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Monitoring the effectiveness of vaccines and antivirals for COVID-19

(COVID1903001, COVID19F09, CID-HKU2-12)

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Health Research Symposium

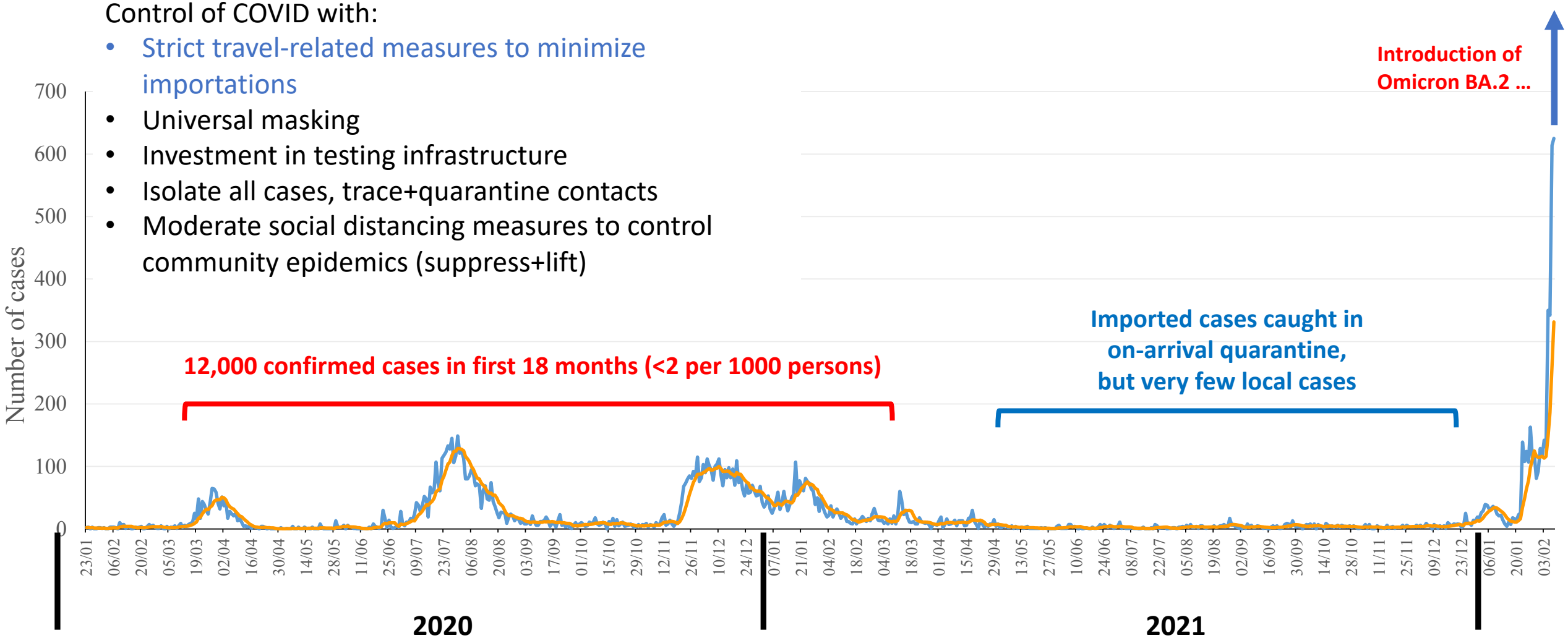
Outline

- Evaluation of COVID-19 vaccines in Hong Kong
- Importance and uniqueness of longitudinal cohort studies
- Evaluation of COVID-19 antivirals in Hong Kong
- Reactogenicity and COVID-19 booster vaccine uptake

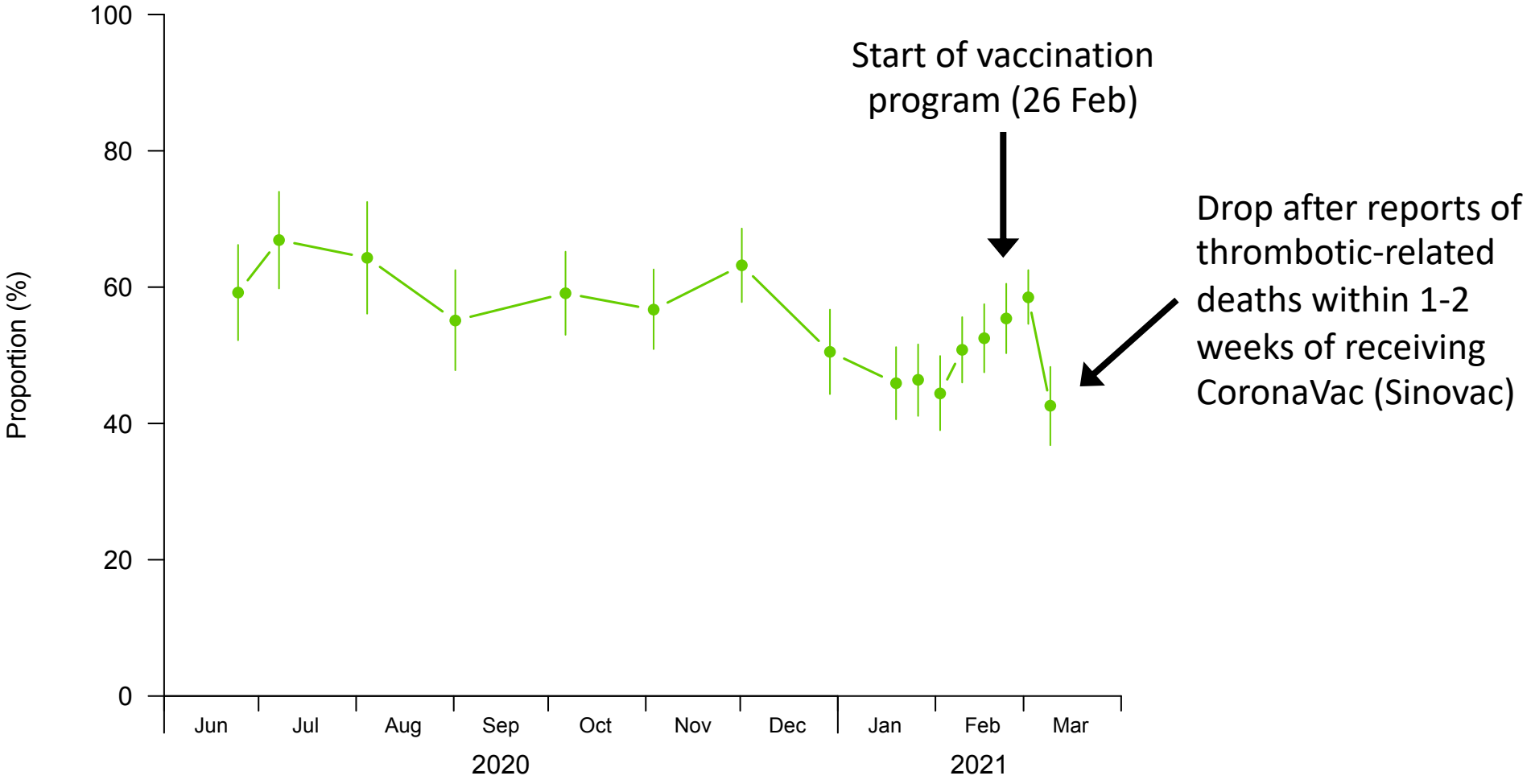
Hong Kong controlled COVID for 2 years without a complete lockdown, buying time for vaccination roll-out

Control of COVID with:

- Strict travel-related measures to minimize importations
- Universal masking
- Investment in testing infrastructure
- Isolate all cases, trace+quarantine contacts
- Moderate social distancing measures to control community epidemics (suppress+lift)

