Table S1. Summary of completeness of diary data in percentage for 149 enrolled participants.

Gender	Age group	n	Day0	Day1	Day2	Day3	Day4	Day5	Day6	Day7
Male	**<60**	24	95.8	100.0	91.7	100.0	95.8	91.7	91.7	95.8
Male	**60+**	35	94.3	97.1	100.0	100.0	100.0	100.0	97.1	97.1
Female	**<60**	56	98.2	96.4	96.4	92.9	92.9	94.6	94.6	92.9
Female	**60+**	34	100.0	100.0	100.0	97.1	100.0	100.0	100.0	100.0
Overall		**149**	**97.3**	**98.0**	**97.3**	**96.6**	**96.6**	**96.6**	**96.0**	**96.0**

Table S2. Maximum local and systemic AE within seven days post the fourth dose vaccination, by gender and age group

AE	Grade	Male <60	Male ≥60	Female <60	Female ≥60	Overall
		N=24	N=35	N=55	N=34	N=148
Pain	Mild	17 (70.8%)	21 (60.0%)	33 (60.0%)	22 (64.7%)	93 (62.8%)
	Moderate	1 (4.2%)	0 (0.0%)	9 (16.4%)	1 (2.9%)	11 (7.4%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Redness	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	1 (0.7%)
	Moderate	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (0.7%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Swelling	Mild	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (0.7%)
	Moderate	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (2.9%)	2 (1.4%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fever	Mild	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Moderate	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (0.7%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Chills	Mild	1 (4.2%)	2 (5.7%)	9 (16.4%)	4 (11.8%)	16 (10.8%)
	Moderate	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (2.9%)	2 (1.4%)
	Severe	0 (0.0%)	1 (2.9%)	2 (3.6%)	0 (0.0%)	3 (2.0%)
Headache	Mild	4 (16.7%)	7 (20.0%)	17 (30.9%)	16 (47.1%)	44 (29.7%)
	Moderate	3 (12.5%)	3 (8.6%)	6 (10.9%)	3 (8.8%)	15 (10.1%)
	Severe	0 (0.0%)	1 (2.9%)	1 (1.8%)	0 (0.0%)	2 (1.4%)
Fatigue	Mild	7 (29.2%)	9 (25.7%)	24 (43.6%)	9 (26.5%)	49 (33.1%)
	Moderate	1 (4.2%)	4 (11.4%)	5 (9.1%)	6 (17.6%)	16 (10.8%)
	Severe	1 (4.2%)	0 (0.0%)	3 (5.5%)	0 (0.0%)	4 (2.7%)
Joint pain	Mild	3 (12.5%)	4 (11.4%)	10 (18.2%)	5 (14.7%)	22 (14.9%)

AE	Grade	Male <60	Male ≥60	Female <60	Female ≥60	Overall
	Moderate	0 (0.0%)	2 (5.7%)	1 (1.8%)	2 (5.9%)	5 (3.4%)
	Severe	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (0.7%)
Aching muscles	Mild	4 (16.7%)	12 (34.3%)	19 (34.5%)	6 (17.6%)	41 (27.7%)
	Moderate	1 (4.2%)	2 (5.7%)	2 (3.6%)	2 (5.9%)	7 (4.7%)
	Severe	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)	1 (0.7%)
Nausea	Mild	0 (0.0%)	2 (5.7%)	6 (10.9%)	0 (0.0%)	8 (5.4%)
	Moderate	1 (4.2%)	0 (0.0%)	1 (1.8%)	2 (5.9%)	4 (2.7%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Loss of appetite	Mild	1 (4.2%)	0 (0.0%)	2 (3.6%)	0 (0.0%)	3 (2.0%)
	Moderate	0 (0.0%)	0 (0.0%)	1 (1.8%)	1 (2.9%)	2 (1.4%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table S3. Geometric mean concentration at 4D, 4D28 and PB28, as well as fold change from 4D to 4D28 and from PB28 to 4D28 for anti-spike IgG and pseudotype virus neutralising antibody by variants.

	Visit	GMC (95% CI)	GMR time point	GMR (95% CI)
Anti-spike IgG				
Wild type	4D	116136 (93784-143815)	---	---
[n=90]	4D28	139531 (116628-166933)	4D28:4D	1.20 (1.07-1.35)
	PB28	19634 (16515-23342)	4D28:PB28	7.11 (5.74-8.80)
Omicron [n=90]	4D	24251 (19446-30243)	---	---
	4D28	30164 (24972-36435)	4D28:4D	1.24 (1.10-1.40)
	PB28	3345 (2804-3989)	4D28:PB28	9.02 (7.27-11.19)
Alpha [n=90]	4D	88243 (71181-109396)	---	---
	4D28	106057 (88583-126976)	4D28:4D	1.20 (1.07-1.35)
	PB28	13274 (11125-15839)	4D28:PB28	7.99 (6.50-9.82)
Beta [n=90]	4D	70776 (57171-87619)	---	---
	4D28	85295 (71217-102155)	4D28:4D	1.21 (1.07-1.35)
	PB28	8976 (7557-10663)	4D28:PB28	9.50 (7.74-11.66)
Delta [n=90]	4D	87779 (71204-108213)	---	---
	4D28	104475 (87489-	4D28:4D	1.19 (1.06-1.33)

