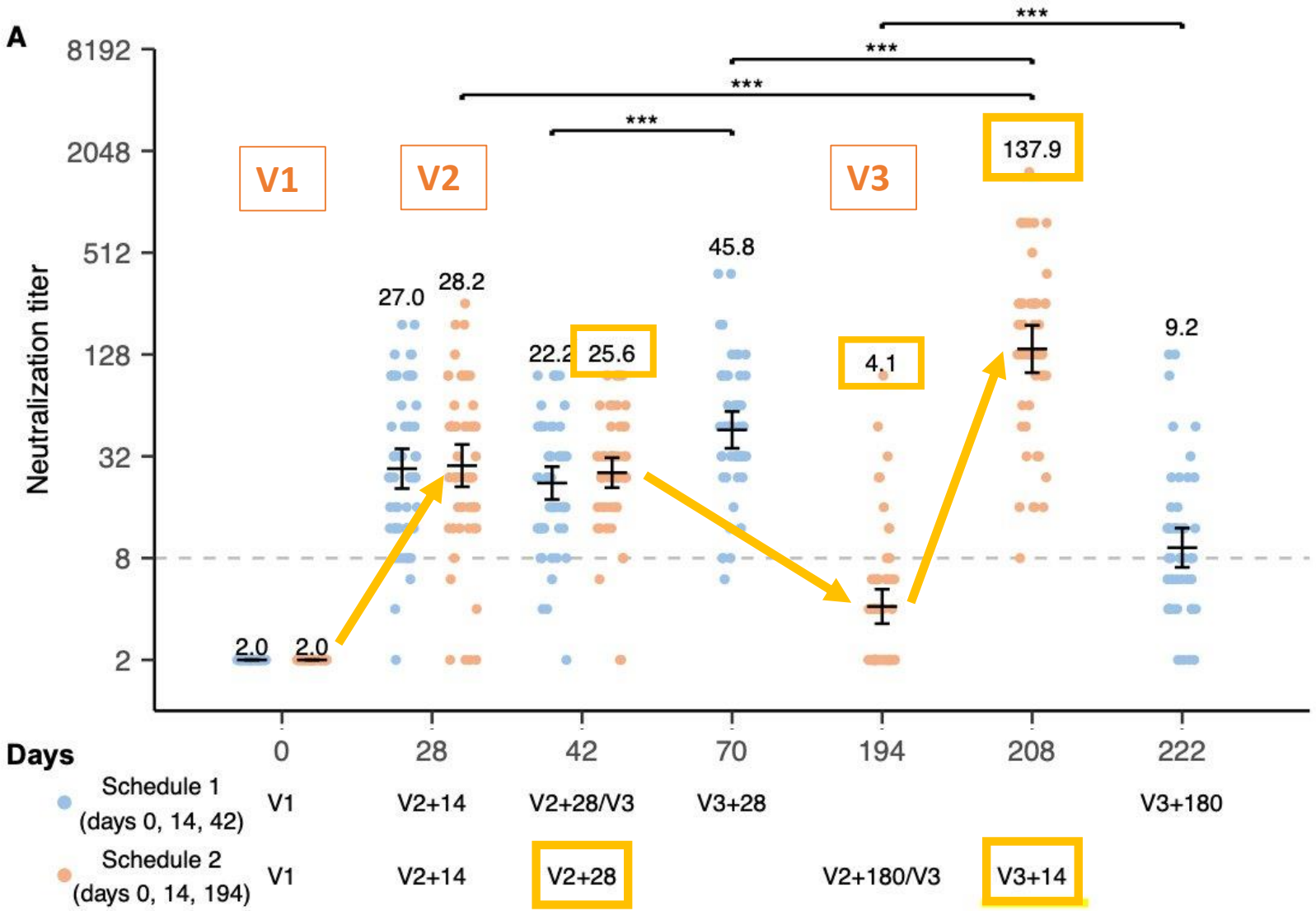
Voysey et al. 2020 Lancet

Antibody responses to third dose – Moderna



Wu et al. 2021 medRxiv

Antibody responses to third dose – Sinovac



Pan et al. 2021 medRxiv

Knowledge gaps

- How many lives could be saved in the next 12 months by providing vaccines (at fractional doses) to more people more quickly?
- Lack of evidence (lack of correlate of protection for severe disease) should not be an excuse for stalling the real-world investigation of fractional doses?
- Objective of fractionation is not to maintain high effectiveness against symptomatic disease, it is to save the most lives. Randomized evaluation (large field trial of full dose vs fractional dose) could give rapid confirmatory evidence on maintenance of efficacy against clinical outcomes
- Fractional dosing for boosters could address waning immunity while preserving antigen supplies for global first doses
- Concerns about promoting escape variants have been addressed in research on first-dose-first strategies (e.g. Cobey et al. 2021 Nat Rev Immunol)

Final comments

“More generally, in future pandemics, researchers and clinicians involved in vaccine development should consider identifying the appropriate vaccine dosage that can save the most lives for a limited amount of antigen, rather than just a dosage that balances efficacy and reactogenicity for the individual person.”

Cowling et al. 2021 Nat Med