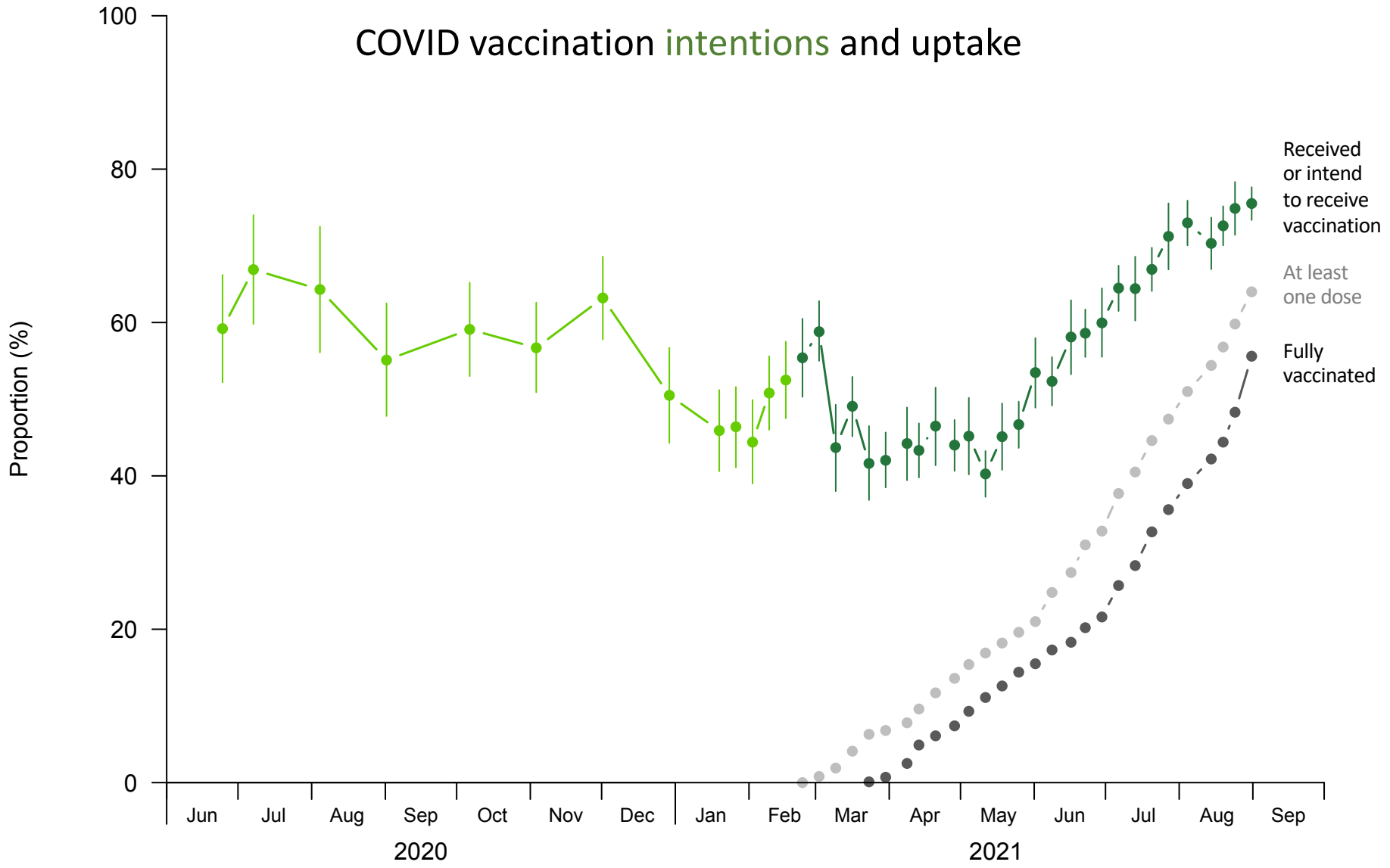


Early data on intention to receive COVID-19 vaccination

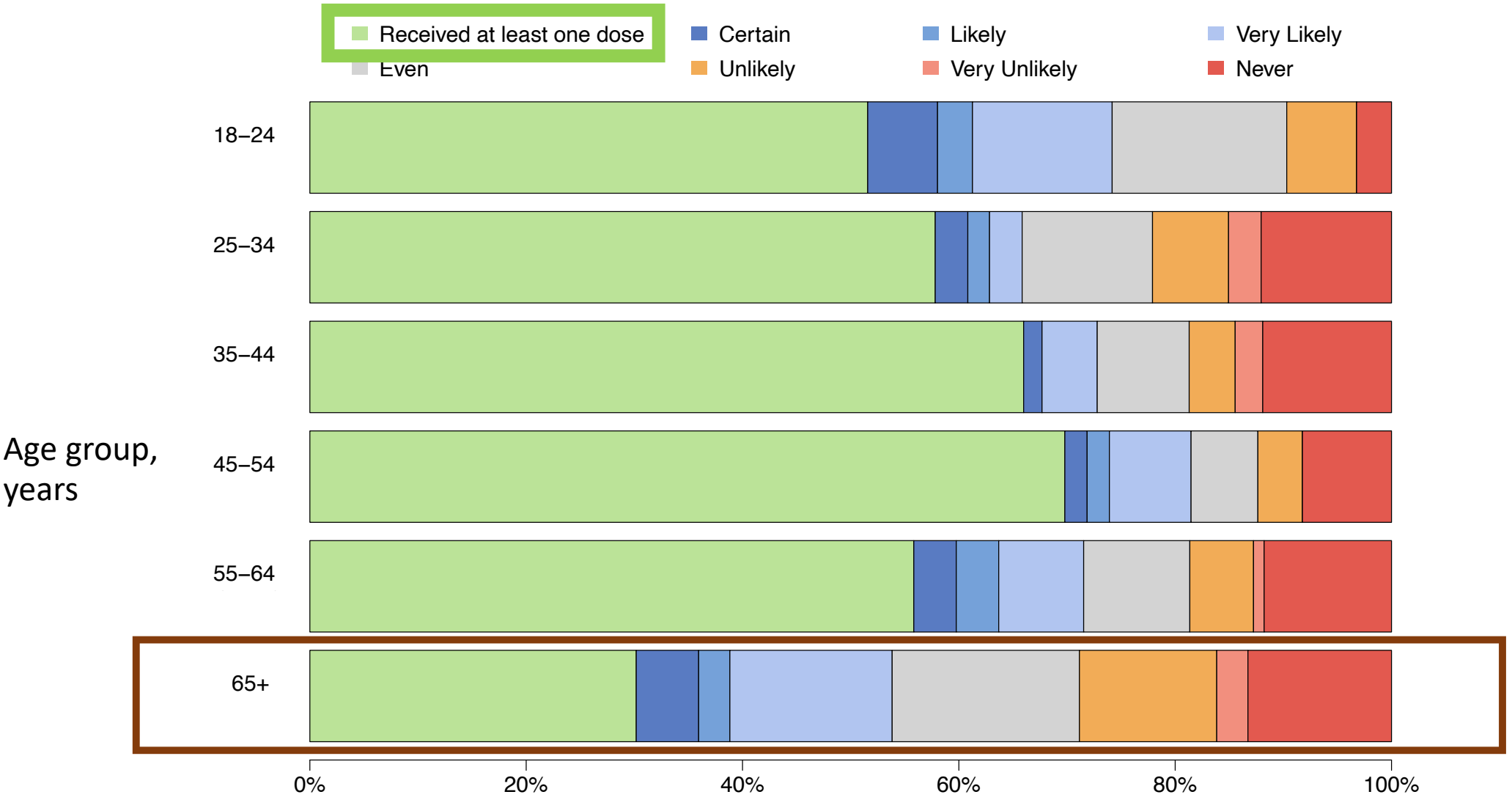


Vaccines initially made available to older adults and then progressively broadened to other age groups and certain occupational groups (e.g. HCWs). CoronaVac vaccine program started first, and BioNTech program 1-2 weeks later

Moderate vaccine uptake by Sep 2021 …

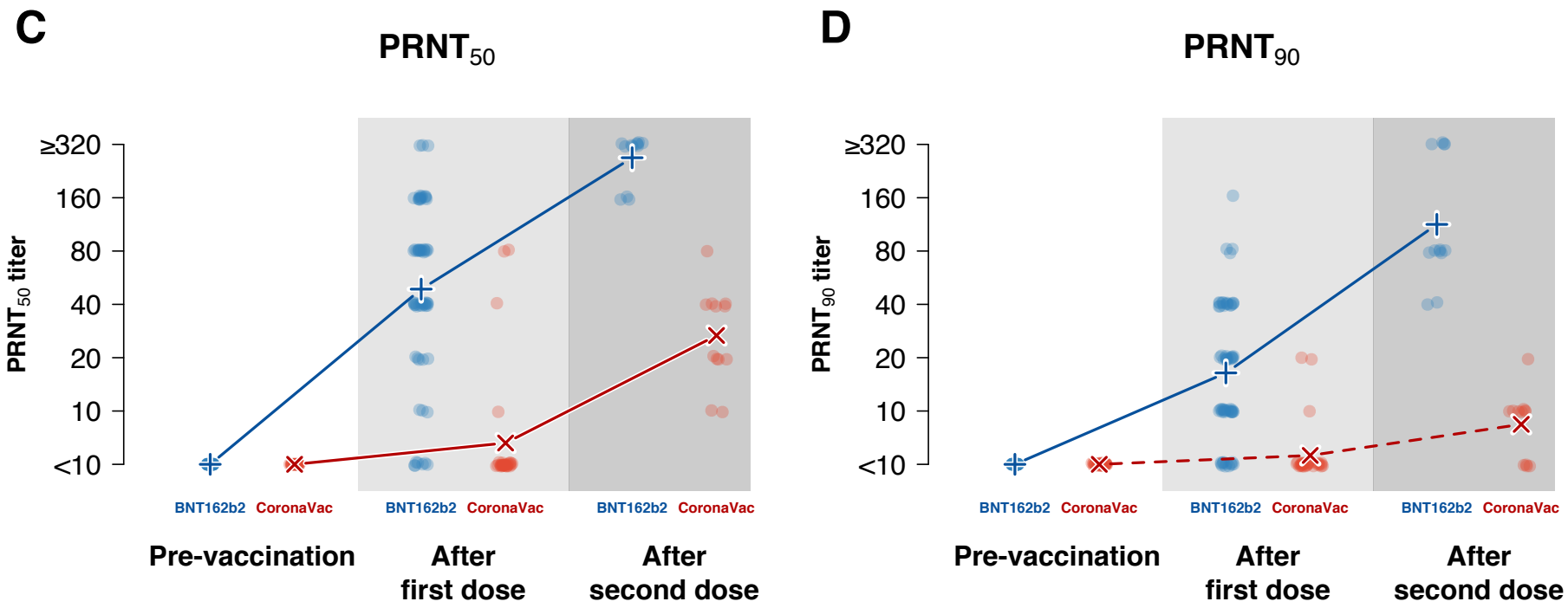


… but low vaccine uptake in older adults, Sep 2021



Just 30% of those ≥65y had received one vaccine dose by 13 September 2021

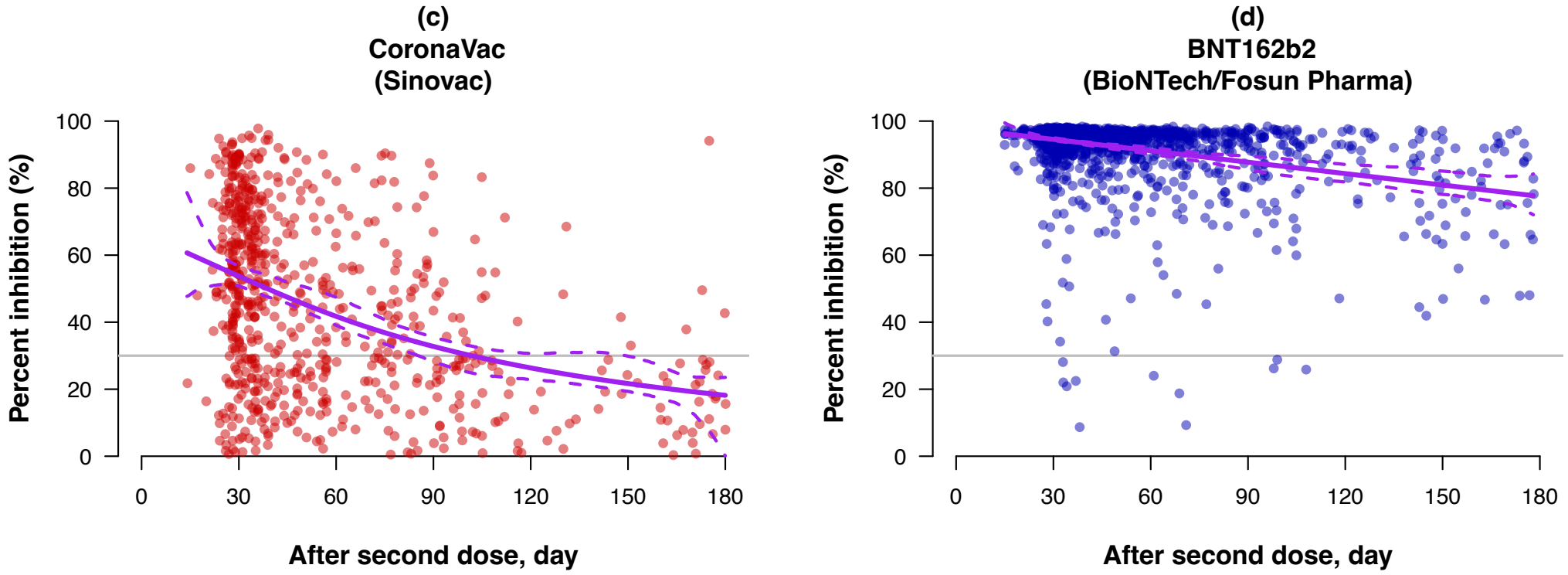
Antibody titers after primary series



Neutralization titers against live SARS-CoV-2 were >10 times higher in adults who were fully vaccinated with the BNT162b2 (BioNTech) vaccine versus CoronaVac (Sinovac)

