

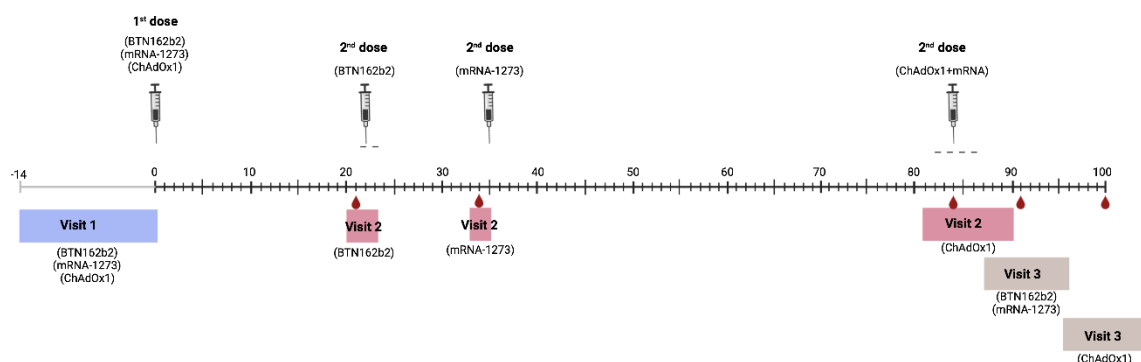
1 SUPPLEMENTARY

2 Supplementary Table 1: Vaccine-related response for CD4+ and CD8+ T cells at day 90.

	Day 90 Spike Specific CD4+ T Cells				Day 90 Spike Specific CD8+ T Cells			
	Tertile 1	Tertile 2	Tertile 3	p-value	Tertile 1	Tertile 2	Tertile 3	p-value
Number of participants, n (%)	154 (33.3)	154 (33.3)	154 (33.3)		151 (33.3)	148 (33.3)	150 (33.3)	
Baseline characteristics								
Age at enrolment, median [Q1,Q3]	70 [57,75]	64 [52,69]	63 [51,69]	<0.001	68 [54,75]	62 [48,70]	65 [55,69]	0.02
Age group, n (%)								
<65	53 (24.8)	77 (36.0)	84 (39.3)	<0.001	62 (29.1)	78 (36.6)	73 (34.3)	0.009
65-74	43 (32.1)	49 (36.6)	42 (31.3)		38 (29.2)	44 (33.8)	48 (36.9)	
≥75	58 (50.9)	28 (24.6)	28 (24.6)		51 (48.1)	26 (24.5)	29 (27.4)	
Sex, n (%)								
Male	77 (34.4)	66 (29.5)	81 (36.2)	0.208	73 (34.0)	64 (29.8)	78 (36.3)	0.315
Female	77 (32.4)	88 (37.0)	73 (30.7)		78 (33.3)	84 (35.9)	72 (30.8)	
Vaccine type, n (%)								
BNT162b2	125 (52.1)	68 (28.3)	47 (19.6)	<0.001	115 (50.4)	66 (28.9)	47 (20.6)	<0.001
mRNA-1273	25 (11.7)	83 (39.0)	105 (49.3)		33 (15.6)	79 (37.3)	100 (47.2)	
ChAdOx1+mRNA	4 (44.4)	3 (33.3)	2 (22.2)		3 (33.3)	3 (33.3)	3 (33.3)	
Days between first and second dose, median [Q1,Q3]	23 [21,28]	35 [21,35]	35 [24,35]	<0.001	24 [21,35]	34 [22,35]	35 [23,35]	<0.001
Days from first vaccine to third study visit, median [Q1,Q3]	91 [89,93]	91 [88,93]	91 [87,96]	0.562	91 [89,94]	91 [89,95]	91 [88,93]	0.338
CCI, n (%)								
0	105 (29.9)	121 (34.5)	125 (35.6)	0.012	103 (30.1)	115 (33.6)	124 (36.3)	0.062
1-2	37 (40.7)	31 (34.1)	23 (25.3)		39 (44.8)	27 (31.0)	21 (24.1)	
>2	12 (60.0)	2 (10.0)	6 (30.0)		9 (45.0)	6 (30.0)	5 (25.0)	
Comorbidities in the previous 5 years, n								
Myocardial infarction	<5*	<5*	<5*	1.000	<5*	<5*	<5*	0.875
Congestive heart failure	5	5	<5*	0.826	7	<5*	<5*	0.367
Peripheral vascular disease	<5*	<5*	<5*	1.000	<5*	<5*	<5*	1.000
