THE LANCET

Supplementary appendix

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Table S1: Baseline characteristics of CAPTURE cohort before the third COVID-19 vaccine dose

			Patients with an evaluable sample prior to 3rd vaccine, n=179		
	Full Cohort	No evaluable sample prior to 3rd vaccine	Detectable NAb to Omicron VOC	No detectable NAb to Omicron VOC	
	n=199	n=20	n=52	n=127	p-value
Age, years (median, IQR)	63 (55-70)	57(48-68)	60 (54-66)	64 (55-71)	0.16
Male, n(%)	113 (57)	9 (45)	31 (60)	73 (57)	0.92
Ethnicity, white, n(%)	179 (90)	19 (95)	46 (88)	114 (90)	0.88
1st and 2nd COVID-19 vaccine, n (%)					
ChAdOx1	133 (67)	14 (70)	32 (62)	87 (69)	0.37
BNT162b2	66 (33)	6 (30)	20 (38)	40 (31)	
Third COVID-19 vaccine, n(%)					
ChAdOx1	0 (0)	0 (0)	0 (0)	0 (0)	
BNT162b2	199 (100)	20 (100)	52 (100)	127 (100)	NA
Previous SARS-CoV-2 Infection, n(%)	22 (11)	0 (0)	16 (31)	6 (5)	**<0.0001**
Cancer type, n(%)					
Solid cancer	115 (58)	15 (75)	37 (71)	63 (50)	**0.0083**
Blood cancer	84 (42)	5 (25)	15 (29)	64 (50)	
Solid cancers	**n=115**	**n=15**	**n=37**	**n=63**	
Cancer stage, n(%)					
Stage I-II	17 (15)	3 (20)	3 (8)	11 (17)	
Stage III	26 (22)	4 (27)	9 (24)	13 (21)	0.42
Stage IV	72 (63)	8 (53)	25 (46)	39 (62)	
Rx prior to 1st vaccine dose, n(%)					
Chemotherapy, <28 days	26 (23)	2 (13)	10 (27)	14 (22)	0.76
Targeted therapy, <28 days	39 (34)	4 (27)	10 (27)	25 (40)	0.29
Anti-PD(L)1 ± anti-CTLA4, <183 days	28 (24)	2 (13)	9 (24)	17 (27)	0.95
No recent SACT	36 (31)	6 (40)	12 (32)	18 (29)	0.73
Rx prior to 3rd vaccine dose, n(%)					
Chemotherapy, <28 days	21(18)	2 (13)	6 (16)	13 (21)	0.78
Targeted therapy, <28 days	41 (36)	3 (20)	13 (35)	25 (40)	0.81
Anti-PD(L)1 ± anti-CTLA4, <183 days	26 (23)	3 (20)	7 (19)	16 (25)	0.62
No recent SACT	36 (31)	7 (47)	12 (32)	17 (27)	0.31
Blood cancers	**n=84**	**n=5**	**n=15**	**n=64**	
Diagnosis, n(%)					
Lymphoma	25 (30)	2 (40)	2 (13)	21 (33)	
Myeloma	29 (35)	0 (0)	5 (33)	24 (38)	
CLL	17 (20)	1 (20)	5 (33)	11 (17)	0.35
Acute Leukaemia	10 (12)	1 (20)	2 (13)	7 (11)	
Myelodysplastic syndrome	3 (4)	1 (20)	1 (7)	1 (2)	
Cancer Status, n(%)					
No diagnosis at primary vaccination	3(4)	0 (0)	1 (7)	2 (3)	
Complete response to SACT/remission	37 (44)	4 (80)	3 (20)	30 (47)	
Never treated	12 (14)	0 (0)	5 (33)	7 (11)	
Progressive disease on SACT/relapse	10 (12)	0 (0)	2 (13)	8 (13)	0.13
Partial response to SACT/remission	17 (20)	1 (20)	3 (20)	13 (20)	
Stable disease	5 (6)	0 (0)	1 (7)	4 (6)	
Rx prior to 1st vaccine dose, n(%)					
Chemotherapy	7 (8)	0 (0)	2 (13)	5 (8)	0.86
Targeted therapy, <28 days	21 (25)	1 (20)	2 (13)	18 (28)	0.39
Anti-CD20 mAb, <12 mths	7 (8)	1 (20)	0 (0)	6 (9)	0.49
BTKi therapy, <28 days	5 (6)	1 (20)	1 (7)	3 (5)	1
No recent SACT	50 (59)	2 (40)	10 (67)	38 (59)	0.82
HSCT, ever	35 (42)	3 (60)	8 (53)	24 (38)	0.41
Autograft, ever	22 (26)	0 (0)	5 (33)	17 (27)	
Allograft, ever	13 (15)	3 (60)	3 (20)	7 (11)	
HSCT, <6 months	7 (8)	1 (20)	1 (7)	5 (8)	1
CAR-T, <6 months	3 (4)	0 (0)	0 (0)	3 (5)	0.92