Lim et al. 2021 Lancet Microbe

Declines in antibody titers up to 6m after 2nd dose



Surrogate virus neutralisation titers declined rapidly in CoronaVac recipients, leading to roll-out of third dose program in late 2021

Cowling et al. 2022 Vaccine

Vaccine effectiveness in HK vs severe Omicron BA.2

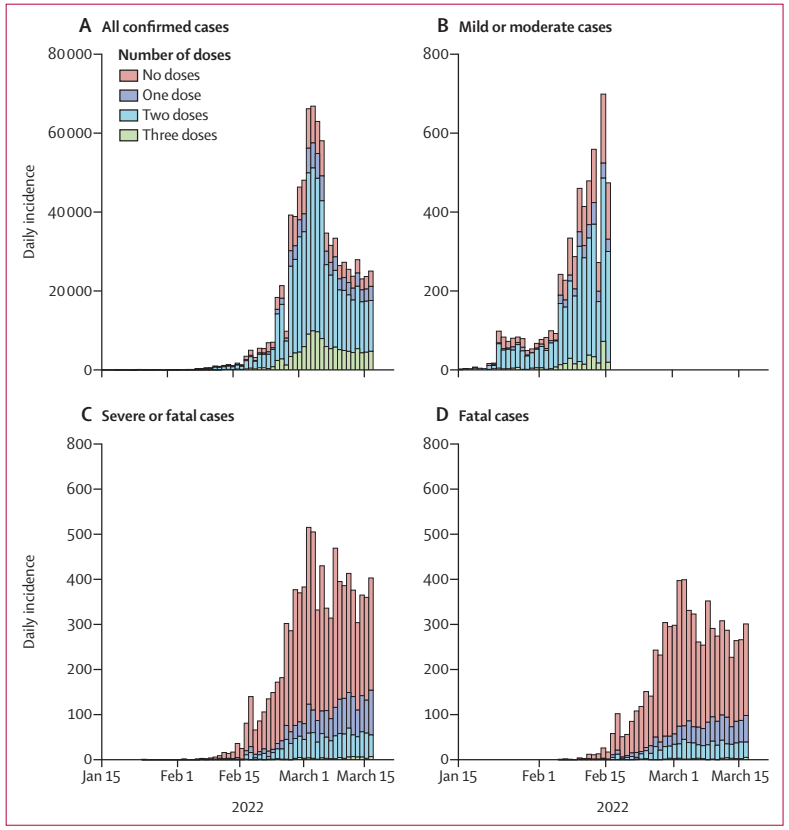


Figure 1: **Daily incidence of cases and deaths by vaccination status**
(A) All confirmed COVID-19 cases. (B) Mild or moderate cases in the early part of the fifth wave before Feb 15, 2022. (C) Severe or fatal cases. (D) Deaths throughout the fifth wave in Hong Kong. Severe disease was defined as having ever been listed as serious or critical during hospitalisation for COVID-19 or having a fatal outcome within 28 days of positive test. Vaccination status was categorised according to the number of doses received plus a 14-day lag for all doses, to allow for the immune response to vaccination. Mild cases were only included up until Feb 15, 2022, to account for change in admission criteria.

	Two doses		Three doses	
	BNT162b2	CoronaVac	BNT162b2	CoronaVac
Severe or fatal disease				
20–59 years	96·3% (94·9–97·3)	91·7% (88·7–94·0)	98·6% (97·5–99·3)	98·8% (97·5–99·5)
60–69 years	91·1% (86·9–94·0)	79·3% (71·8–85·0)	98·9% (97·3–99·6)	97·4% (95·2–98·7)
70–79 years	89·8% (85·1–93·1)	74·3% (66·5–80·3)	99·0% (97·4–99·7)	95·4% (92·2–97·4)
≥80 years	86·9% (80·5–91·3)	58·2% (45·1–68·2)	97·1% (93·8–98·7)	97·3% (94·9–98·7)
Death				
20–59 years	96·8% (95·1–98·0)	93·3% (89·9–95·6)	99·2% (97·9–99·7)	99·4% (98·1–99·9)
60–69 years	92·7% (88·6–95·4)	84·3% (77·8–89·0)	99·0% (97·2–99·8)	99·0% (97·3–99·8)
70–79 years	92·3% (88·0–95·2)	76·7% (68·5–82·8)	99·4% (97·9–99·9)	97·0% (94·2–98·6)
≥80 years	90·3% (84·9–93·9)	63·0% (50·3–72·5)	97·5% (94·2–99·0)	97·9% (95·7–99·1)

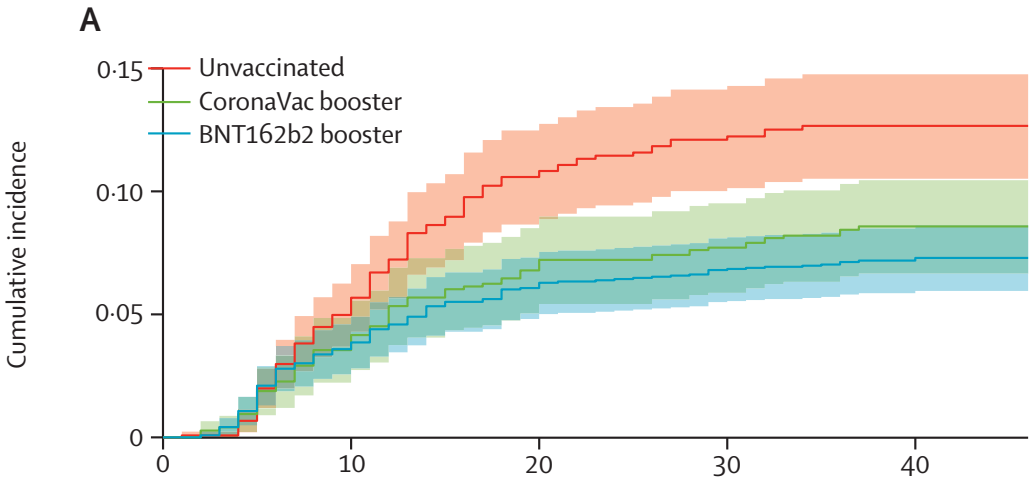
All three dose VE estimates are very high

WHO had – by this time— recommended three doses of inactivated vaccines as a primary series in older adults

McMenamin et al. 2022 Lancet Infect Dis

Vaccine effectiveness in Hong Kong vs infection

Incidence of infections



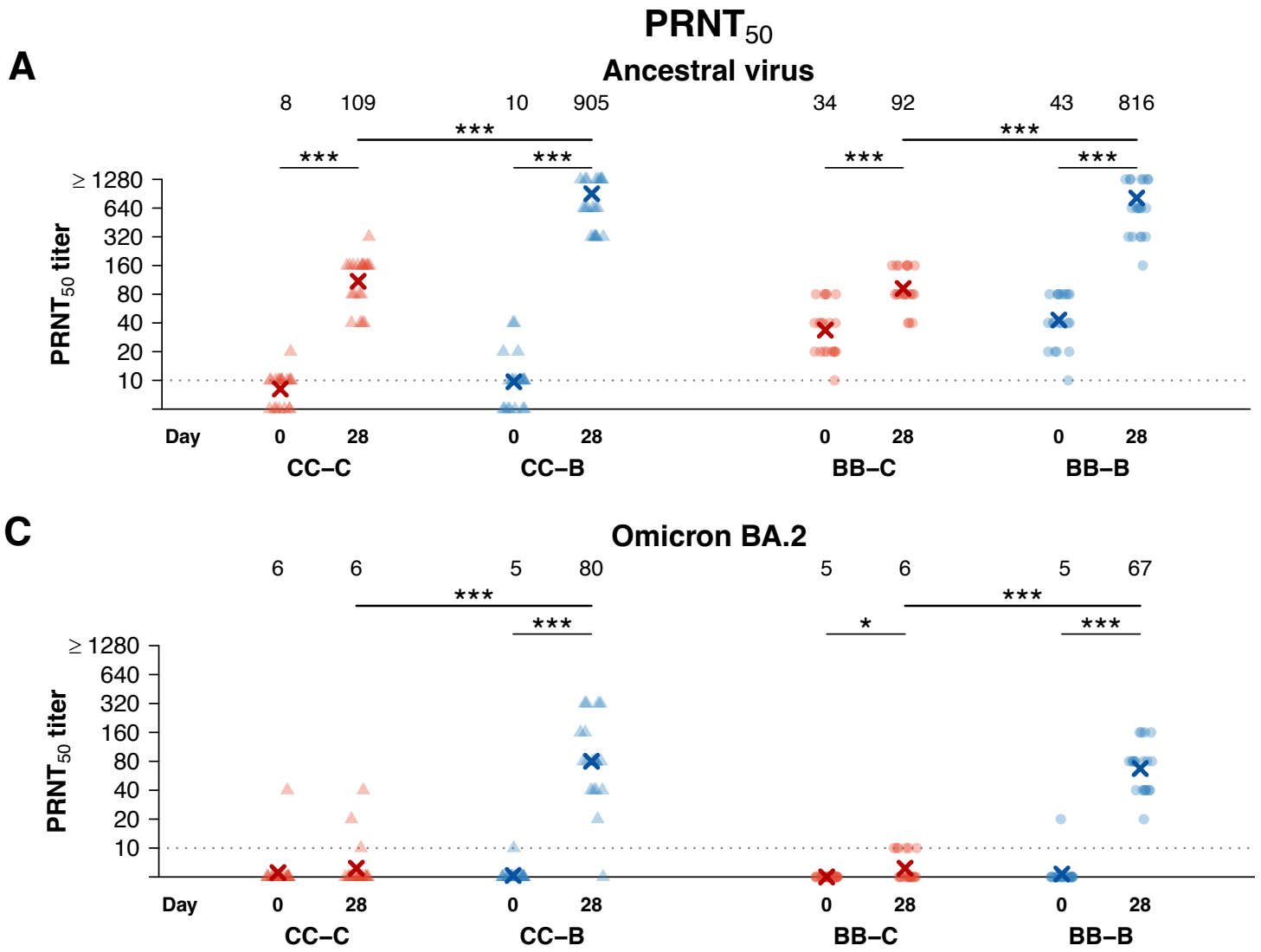
Number at risk					
Unvaccinated	1271	950	733	654	215
CoronaVac booster	715	789	871	946	343
BNT162b2 booster	1152	1406	1753	2106	859
Cumulative number of events					
Unvaccinated	0	62	109	120	123
CoronaVac booster	0	32	59	64	72
BNT162b2 booster	0	50	90	102	110