		124759)		
	PB28	11902 (9983-14191)	4D28:PB28	8.78 (7.16-10.77)
Gamma [n=90]	4D	77107 (61914-96029)	---	---
	4D28	92992 (77083-112186)	4D28:4D	1.21 (1.07-1.36)
	PB28	10627 (8985-12570)	4D28:PB28	8.75 (7.02-10.91)
Pseudovirus neutralising antibody				
Wuhan [n=90]	4D	972 (733-1291)	---	---
	4D28	1231 (979-1549)	4D28:4D	1.27 (1.07-1.49)
	PB28	110 (87-141)	4D28:PB28	11.16 (8.26-15.07)
Omicron [n=30]	4D	492 (235-1029)	---	---
	4D28	639 (354-1154)	4D28:4D	1.30 (0.77-2.20)
	PB28	22 (19-25)	4D28:PB28	29.32 (15.96-53.86)

PB28: 28 days post the 2nd dose; 4D: day of administering the 4th dose; 4D28: 28 days post the 4th dose

Table S4. Odds ratio of SARS-CoV-2 infection 14 to 180 days after fourth dose vaccination as estimated by logistic regression analysis, adjusting for age group and job status.

Variable*	**Odds Ratio (CI)**
Anti-spike IgG (wild type) at 4D	0.27 (95% CI: 0.11, 0.67)
Anti-spike IgG (wild type) at 4D28	0.49 (95% CI: 0.17, 1.42)
Anti-nucleocapsid IgG at 4D	0.47 (95% CI: 0.32, 0.69)
Anti-nucleocapsid IgG at 4D28	0.58 (95% CI: 0.39, 0.86)
Pseudotype neutralising virus (Wuhan) at 4D	0.32 (95% CI: 0.16, 0.62)
Pseudotype neutralising virus (Wuhan) at 4D28	0.35 (95% CI: 0.14, 0.82)
Sero positive at 4D (by anti-nucleocapsid)	0.16 (95% CI: 0.05, 0.50)
COVID infection 6 months prior (yes/no)	0.61 (95% CI: 0.30, 1.25)

4D: day of administering the 4^{th} dose; 4D28: 28 days post the 4^{th} dose

*Antibody measures were log-transformed prior to regression analysis

Figure S1. Maximum local and systemic adverse events in the first seven days following vaccination by gender and age group.

