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Supplemental information

SARS-CoV-2 vaccine-induced antibodies protect against Omicron breakthrough infection

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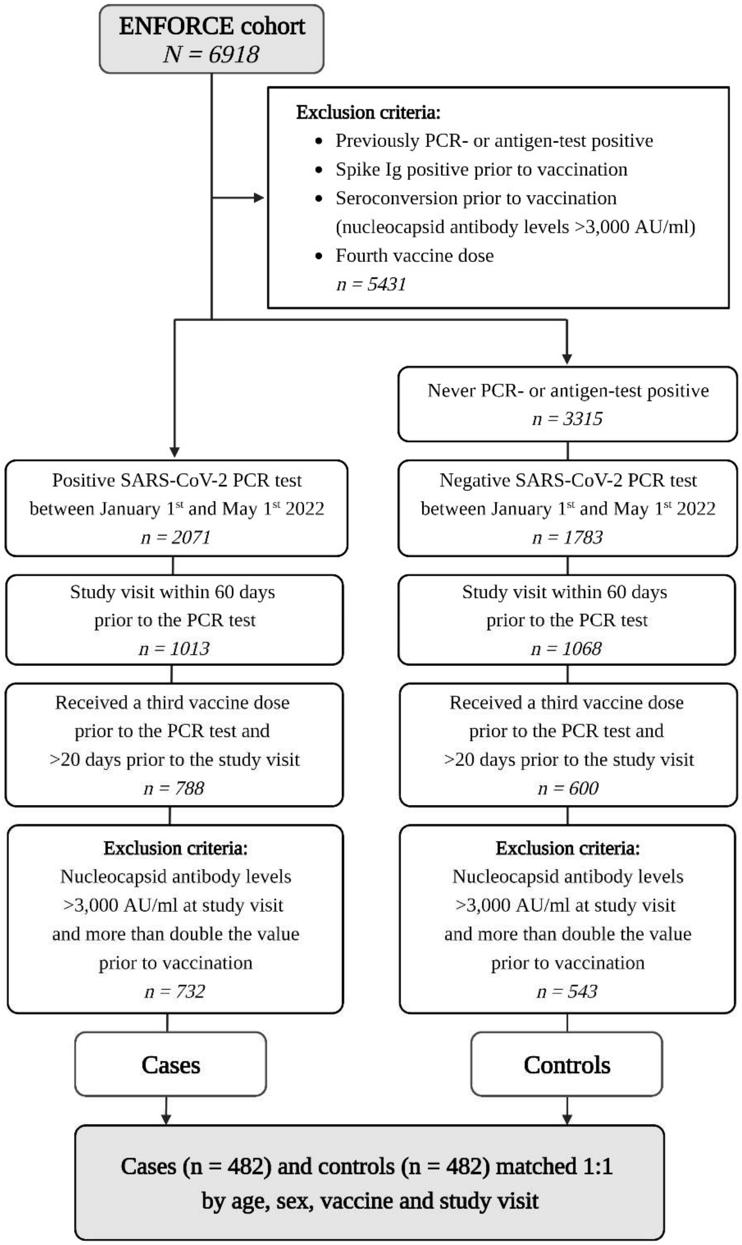
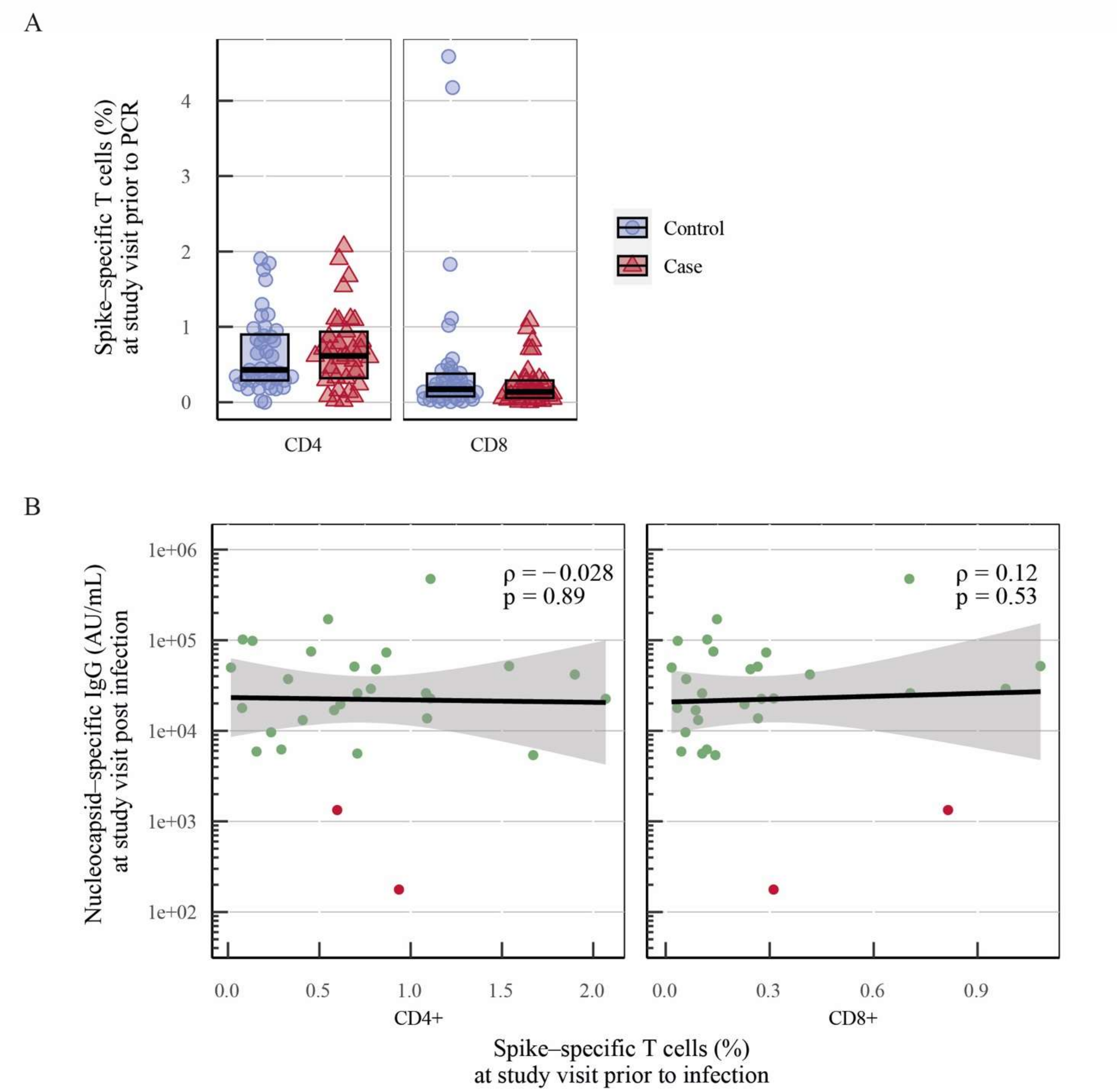
Supplementary figure 1 – Selection criteria for study participants, related to figure 1.