	Vaccine Effectiveness (%) (95% CI)
One dose BNT162b2	16·5 (-19·5, 41·6)
One dose CoronaVac	-1·6 (-39·8, 26·2)
Two doses BNT162b2 (≥3 months)	1·1 (-22·4, 20·1)
Two doses CoronaVac (≥3 months)	5·4 (-25·6, 28·8)
Two doses BNT162b2 (<3 months)	27·6 (-6·3, 50·7)
Two doses CoronaVac (<3 months)	22·7 (-15·2, 48·2)
Three doses BNT162b2	**41·4 (23·2, 55·2)**
Three doses CoronaVac	**32·4 (9·0, 49·8)**
CoronaVac + CoronaVac + BNT162b2	31·3 (-1·0, 53·3)

Cohort of 8636 individuals conducting weekly rapid tests from March 2022 onwards, infections here are almost all Omicron BA.2

Tsang et al. 2022 Lancet Infect Dis

Homologous and heterologous booster trial



219 individuals who previously received 2xCoronaVac were randomized to a third dose of BNT162b2 or CoronaVac

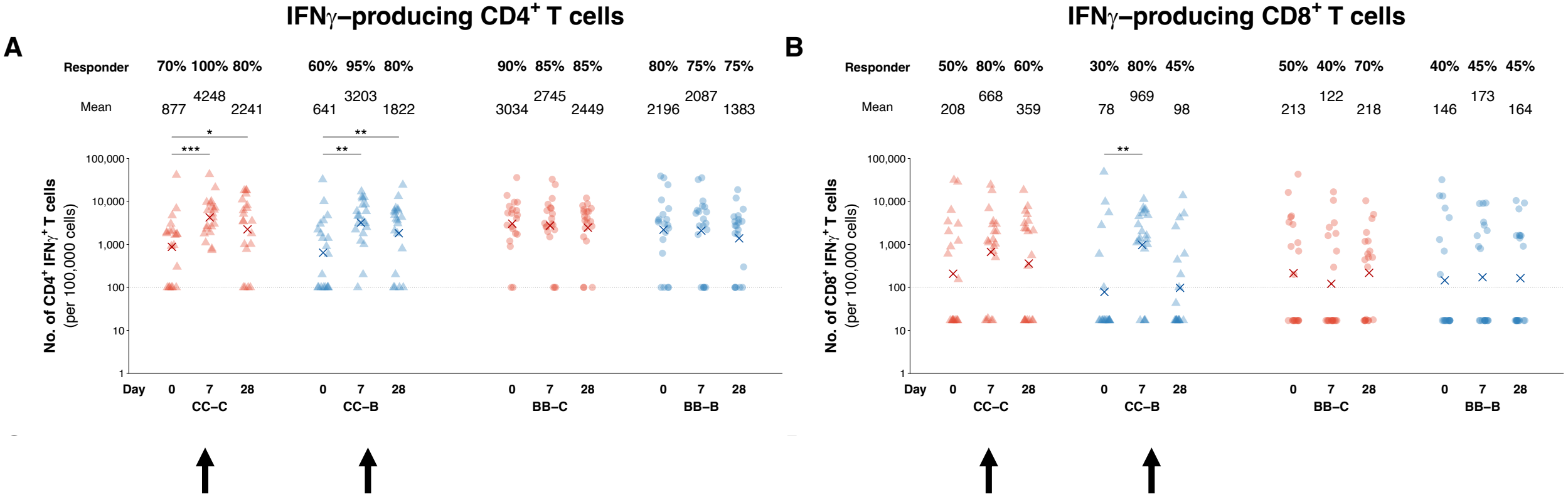
232 individuals who previously received 2xBNT162b2 were randomized to a third dose of BNT162b2 or CoronaVac

Sera collected at day 0 and day 30

Live virus neutralization done on a subset

Leung et al. 2023 Lancet Microbe

T cell responses stronger in CC-C and CC-B arms

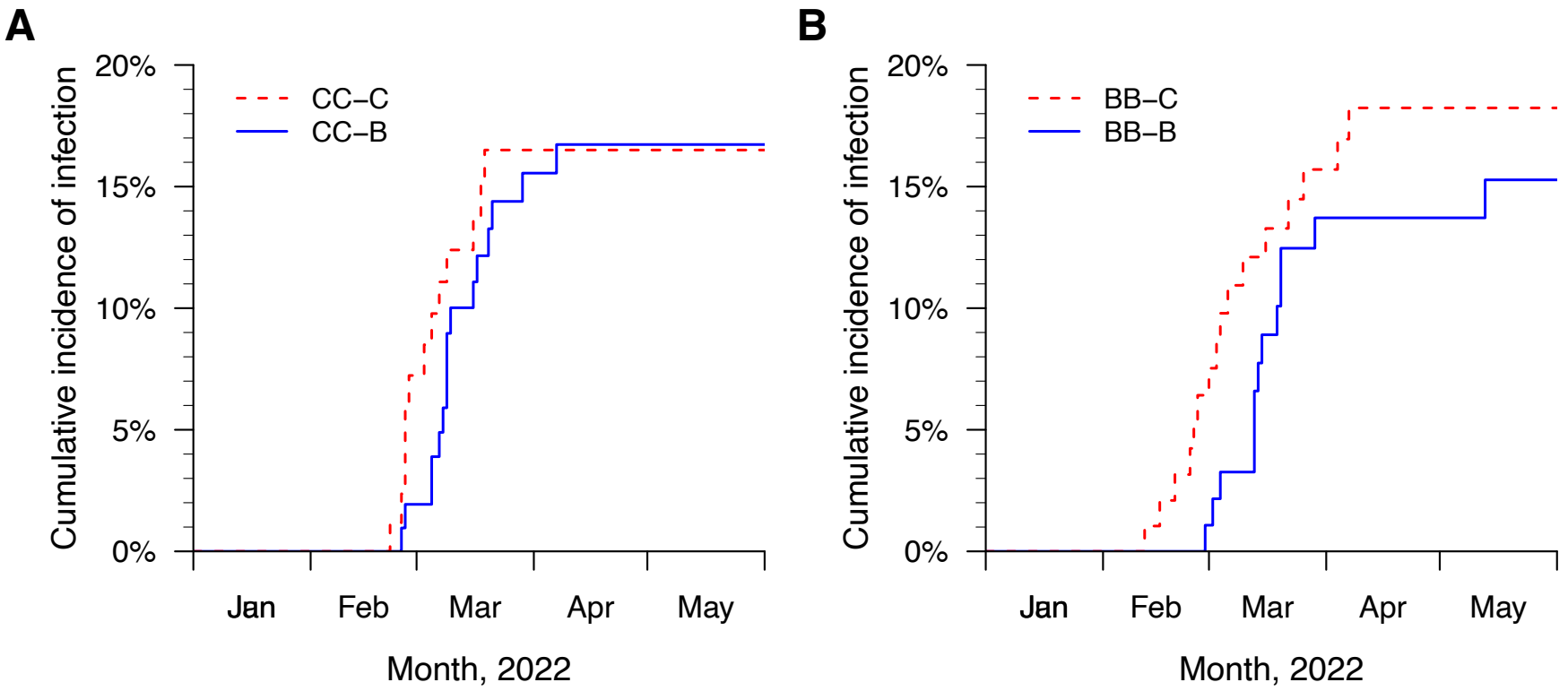


Strongest responses here …

… and here

Leung et al. 2023 Lancet Microbe

Similar incidence of infections (Omicron BA.2 predominant)



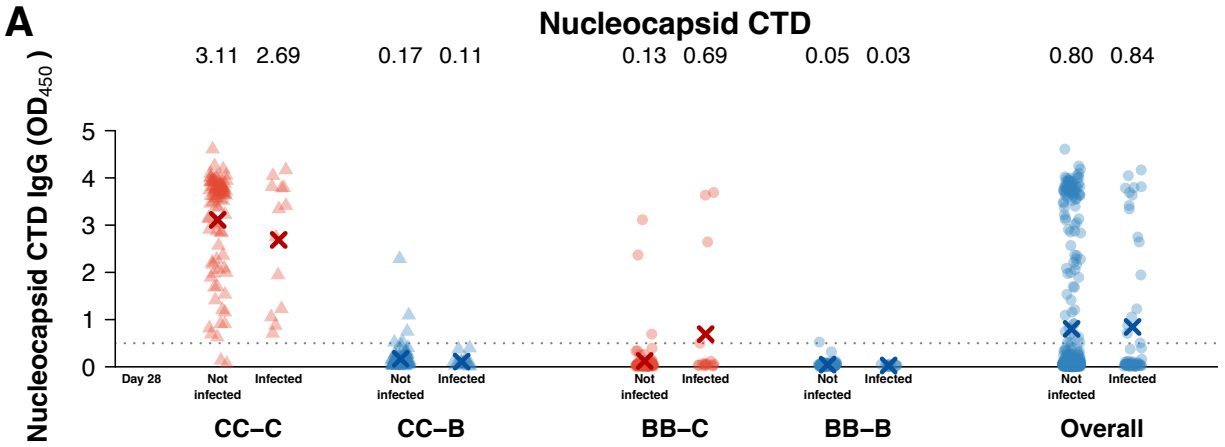
Previous slides showed substantially higher antibody titers against Omicron BA.2 in recipients of the BNT162b2 booster (CC-B and BB-B groups), improved cellular immune responses in those primed with CoronaVac (CC-C and CC-B groups), but minimal differences in incidence of infections (above). VE studies also indicate small differences in VE between CC-C, CC-B and BB-B combinations. Interesting.