Cerebrovascular disease	8	5	6	0.769	<5*	6	8	0.474
Dementia								
Chronic pulmonary disease	10	<5*	<5*	0.168	8	<5*	6	0.548
Rheumatological disease	7	<5*	<5*	0.089	<5*	5	<5*	0.184
Peptic ulcer disease			<5*	0.332		<5*		0.108
Mild liver disease	5	<5*		0.106	6	<5*	<5*	0.089
Diabetes without chronic complications	8	<5*	5	0.551	6	5	6	1.000
Diabetes with chronic complications	<5*			1.000	<5*			1.000
Hemiplegia or paraplegia								
Any malignancy, including leukemia and lymphoma	20	14	21	0.442	22	18	12	0.182
Moderate or severe liver disease	<5*			0.036	<5*	<5*		0.280
Metastatic solid tumor	<5*		<5*	1.000	<5*		<5*	1.000
AIDS/HIV	<5*	<5*	<5*	0.913	<5*	<5*	<5*	0.651
Renal disease	<5*	<5*		0.379	<5*	<5*	<5*	0.626
Organ transplantation	8	10	8	0.905	14	6	6	0.107
Day 90 immune response								
Serological vaccine responder group, n (%)								
Hypo	18 (50.0)	11 (30.6)	7 (19.4)	<0.001	22 (61.1)	6 (16.7)	8 (22.2)	0.001
Moderate	55 (52.4)	29 (27.6)	21 (20.0)		40 (39.6)	38 (37.6)	23 (22.8)	
High	80 (25.2)	112 (35.2)	126 (39.6)		88 (28.5)	103 (33.3)	118 (38.2)	
Total SARS CoV-2 Spike IgG Antibodies (· 10 ⁵ AU/mL), median [Q1,Q3]	1.15 [0.48,3.20]	3.03 [1.35,4.65]	4.04 [1.76,4.68]	<0.001	1.30 [0.55,3.56]	3.16 [1.64,4.55]	3.95 [1.48,4.66]	<0.001
Post day 90								
Breakthrough Infection, n (%)								
Yes	48 (35.3)	37 (27.2)	51 (37.5)	0.183	43 (32.1)	49 (36.6)	42 (31.3)	0.568
No	106 (32.5)	117 (35.9)	103 (31.6)		108 (34.3)	99 (31.4)	108 (34.3)	
Follow-up days, median [Q1,Q3]	252 [236,266]	224 [196,257]	215 [194,251]	<0.001	249 [226,270]	223 [188,258]	216 [201,250]	<0.001

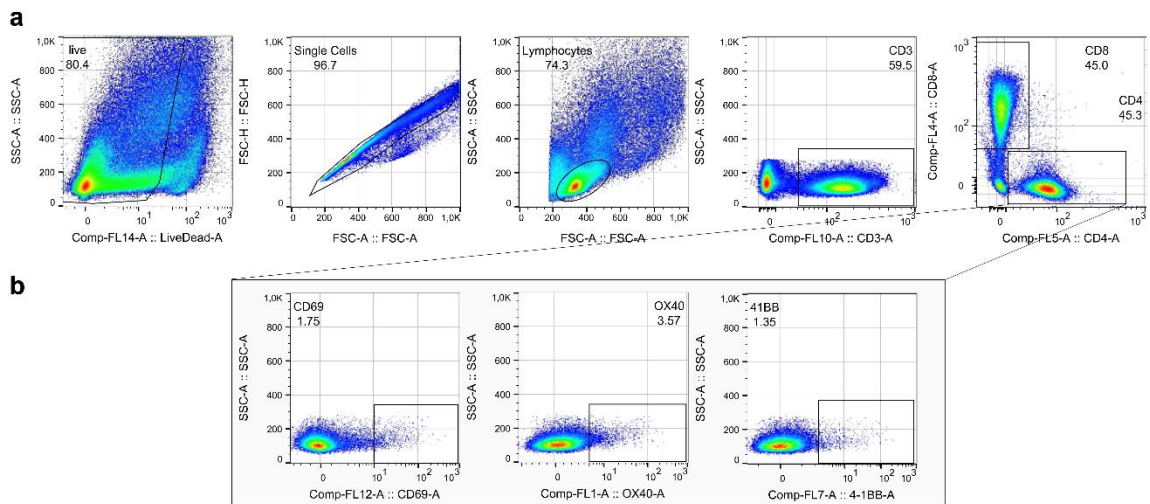
3 * Groups with small numbers (<5 participants per cell) where there is the potential that individual participants could be identified or be
4 able to identify themselves have been edited to maintain participant confidentiality. Charlson Comorbidity Index (CCI).