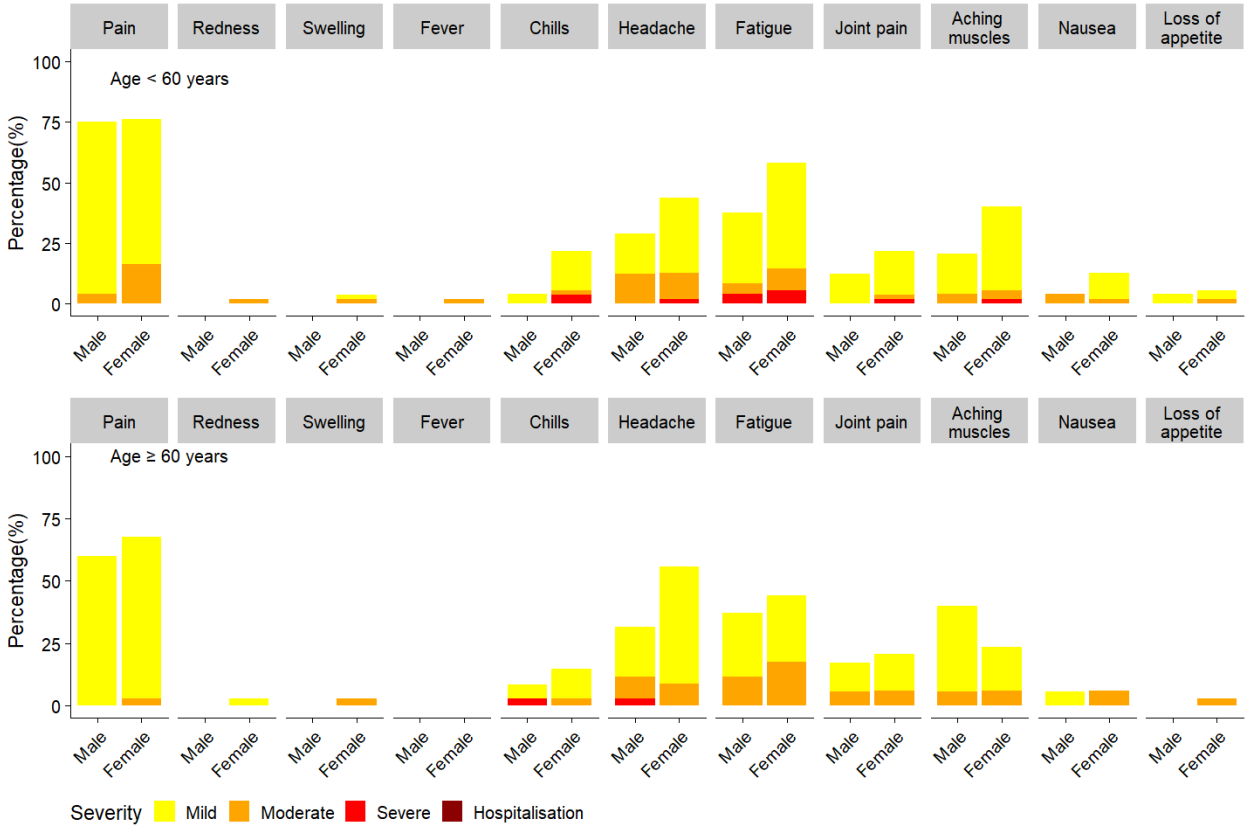
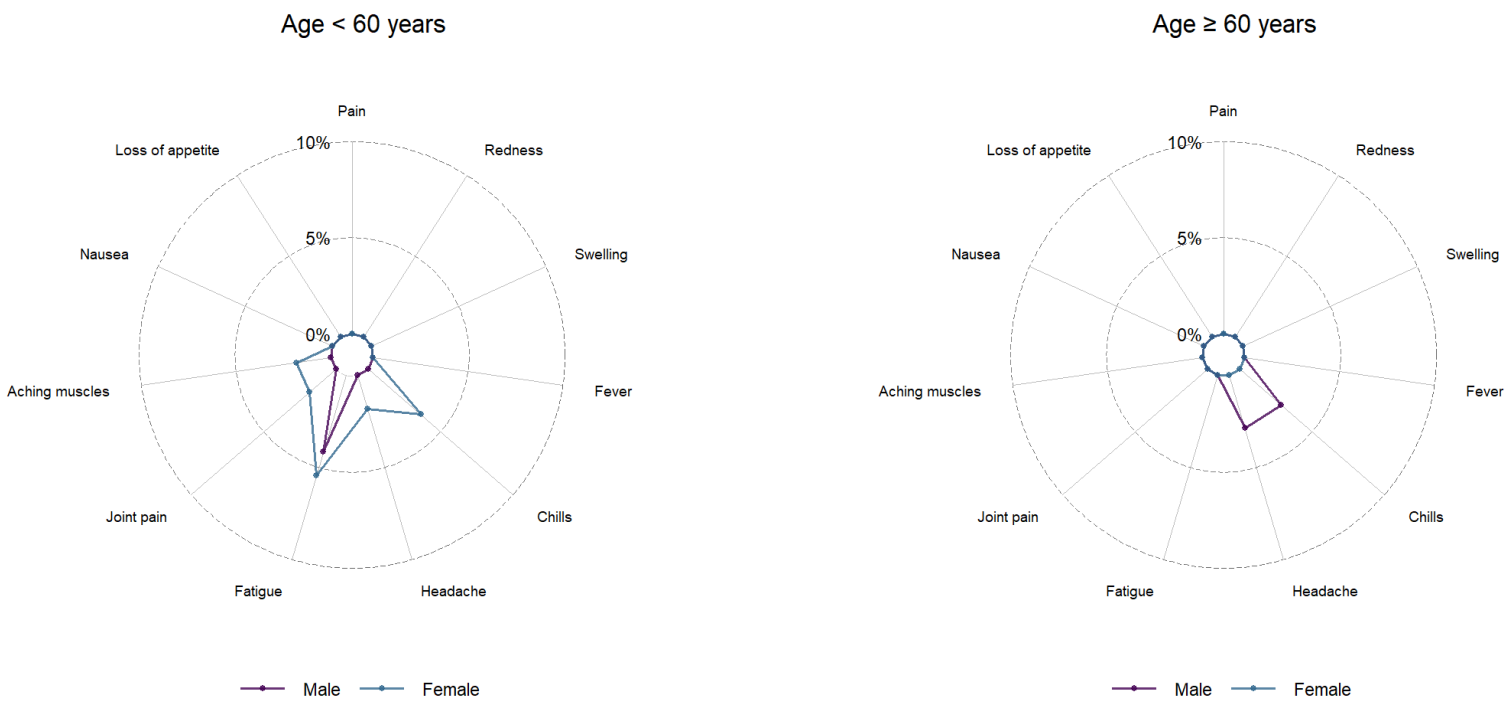


Figure S2. Solicited local and systemic adverse events in the first seven days following vaccination by gender and age group for the 149 participants enrolled.

(A)