Leung et al. 2023 Lancet Microbe

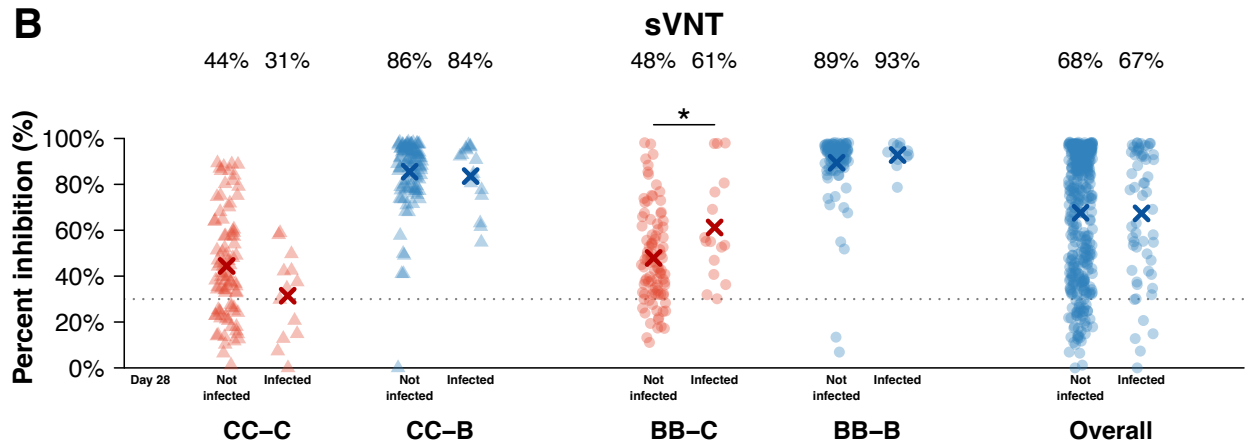
Post-vaccination antibody levels

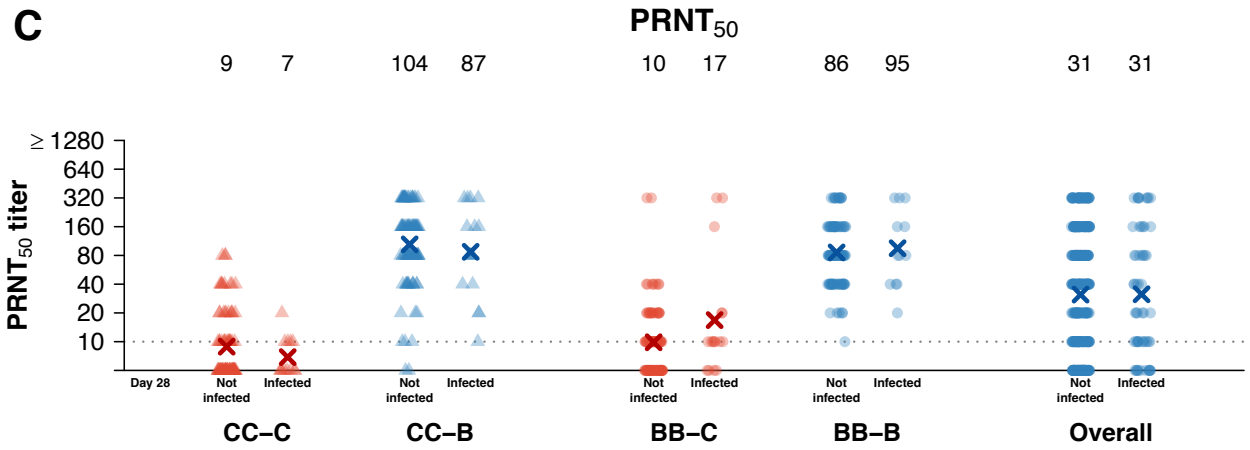
Omicron BA.2

Each column shows the post-vaccination titers for subsequently uninfected individuals and then for the infected individuals. Higher titers in uninfected participants would represent a correlation with protection



Perhaps N-gene correlated with protection in CC-C ?





Surprising that $PRNT_{50}$ against Omicron BA.2 is not correlated with protection against BA.2 in CC-B and BB-B?

Unpublished data

Prior vaccination on T cell responses: S versus NEM specificity

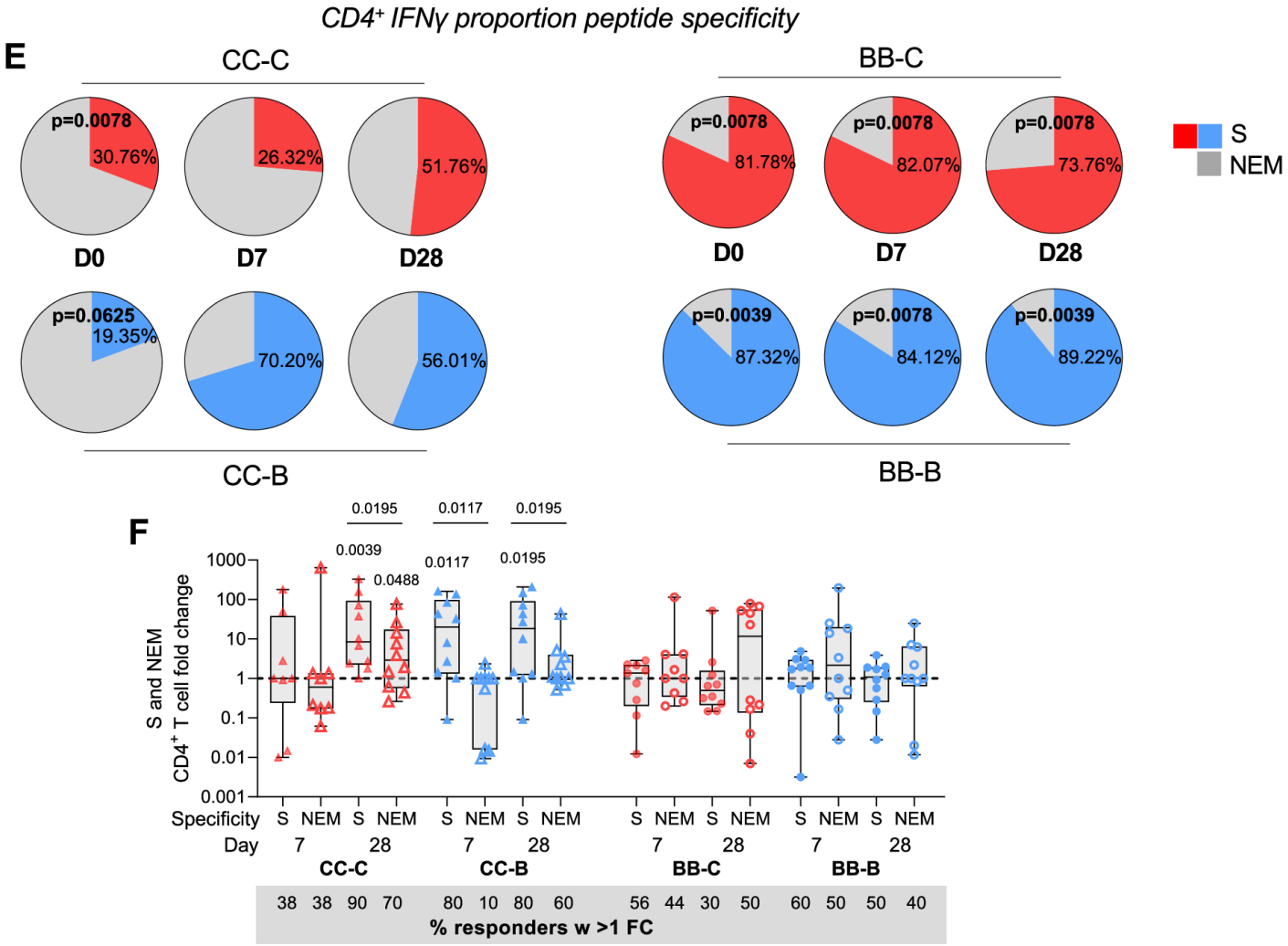


Fig E. Greater % of total CD4⁺ T cell IFNg response was directed towards Spike (S) than Nucleocapsid-Envelope-Membrane (NEM) ancestral SARS-CoV-2 viral proteins in the BB- than CC-primed group, regardless of third-dose type

Fig F. In CC-primed group, C as third dose promoted response both to S and NEM, while B promoted response to S only.
In BB-prime group, no significant changes in responses to either S or NEM from pre-vaccination for both C and B as third dose

Cohen et al. 2024 Nat Commun

6 months after third dose, T cell memory to S declined to baseline; memory to NEM differed by vaccine group