Participants for the study were selected from the ENFORCE cohort based on the presented exclusion and inclusion criteria with the number of remaining participants.

Supplementary figure 2 – Examination of cellular immunity, related to figure 2 and 4.



SARS-CoV-2 spike-specific CD4+ and CD8+ T cell frequencies were quantified in an unmatched subpopulation of the study cohort, who donated PBMCs (n=40, 54.8% for cases and n=33, 45.2% for controls). **A)** Boxplot showing the median percentage of spike-specific CD4+ T cells and CD8+ T cells with lower and upper quartiles. Wilcoxon rank sum test was performed to compare cellular responses in cases and controls and no statistically significant differences were found. **B)** Spearman correlations between infection-induced nucleocapsid-specific IgG (AU/mL) and vaccine-induced spike-specific CD4+ and CD8+ T cells (%) (Wuhan-Hu-1). No correlation was found.

Supplementary table 1 – Grouping of ACE2 data, related to figure 2 and 3.

Variant	Grouping	Total N	Cases	Controls	ACE2-blocking antibodies (AU/mL)	Median (AU/mL)
Wildtype	Q1	193	110	83	<376.89	165.88
	Q2	74	41	33	376.89 – 1,000	552.97
	Q3-Q5	697	331	366	>1,000	10,000
Omicron BA.1	Q1	193	110	83	<20.67	11.08
	Q2	193	110	83	20.67 – 49.72	33.00
	Q3	193	98	95	49.72 – 102.79	72.81
	Q4	193	84	109	102.79 – 217.64	150.25
	Q5	192	80	112	>217.64	469.76
Omicron BA.2	Q1	193	111	82	<60.05	25.98
	Q2	193	109	84	60.05 – 193.05	116.83
	Q3	193	101	92	193.05 – 680.62	347.58
	Q4	45	19	26	680.62 – 1,000	808.48
	Q5	340	142	198	>1,000	10,000

ACE2 data were not normally distributed and were therefore split into five groups for Omicron BA.1 and BA.2. For wildtype, many samples reached the assay detection limit and were therefore split into three groups. The actual titers of ACE2-blocking antibodies in AU/mL and the median titer in AU/mL are described for each grouping.

Supplementary table 2 – Demographics of participants included in T cell immunity analysis, related to supplementary figure 2 and figure 2 and 4.