5 *Supplementary Figure 1: Timeline of vaccine doses and study visits.*

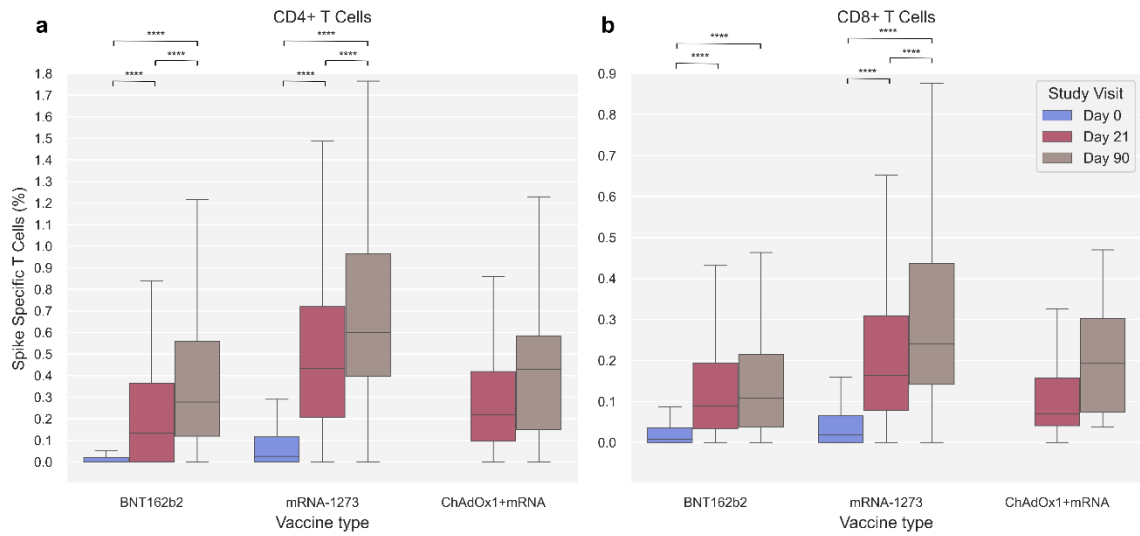


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7 Vaccine doses are depicted above the timeline by syringes at the median value and horizontal dotted lines showing
8 IQR. Study visits are depicted below the timeline by blood drops at median and boxes showing IQR. Day 0 was
9 defined as the day of the first vaccine dose. The median number of days from first vaccine dose to visit 2 (day 21)
10 was 21, 34, and 84 days for BNT162b2, mRNA-1273, and ChAdOx1, respectively. The median number of days
11 from first vaccine dose to visit 3 (day 90) was 91 days for BNT162b2 and mRNA-1273, and 100 days for ChAdOx1.
12 The figure was created with BioRender.com.

Supplementary Figure 2: Gating strategy in AIM assay.