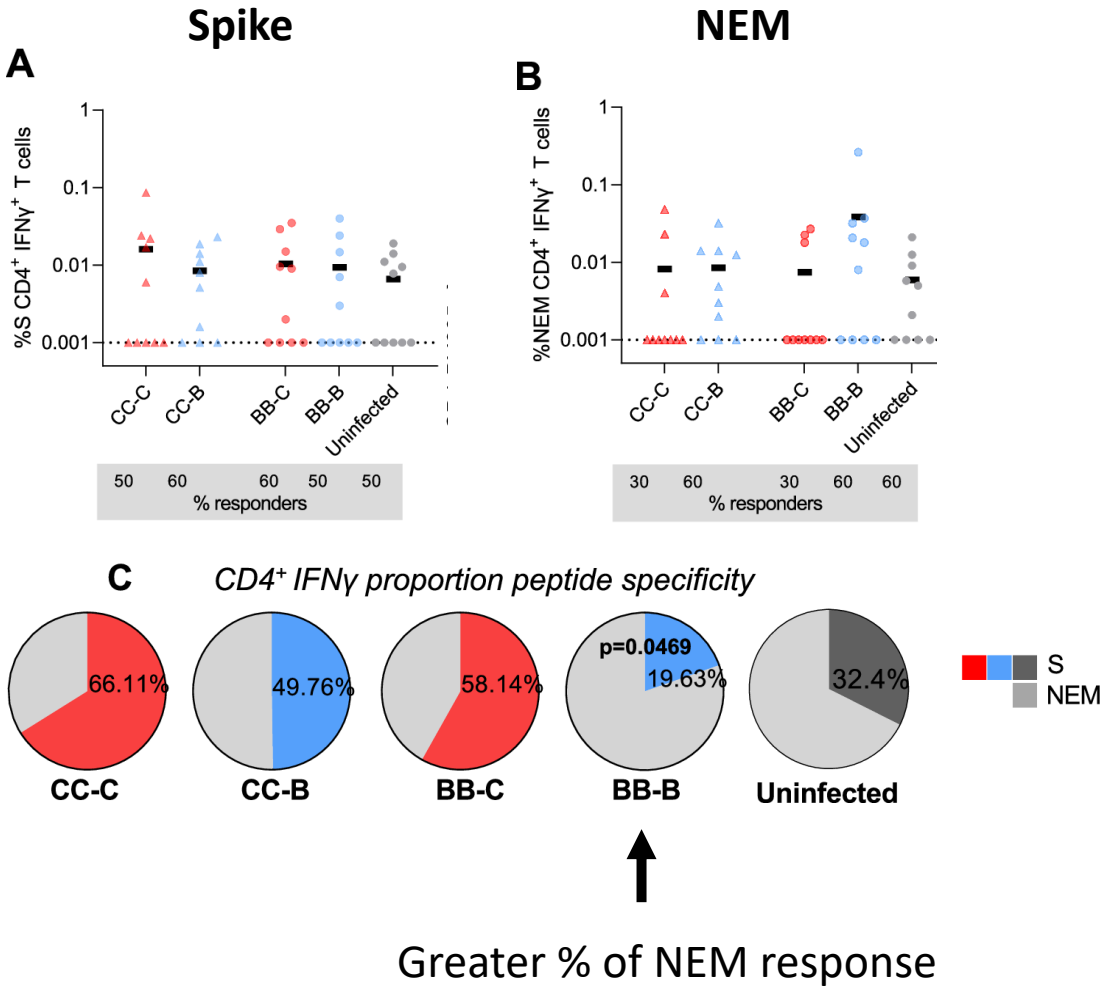


Fig A,B. S and NEM $CD4^+$ T cell IFNg response magnitude for all 4 groups 6 months after third dose declined to equivalent level of that in pre-pandemic uninfected (negative) controls (slightly higher NEM response in BB-B)

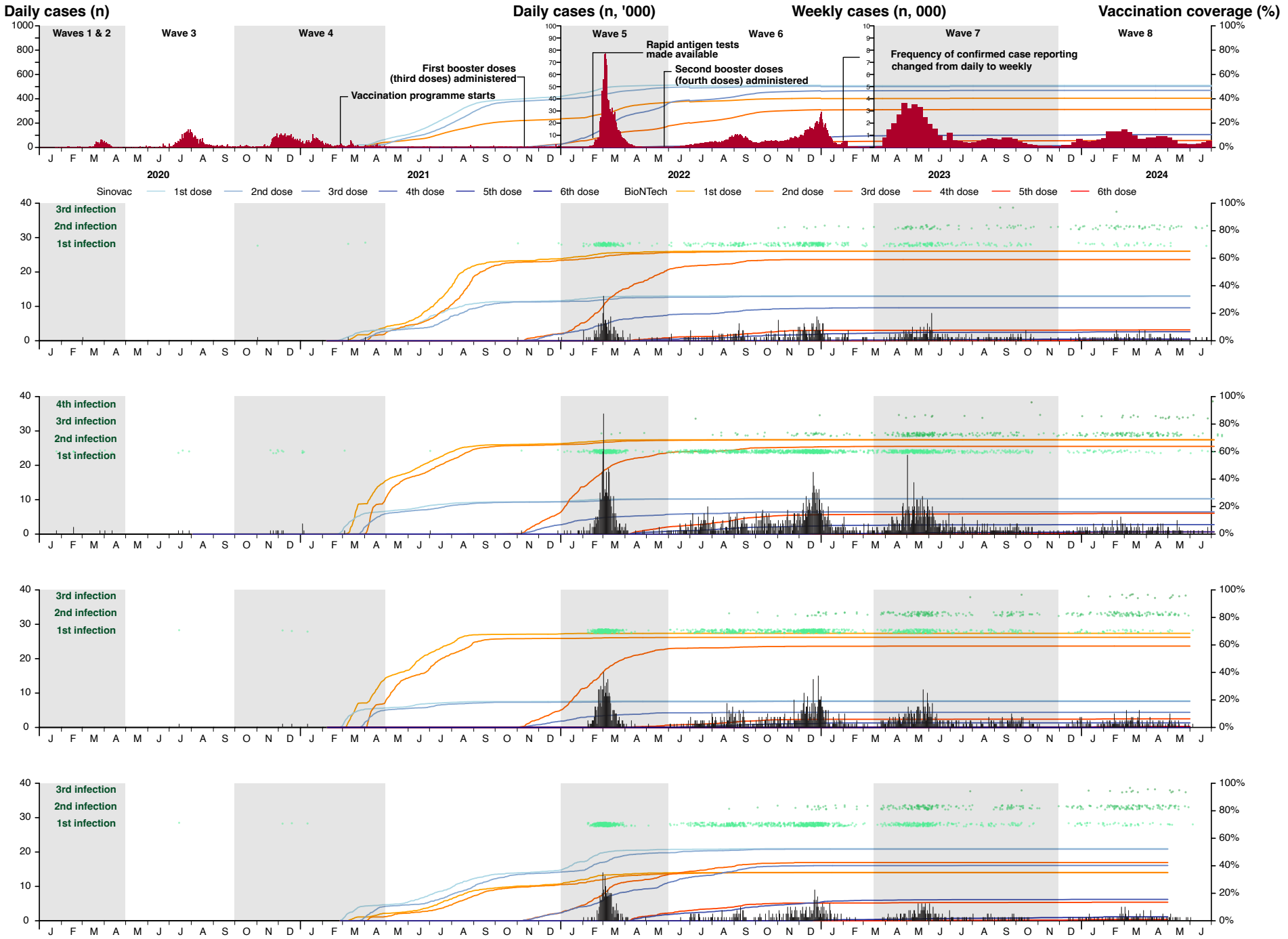
Fig C. Much more decline in S than NEM response in BB-B led to greater % of response directed to NEM 6 months after third-dose compared to other vaccine combinations

Cohen et al. 2024 Nat Commun

Cohort studies

Study name	Brief summary	Study years	Age group	Sample size	Frequency of blood draws	Illness swabs for PCR
COVAR	Observational cohort of adults after COVID vax	2021-now	≥18 years	~1000	Rolling every 6 months and 1m after each covid vax	✓
EPI-HK	Community cohort of immunity and infections	2020-now	All ages	~2000	Rolling every 6 months and 1m after each covid vax	✓
HCW	Observational cohort of healthcare workers	2020-now	18-65 years	~1200	Rolling every 6 months and 1m after each covid vax	✕
PIVOTe	Extended follow-up of an elderly cohort (previously a flu vaccine trial 2017-2021)	2021-now	69-88 years in 2021	~1200	Autumn and spring	✓