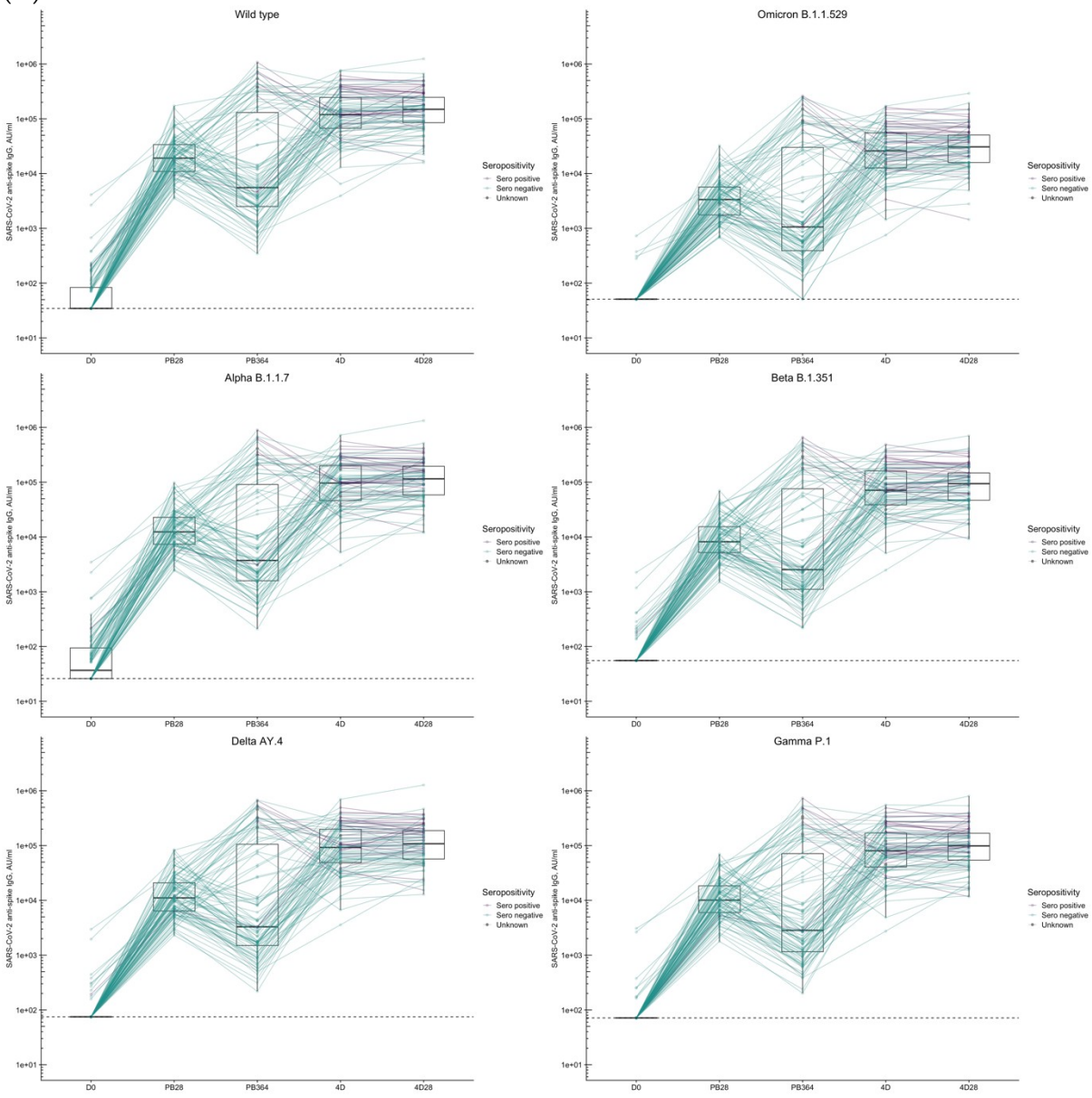


(B)

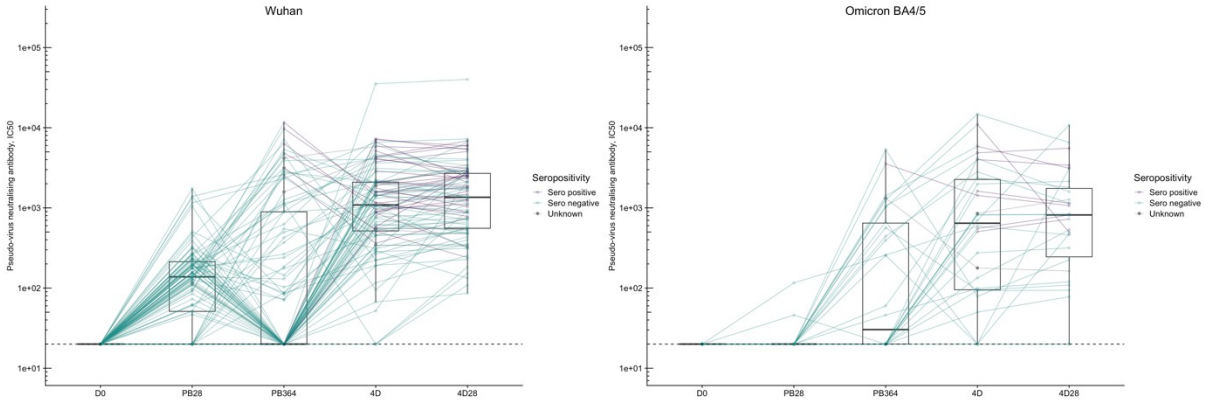
(A) Severe (grade 3–4) local and systemic adverse events. (B) Moderate or severe (grade 2–4) local and systemic adverse events. For each solicited adverse event, the highest severity within the first seven days after fourth-dose vaccination at an individual level was used to draw the plot.

Figure S3. (A)Anti-spike IgG antibody for variants for pre-first dose (D0), 28 and 364 days after second dose (PB28, PB364), Pre-fourth dose (4D) and 28 days after fourth dose (4D28) across variants n=90 (B) Pseudotype virus neutralising antibody against Wuhan n=90 and Omicron BA 4/5 n=30 and (C) anti-nucleocapsid and anti-Receptor binding domain IgG antibody n=90.