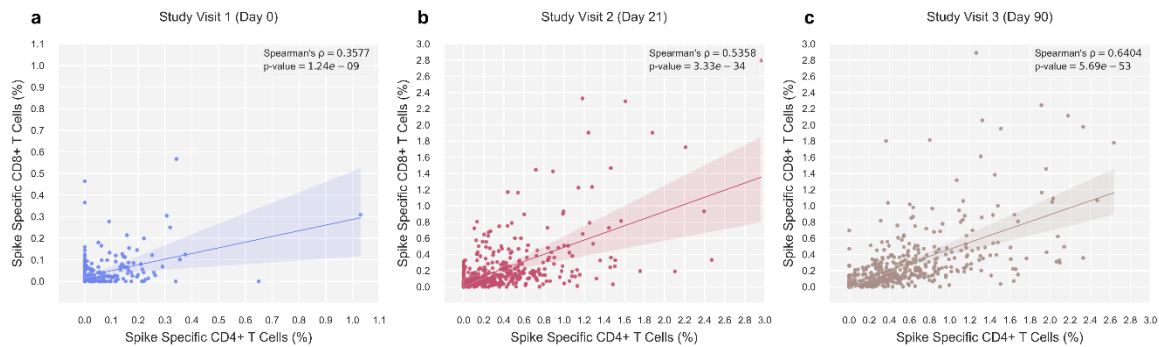


(a) Gating strategy to identify CD4+ and CD8+ T cells. (b) Example of gating strategy for the three AIMs (CD69, OX40, and 41BB) for CD4+ T cells; identical gating was done for CD8+ T cells. Figure created in FlowJo Layout Editor with representative substudy participant sample.

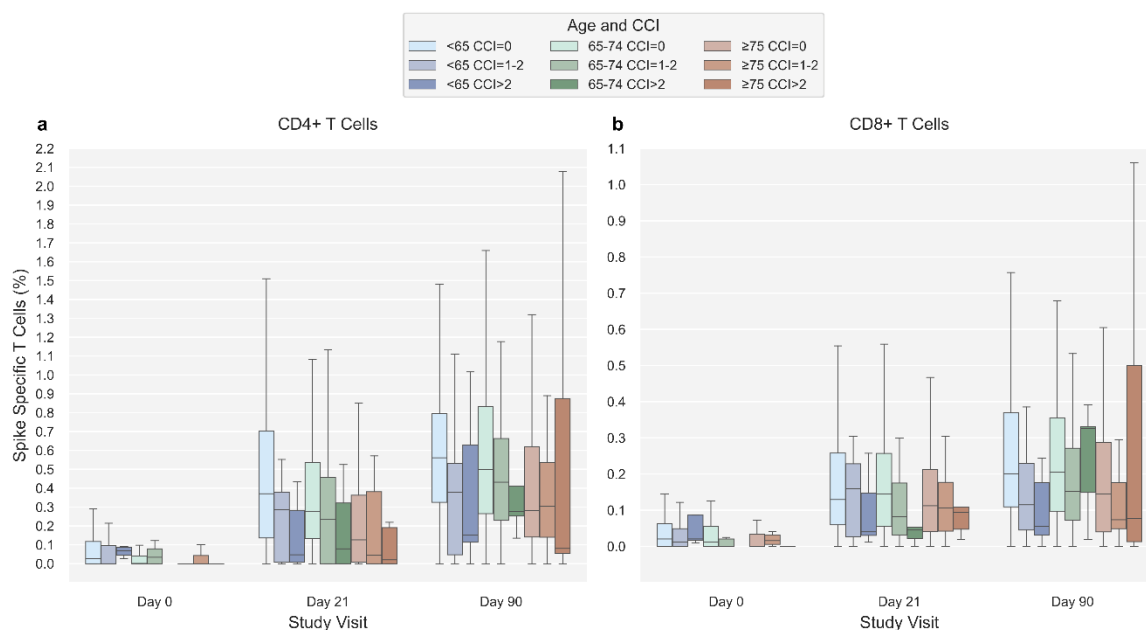


SARS-CoV-2 Spike-specific CD4+ (a) and CD8+ (b) T cells at days 0 (blue), 21 (red), and 90 (brown) stratified by vaccine type. For CD4+ T cells, group sizes are; BNT162b2, n=127 (day 0), n=212 (day 21), n=240 (day 90); mRNA-1273, n=159 (day 0), n=197 (day 21), n=213 (day 90); ChAdOx1+mRNA, n=0 (day 0), n=51 (day 21), n=9 (day 90). For CD8+ T cells, group sizes are; BNT162b2, n=115 (day 0), n=198 (day 21), n=228 (day 90); mRNA-1273, n=157 (day 0), n=195 (day 21), n=212 (day 90); ChAdOx1+mRNA, n=0 (day 0), n=51 (day 21), n=9 (day 90). Data was compared using unpaired, non-parametric Mann–Whitney U test. Error bars show the distribution within 1.5 times IQR. p-value annotation legend: *: $1.00 \cdot 10^{-02} < p \leq 5.00 \cdot 10^{-02}$, **: $1.00 \cdot 10^{-03} < p \leq 1.00 \cdot 10^{-02}$, ***: $1.00 \cdot 10^{-04} < p \leq 1.00 \cdot 10^{-03}$, ****: $p \leq 1.00 \cdot 10^{-04}$.