	Cases (n=33)	**Control** (n=40)	*P-value*
Age at enrolment (median, IQR)	59 (47–68)	65 (54–73)	*0.164*
Age Group (n, %)			*0.655*
<55	12 (36.4)	11 (27.5)	.
55-65	7 (21.2)	8 (20.0)	.
>65	14 (42.4)	21 (52.5)	.
Sex (n, %)			*0.987*
Female	18 (54.5)	23 (57.5)	.
Male	15 (45.5)	17 (42.5)	.
Vaccine type (n, %)			*0.689*
Pfizer-BioNTech	16 (48.5)	19 (47.5)	.
Moderna	9 (27.3)	14 (35.0)	.
AstraZeneca/mRNA	8 (24.2)	7 (17.5)	.
Study visit (n, %)			*0.865*
28 days after 3rd dose	31 (93.9)	39 (97.5)	.
Up to 170 days after 3rd dose	2 (6.1)	1 (2.5)	.
Charlson Comorbidity Index (n, %)			*0.958*
0	27 (81.8)	32 (80.0)	.
1-2	5 (15.2)	7 (17.5)	.
>2	1 (3.0)	1 (2.5)	.
Days from study visit to PCR test (median, IQR)	37 (26–48)	32 (16–38)	*0.091*

The demographic characteristics of the unmatched subpopulation who donated PBMCs and were included in the T cell immunity analysis. The categorical variables are described as number of participants (n) and the percentage (%), while the continuous variables are described as the median and the interquartile range (IQR).

Supplementary table 3 – Demographics of participants stratified by sex, related to figure 3.

	Males (n=394)	**Females** (n=570)	*P-value*
Age at enrolment (median, IQR)	68 (59–75)	63 (55–69)	*<.0001*
Age Group (n, %) *			*<.0001*
<55	66 (16.8)	134 (23.5)	.
55-65	106 (26.9)	198 (34.7)	.
>65	222 (56.3)	238 (41.8)	.
Vaccine type (n, %) *			*<.0001*
Pfizer-BioNTech	228 (57.9)	252 (44.2)	.
Moderna	160 (40.6)	254 (44.6)	.
AstraZeneca/mRNA	6 (1.5)	64 (11.2)	.
Study visit (n, %) *			*0.0006*
28 days after 3rd dose	376 (95.4)	564 (98.9)	.
Up to 170 days after 3rd dose	18 (4.6)	6 (1.1)	.
Charlson Comorbidity Index (n, %)			*0.0116*
0	290 (73.6)	455 (79.8)	.
1-2	87 (22.1)	106 (18.6)	.
>2	17 (4.3)	9 (1.6)	.
Days from study visit to PCR test (median, IQR)	35 (22–48)	32 (20–46)	*0.1434*

*matched variable

The demographic characteristics of participants (N=964) stratified by sex. The categorical variables are described as number of participants (n) and the percentage (%), while the continuous variables are described as the median and the interquartile range (IQR). The matched variables are indicated with an asterisk (*).

Supplementary table 4 – Spike-specific IgG levels stratified by sex, related to figure 3.

		Geometric Mean				**Adjusted Odds Ratio**	
Variant	**n**	**Cases** *95% CI*	**Controls** *95% CI*	**GM ratio** *95% CI*	*P-value*	**aOR** *95% CI*	*P-value*
			Females				
Wildtype	285	1,743,039 *1530923–1984546*	2,303,629 *2061448–2574262*	0.75 *0.65–0.89*	*0.0006*	0.49 *0.31–0.77*	*0.002*
Omicron BA.1	285	510,015 *445785–583500*	689,830 *609829–780327*	0.73 *0.62–0.88*	*0.0005*	0.52 *0.34–0.79*	*0.002*
Omicron BA.2	285	477,124 *417909–544729*	646,169 *570431–731963*	0.73 *0.62–0.87*	*0.0006*	0.53 *0.35–0.79*	*0.002*
			Males				
Wildtype	196	1,747,660 *1518722–2011108*	1,782,834 *1538972–2065337*	0.98 *0.81–1.18*	*0.831*	0.84 *0.49–1.45*	*0.529*
Omicron BA.1	197	504,552 *434621–585735*	493,824 *412353–591391*	1.02 *0.83–1.26*	*0.838*	1.00 *0.63–1.58*	*0.990*
Omicron BA.2	196	446,818 *386455–516611*	451,155 *380356–535131*	0.99 *0.81–1.21*	*0.925*	0.88 *0.55–1.43*	*0.618*

Quantification of spike-specific IgG levels stratified by sex prior to a positive (case) or negative PCR test (control) showing the geometric mean (GM) with 95% CI and GM ratio cases-to-controls. Multivariable logistic regression showing the adjusted odds ratios (aORs) and 95% CI for breakthrough infection for a log10-fold increase of spike-specific IgG levels. The analysis adjusts for the matched variables: age group, sex, vaccine, and study visit, and for the unmatched variables: vaccine priority group, Charlson comorbidity index (CCI), visit year, days from study visit to PCR test, and days from third vaccination to PCR test.