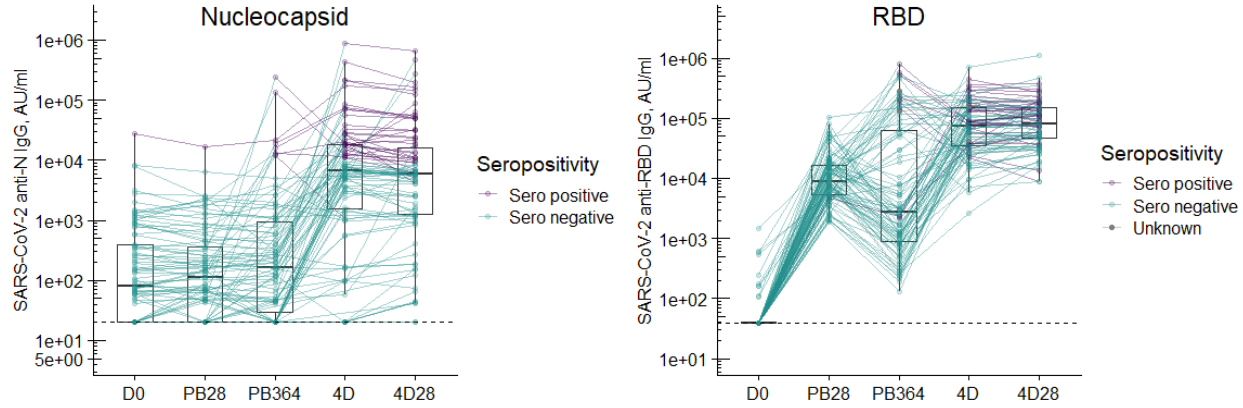
(A)



(B)

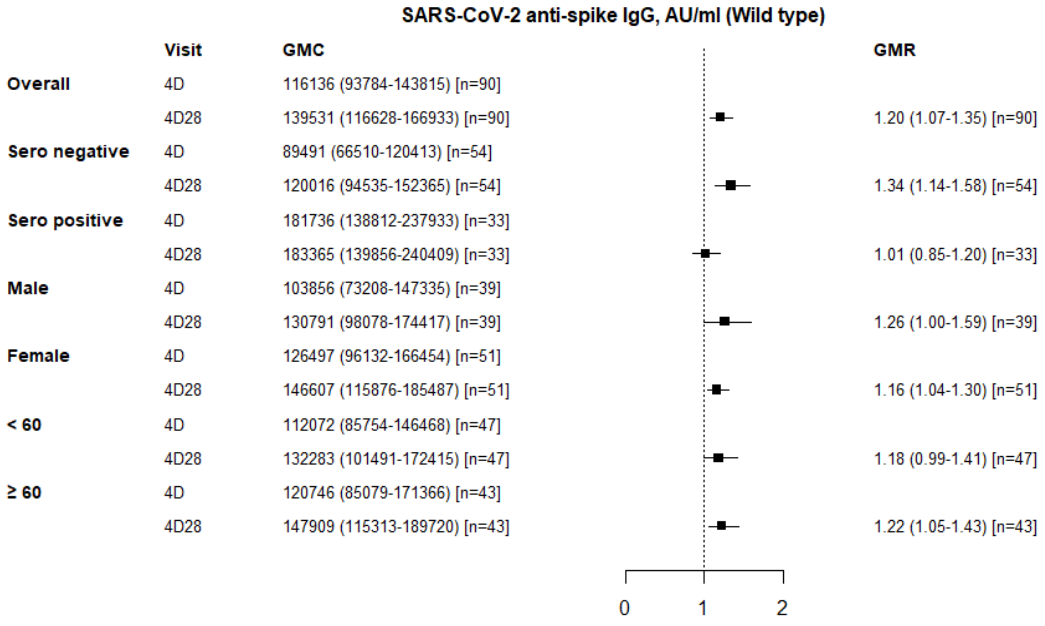


(C)

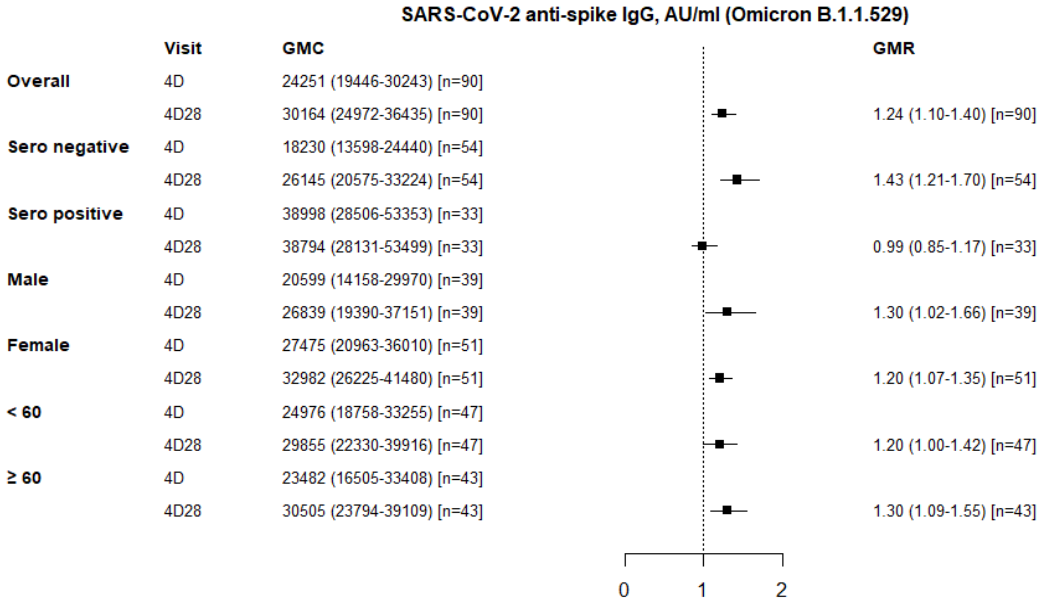


D0: day of administering the 1st dose; PB28: 28 days post the 2nd dose; PB364: 364 days post the 2nd dose; 4D: day of administering the 4th dose; 4D28: 28 days post the 4th dose