28 *Supplementary Figure 4: Correlation between SARS-CoV-2 Spike CD4+ and CD8+*
29 *response.*

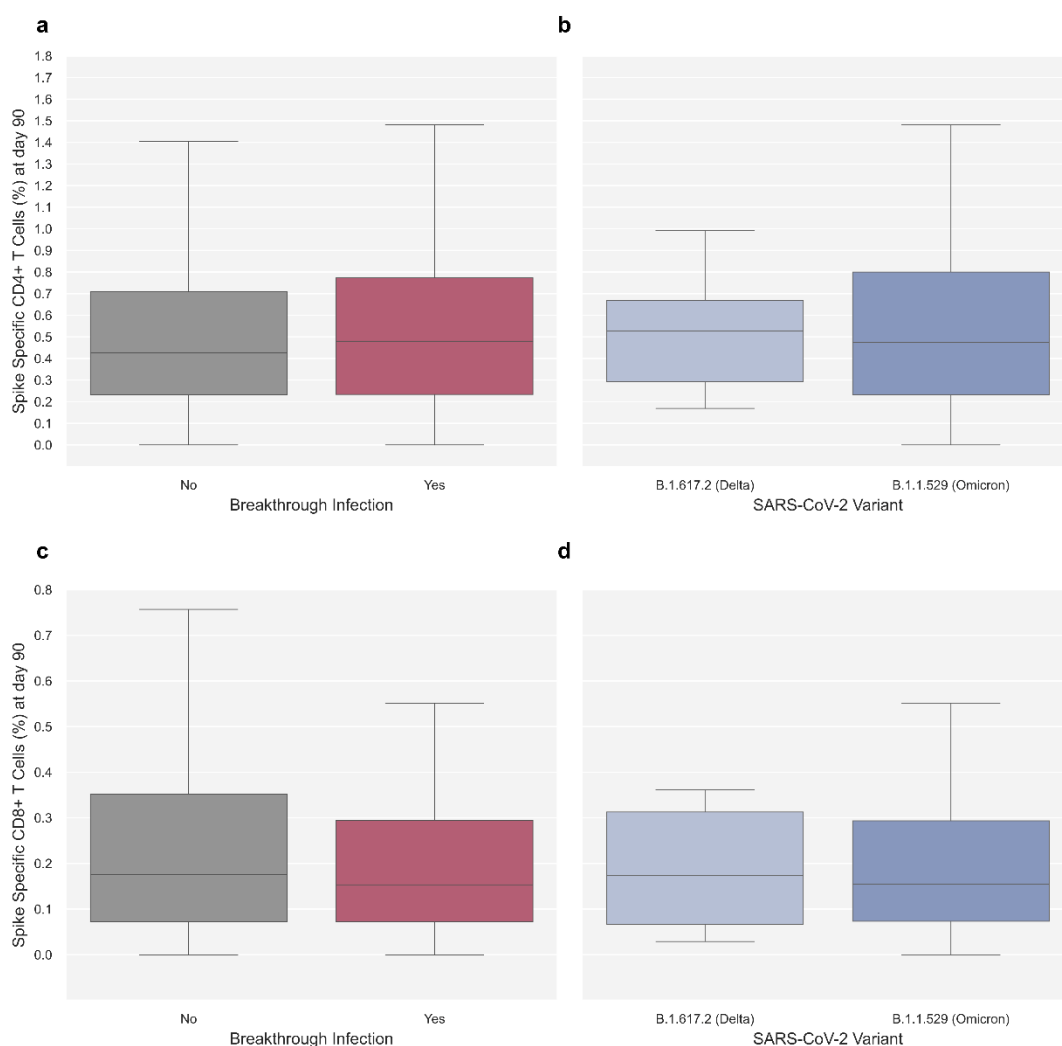


30
31 *Correlation between SARS-CoV-2 Spike-specific CD4+ (horizontal axis) and CD8+ (vertical axis) T cells at (a) day*
32 *0 (blue, n=272), (b) day 21 (red, n=442), and (c) day 90 (brown, n=447). Data was plotted with a linear regression*
33 *model fit. Translucent bands around the regression line show the 99% confidence interval for the regression*
34 *estimate. The confidence interval was estimated using a bootstrap.*