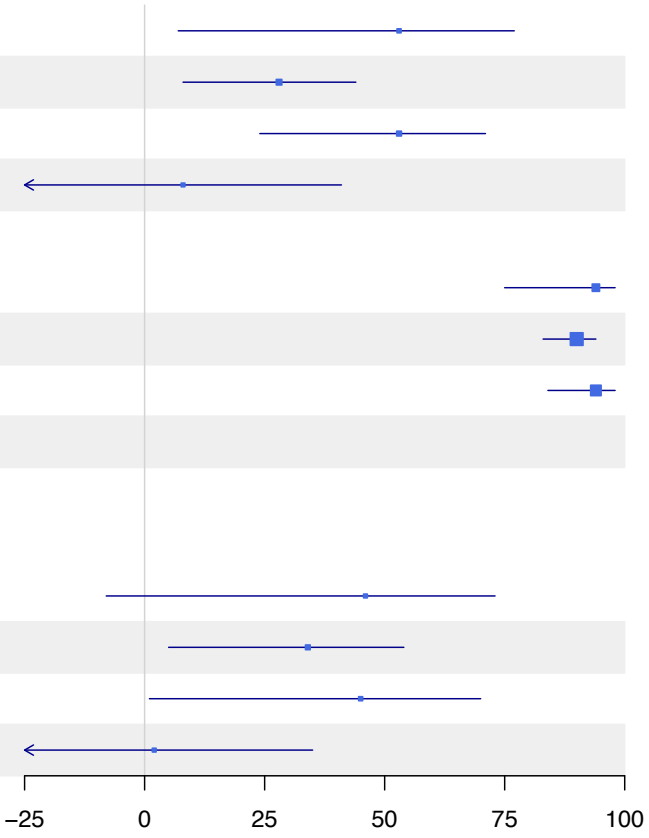
Surveillance data



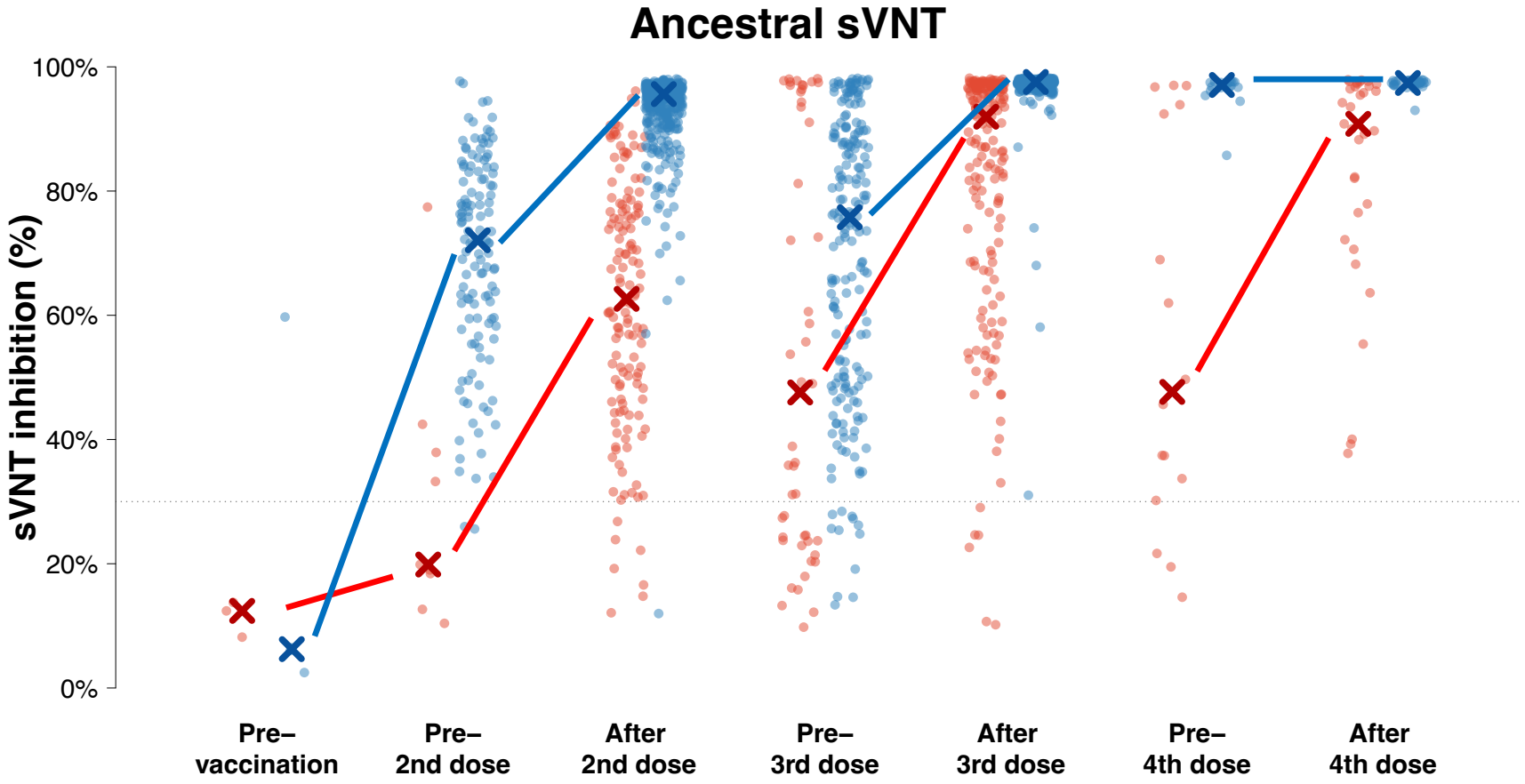
Vaccine effectiveness of booster doses

COVID–19 vaccine effectiveness estimates for the 6th wave

Reference group	Vaccination history	Study	Risk sets	Infections	VE	95% CI lower limit	95% CI upper limit
BBB							
	BBBB						
		COVAR	79	14	53	7	77
		EPI–HK	401	142	28	8	44
		HCW	100	33	53	24	71
		PIVOTe	137	45	8	–45	41
	BBBV						
		COVAR	128	4	94	75	98
		EPI–HK	445	23	90	83	94
		HCW	192	10	94	84	98
CCC							
	CCCC						
		COVAR	74	20	46	–8	73
		EPI–HK	240	92	34	5	54
		HCW	81	31	45	1	70
		PIVOTe	264	56	2	–47	35

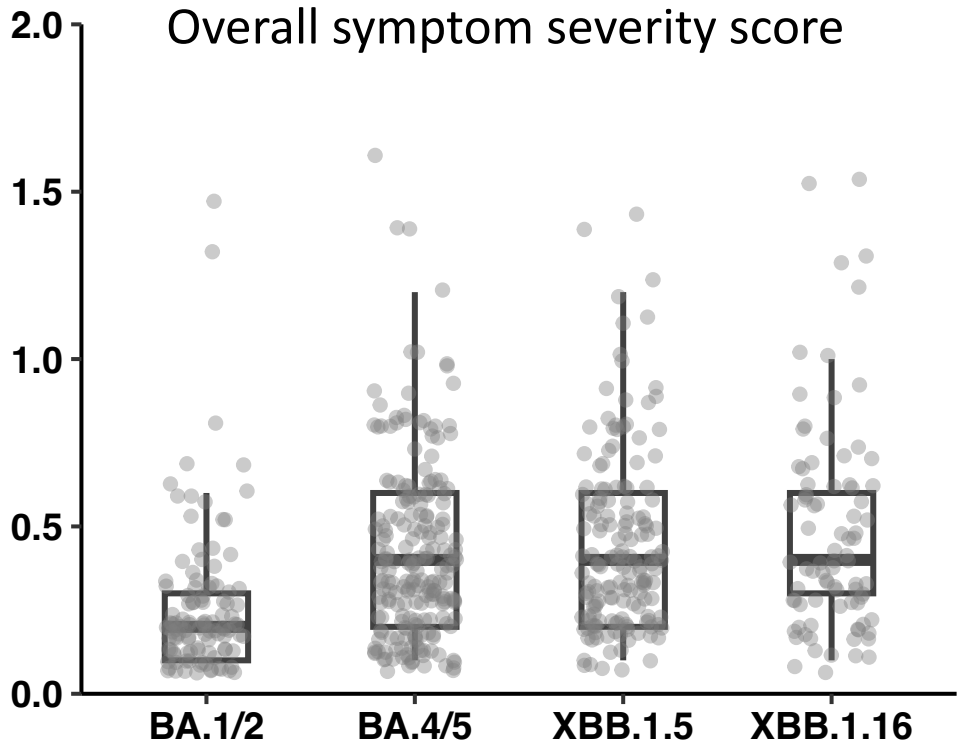


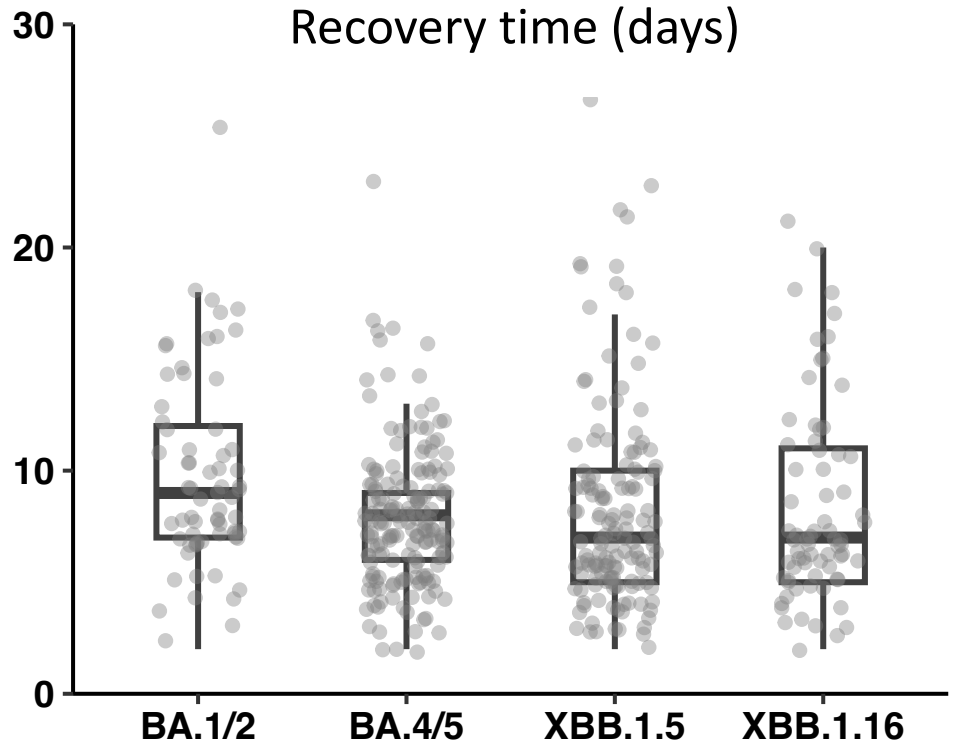
Immunogenicity of booster doses



In the COVAR cohort, we identified substantial boosting of antibodies following BNT162b2 vaccine doses, and more modest increases following CoronaVac vaccine doses. Similar observations with antibodies against BA.5 and other subvariants, but levels lower. Next steps – correlating antibody levels with protection against infection and re-infection

Severity of Omicron subvariants





In the PIVOTe cohort of older adults, we identified 601 first-time infections with various SARS-CoV-2 Omicron subvariants over a 2.5-year period. “Intrinsic” severity of Omicron subvariants seems to remain high even in vaccinated older adults

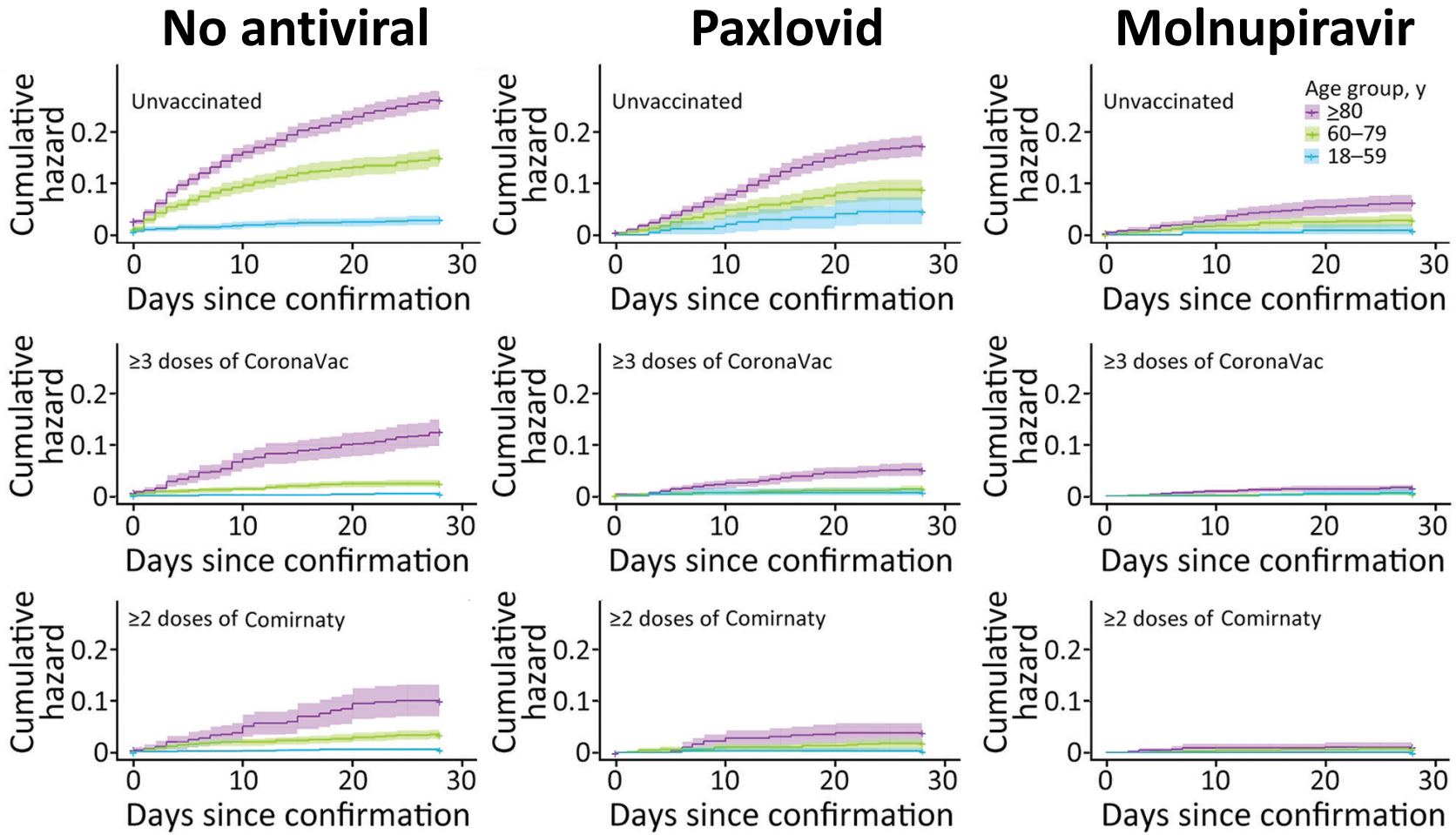
See also Wong JY et al. 2023 J Infect Dis