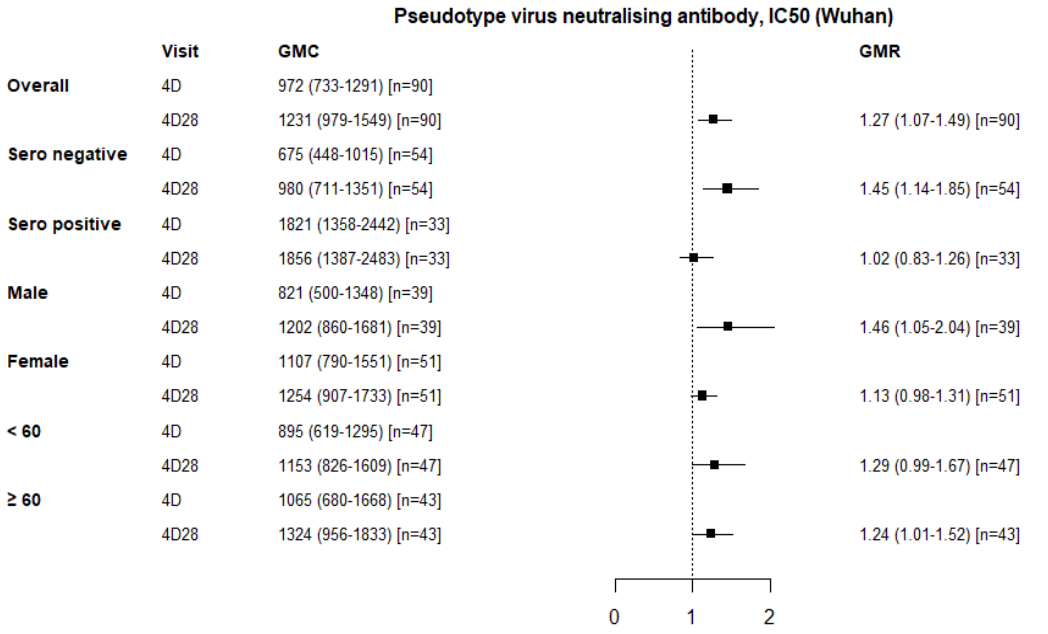
Figure S4. Overall and subgroup analysis by sero status before fourth dose, sex and age group (<60 years, ≥60 years) of geometric mean concentration at 4D and 4D28, and fold change for Anti-spike IgG against wild type (A) and Omicron (B) variants and pseudotype virus neutralizing antibody against wild type (C) and Omicron (D) variants.



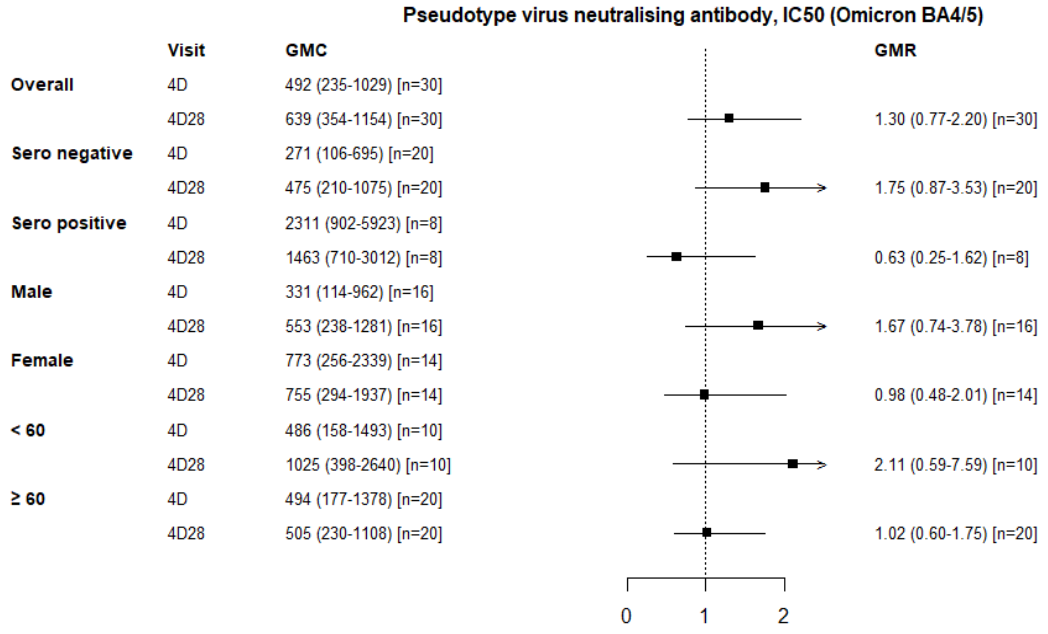
(A)



(B)



(C)



(D)

4D: day of administering the 4th dose; 4D28: 28 days post the 4th dose

Figure S5. Number of SARS-CoV-2 self-reported cases from August 2021 to March 2023 by 149 participants received fourth dose in COV009.