36 SARS-CoV-2 Spike-specific CD4+ (a) and CD8+ (b) T cells at day 0, 21, and 90 stratified by age group (<65 years
37 [blue], 65-74 years [green], ≥75 years [red]) and Charlson Comorbidity Index (CCI) (CCI=0 [light color], CCI=1-2
38 [medium color], CCI>2 [dark color]). For CD4+ T cells (left), group sizes are; at day 0 n=121 (<65 CCI=0), n=17
39 (<65 CCI=1-2), n=4 (<65 CCI>2), n=47 (65-75 CCI=0), n=7 (65-74 CCI=1-2), n=0 (65-74 CCI>2), n=81 (≥75 CCI=0),
40 n=8 (≥75 CCI=1-2), n=1 (≥75 CCI>2); at day 21 n=195 (<65 CCI=0), n=28 (<65 CCI=1-2), n=11 (<65 CCI>2), n=74
41 (65-75 CCI=0), n=42 (65-74 CCI=1-2), n=7 (65-74 CCI>2), n=75 (≥75 CCI=0), n=23 (≥75 CCI=1-2), n=5 (≥75
42 CCI>2); at day 90 n=175 (<65 CCI=0), n=30 (<65 CCI=1-2), n=9 (<65 CCI>2), n=89 (65-75 CCI=0), n=40 (65-74
43 CCI=1-2), n=5 (65-74 CCI>2), n=87 (≥75 CCI=0), n=21 (≥75 CCI=1-2), n=6 (≥75 CCI>2). For CD8+ T cells (left),
44 group sizes are; at day 0 n=120 (<65 CCI=0), n=15 (<65 CCI=1-2), n=4 (<65 CCI>2), n=47 (65-75 CCI=0), n=7 (65-
45 74 CCI=1-2), n=0 (65-74 CCI>2), n=71 (≥75 CCI=0), n=7 (≥75 CCI=1-2), n=1 (≥75 CCI>2); at day 21 n=195 (<65
46 CCI=0), n=27 (<65 CCI=1-2), n=11 (<65 CCI>2), n=72 (65-75 CCI=0), n=39 (65-74 CCI=1-2), n=7 (65-74 CCI>2),
47 n=67 (≥75 CCI=0), n=21 (≥75 CCI=1-2), n=5 (≥75 CCI>2); at day 90 n=175 (<65 CCI=0), n=29 (<65 CCI=1-2), n=9
48 (<65 CCI>2), n=88 (65-75 CCI=0), n=37 (65-74 CCI=1-2), n=5 (65-74 CCI>2), n=79 (≥75 CCI=0), n=21 (≥75 CCI=1-
49 2), n=6 (≥75 CCI>2). Error bars show the distribution within 1.5 times IQR.

Supplementary Figure 6: SARS-CoV-2 Spike-specific T cells at day 90 stratified by breakthrough infections with B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants.



A total of 167 breakthrough infections were recorded in the entire cohort of 655 participants; 1 unknown variant, 10 B.1.617.2 (Delta), and 156 B.1.1.529 (Omicron) variant. The figure shows breakthrough infections relative to SARS-CoV-2 Spike-specific CD4+ T cells (a, b), CD8+ T cells (c, d) at day 90. 136 of 462 participants with CD4+ T cell data experienced breakthroughs (a); 10 Delta and 125 Omicron variant (b). 134 of 449 participants with CD8+ T cell data experienced breakthroughs (c); 10 Delta and 123 Omicron variant (d). Data was compared using unpaired, non-parametric Mann-Whitney U test. Error bars show the distribution within 1.5 times IQR. p-value annotation legend: *: $1.00 \cdot 10^{-02} < p \leq 5.00 \cdot 10^{-02}$, **: $1.00 \cdot 10^{-03} < p \leq 1.00 \cdot 10^{-02}$, ***: $1.00 \cdot 10^{-04} < p \leq 1.00 \cdot 10^{-03}$, ****: $p \leq 1.00 \cdot 10^{-04}$.