COVID-19 antivirals

- Two COVID-19 antivirals being used in Hong Kong
  - Paxlovid (nirmatrelvir/ritonavir) (often first choice, but various contraindications)
  - Molnupiravir
- Both antivirals are extremely effective in (1) reducing risks of hospitalization and mortality when given early to ambulatory COVID-19 patients in the community, and (2) reducing risks of mortality when given early to hospitalized COVID-19 patients
- However, assessments of antiviral effectiveness should also incorporate patients' vaccination history

Wong CKH et al. 2022 Lancet
Wong CKH et al. 2023 Lancet Infect Dis
Wong CKH et al. 2024 Nat Comms
and many others

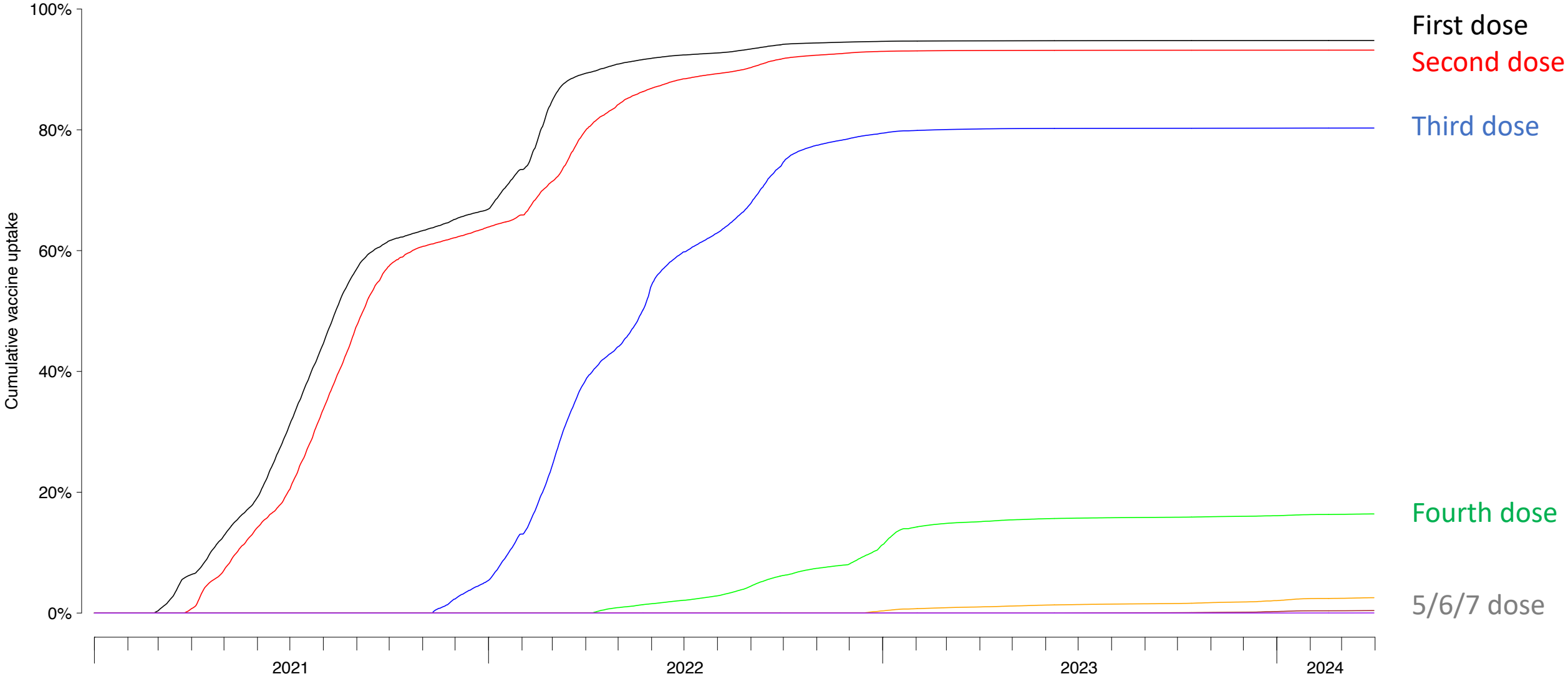
Antiviral effectiveness by vaccination history



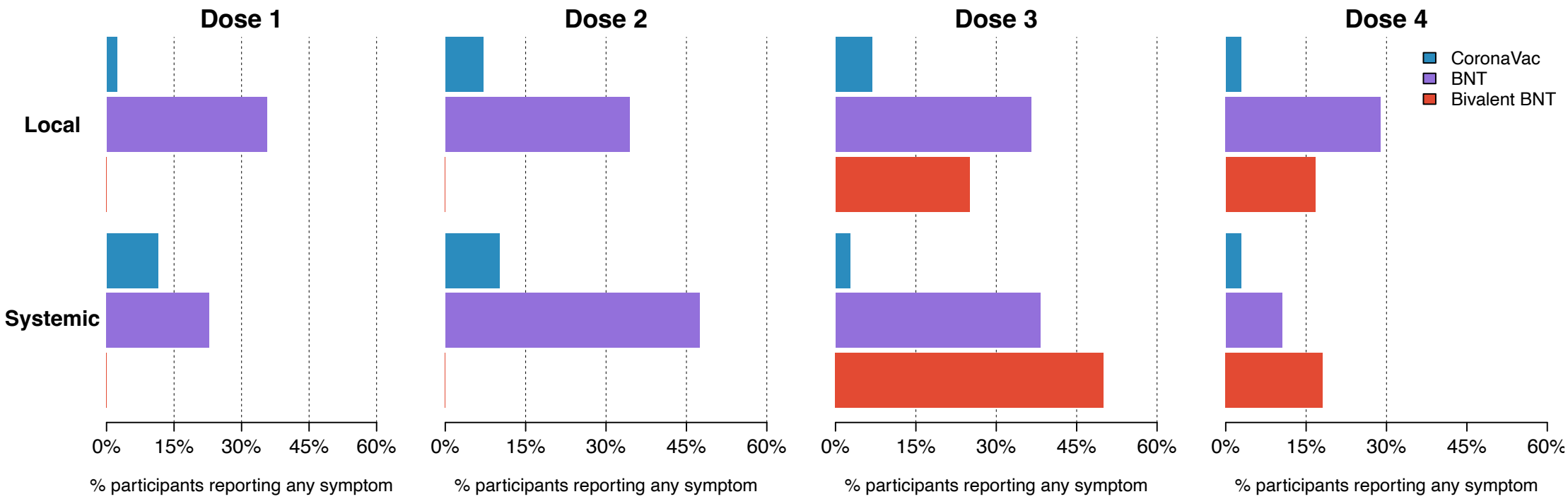
Antivirals have a significant effect on all-cause mortality, as do vaccines. There does not seem to be a “synergistic” effect.

Cheung YYH et al. 2024 Emerg Infect Dis
Cheung YYH et al. 2024 Int J Infect Dis

Very low booster uptake in 2023 and 2024



Reactogenicity of COVID-19 vaccines



- Reactions most frequently reported one day post-vaccination
- Most frequently reported local reaction was pain and tenderness and systemic reaction was feverishness and fatigue
- Reporting “absence from work after prior vaccination” was associated with 62% lower odds of receiving a subsequent booster dose

Unpublished data

Comments and reflections

- COVID-19 vaccines and antivirals saved many lives in Hong Kong and elsewhere
- Inactivated vaccines provided comparable protection to mRNA vaccines, despite very different humoral immune responses
- T cell response specificity to structural viral proteins (S, N, E, M) affected by prior vaccination type; S and NEM T cell response (and other CoPs not shown here) may explain protection from inactivated vaccines; differential waning may lead to greater difference in T cell response specificity between vaccine groups over time
- Community-based cohorts have allowed monitoring of incidence of infections, vaccine effectiveness, and individual and population immunity (through to 2024)
- Reactogenicity is likely affecting uptake of mRNA booster doses

Acknowledgments

- All of our work would not have been possible without sustained infrastructure support via HMRF commissioned grants since 2004
- The specific projects presented today were supported by various HMRF grants (incl. COVID1903001, COVID19F09, CID-HKU2-12 and others)
- Work on vaccines done with Nancy Leung, Malik Peiris, Sophie Valkenburg, Dennis Ip, Gabriel Leung, Martina McMenamin, Samuel Cheng, Carolyn Cohen, Wey Wen Lim, Echo Chen, Faith Ho, Eunice Shiu, Niki Au, Amber Lai, Caitriona Murphy, Xuanrui Zhang, and many other colleagues in HKU SPH
- Work on antivirals done with Eddy Lam and Harrison Cheung