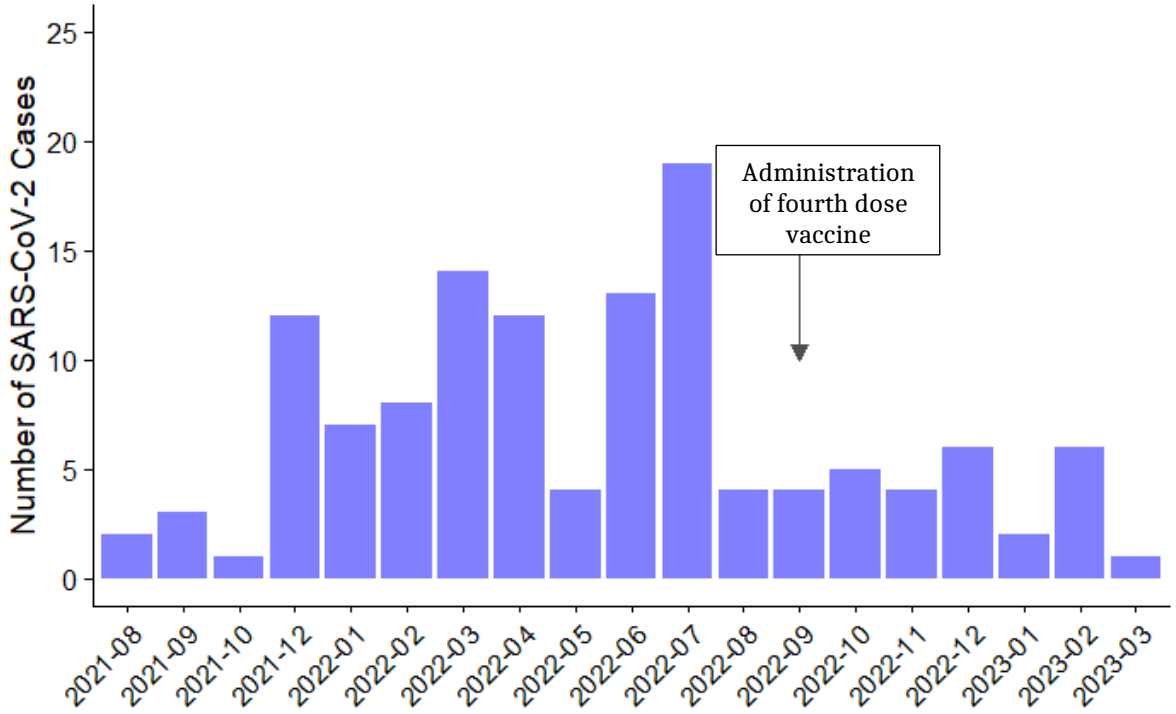
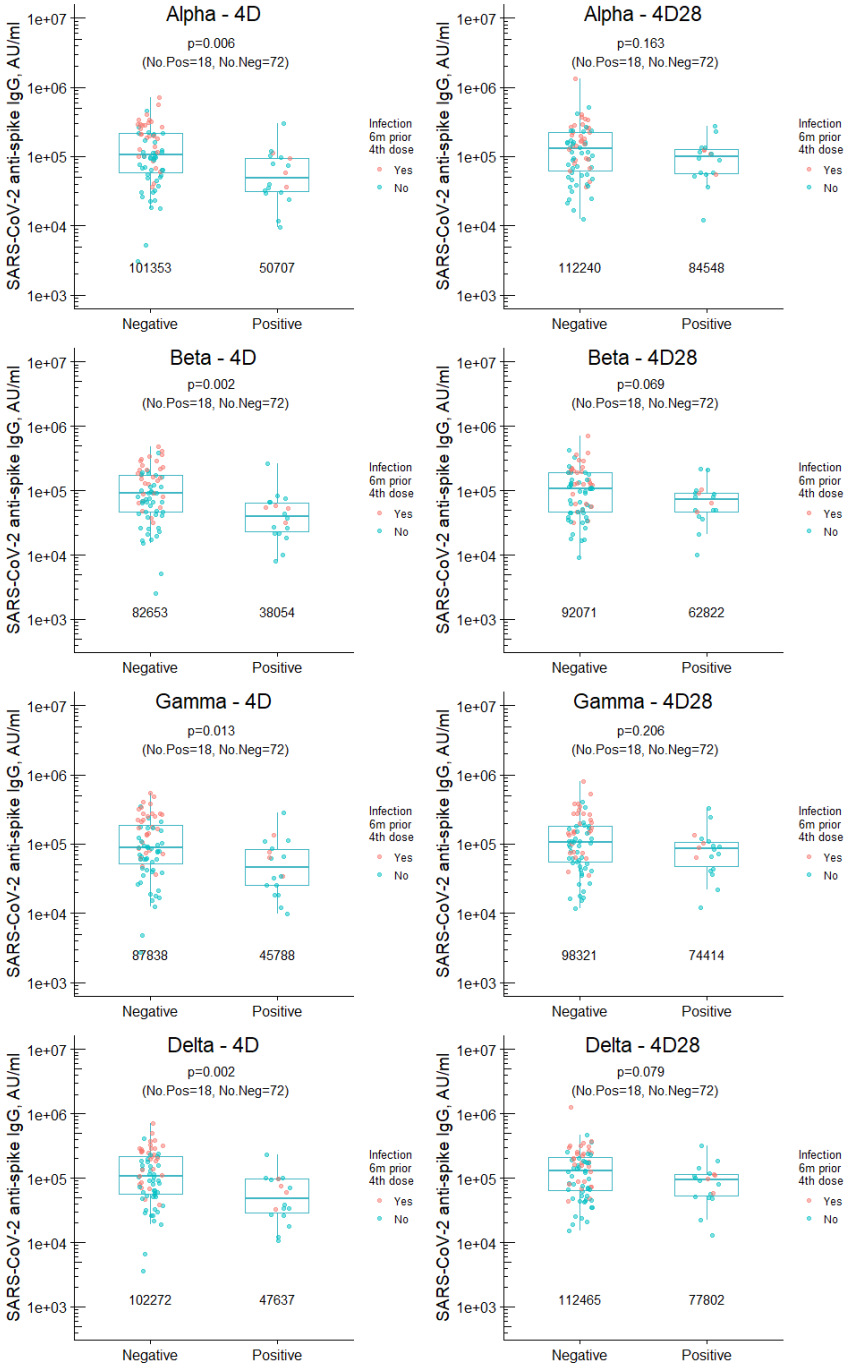
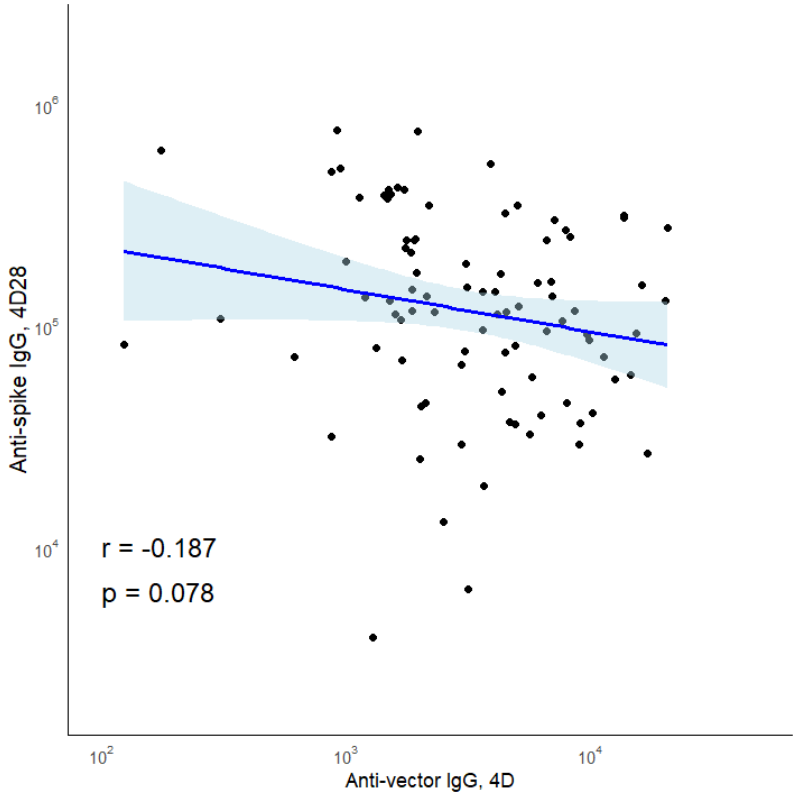


Figure S6. Anti-spike IgG antibody against Alpha, Beta, Gamma and Delta variants measured at day of administering the fourth dose, and 28 days after, in positive cases and negative non-cases occurred 14 to 180 days after the fourth dose. Different colours indicate self-reported infections from 6 months prior to the fourth dose (red) and non-infection (teal).



4D: day of administering the 4th dose; 4D28: 28 days post the 4th dose.

Figure S7. Correlation between anti-vector antibody responses at before the fourth dose and anti-spike IgG against wild type at 28 days post the fourth dose.



4D: day of administering the 4th dose; 4D28: 28 days post the 4th dose

Additional Methods: Anti- ChAdOx1 IgG Elisa

An in-house anti-ChAdOx1 IgG Elisa assay was used to assess anti-vector antibodies. Polystyrene plaNunc MaxiSorp 96-well flat-bottomed plates Elisa (Thermo-Fisher Ltd. UK; 442404) were coated with ChAdOx1-SARS-CoV-2 RBD, stock concentration 1.26e12 VP/ml (Viral Vector Core Facility, Jenner Institute,) dissolved in 1x phosphate buffered saline, pH 7.2 (Gibco™, Thermo-Fisher Ltd, UK; 22012-019) coating buffer and incubated at 4°C overnight. Plates were handwashed five times using phosphate buffered saline with 0.05% tween concentration (1xPBST) then blocked with casein (Blocker™ Casein in PBS, Thermo-Fisher Ltd. UK; 37528) at 37°C for two hours. Samples were diluted in casein and run at

three dilutions in twofold serial dilution, with 1:150 as the lowest dilution (1:150, 1:450, 1:1350) at 50µl per well in triplicate and incubated at 25°C for two hours. Test samples were plated prior to assay controls. Plates were washed 5 times with 1xPBST and Goat anti-human IgG Fc specific alkaline phosphatase conjugate (Sigma-Aldrich; A9544) added at 1:1000 dilution at 25°C for 2 hours. Plates were washed 5 times with 1xPBST) and 100µl per well of development substrate 4-Nitrophenyl phosphate (pNPP) were added (Sigma-Aldrich, Merck KGaA, Darmstadt, Germany; N2765). Plates were read with the Biotek ELx808 ELISA reader and Gen5 v3.09 software (Agilent, Santa Clara, USA; serial no:1702166). Final reads were taken when the third serial dilution of the standard curve reached an optical density (OD) value of 1.0 when read at 405(nm).