Rx prior to 3rd vaccine dose, n(%)					
Chemotherapy, <28 days	13 (15)	0 (0)	3 (20)	10 (16)	0.98
Targeted therapy, <28 days	26 (31)	1 (20)	5 (33)	20 (31)	0.88
Anti-CD20 mAb, <12 mths	10 (12)	1 (20)	0 (0)	9 (14)	0.15
BTKi therapy, <28 days	5 (6)	1 (20)	1 (7)	3 (5)	0.75
No recent SACT	40 (48)	2 (40)	7 (47)	31 (48)	0.90

Third vaccine dose cohort: all patients received a third COVID-19 vaccine (n=199); the cohort is split according to presence or absence of detectable NAbs to the Omicron variant of concern *before* the third vaccine dose (matched samples available in 179/199 patients). Values are numbers and percentages n(%) unless otherwise stated. Comparison of baseline characteristics was performed using either MacNemar, Chi2, Mann-Whitney U test as appropriate; a p-value of <0.05 was considered significant.

BTK-I, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cell; CLL, chronic lymphocytic leukaemia; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HSCT, hematopoietic stem cell transplant; IQR, interquartile range; mAB, monoclonal antibody; NR, non-responders; PD-1, programmed death ligand-1; Rx, treatment; SACT, systemic anti-cancer therapy; WT, wildtype.

Table S2: Association of clinical parameters with detectable NAb against Omicron

		Detectable NAb against Omicron	
	Patients (n)	**OR(95%CI)**	**p-value**
Cancer patients, n=199			
Intercept		1.64(0.85-3.21)	0.22
Cancer Type			
Solid (vs. blood cancer)	115/199	7.51(4.05-14.63)	<0.0001*
Vaccine Type (1st and 2nd dose)			
BNT162b2 (vs ChAdOx1)	66/199	0.91(0.49-1.73)	0.82
Age			
>60 years (vs <= 60 years)	107/199	0.60(0.32-1.09)	0.17
Sex			
Male (vs female)	113/199	1.12(0.61-2.07)	0.76
Blood cancer patients, n=84			
Intercept		18.96(2.77-194.74)	0.020
Diagnosis (vs Myeloma)			
Acute leukemia	10/84	0.10(0.008-0.78)	0.088
Chronic lymphocytic leukemia	17/84	0.27(0.03-2.15)	0.31
Myelodysplastic syndrome	3/84	0.32(0.02-7.08)	0.52
Lymphoma	25/84	0.18(0.02-1.26)	0.17
Vaccine Type (1st and 2nd dose)			
BNT162b2 (vs ChAdOx1)	31/84	0.53(0.18-1.55)	0.33
Age			
>60 years (vs <= 60 years)	46/84	1.56(0.49-5.20)	0.53
Status after most recent anti-cancer therapy (vs complete response)			
Never treated	12/84	0.85(0.16-4.95)	0.87
Progressive disease	10/84	0.08(0.01-0.46)	0.027*
Partial response	17/84	0.22(0.03-1.30)	0.18
Stable disease	5/84	0.06(0.003-0.54)	0.056
Anti-cancer therapy †			
B-cell depleting therapy (anti-CD20 [within 12 months] or BTKi [within 28 days])	15/84	0.04(0.003-0.21)	0.0074*
Targeted therapy within 28 days	26/84	0.64(0.10-3.19)	0.66
Chemotherapy within 28 days	13/84	1.71(0.34-11.04)	0.60
HSCT or CAR-T within 6 months	10/84	0.21(0.03-1.20)	0.15

NAb were binned in detected (>= 40) or undetected (<40) †For anti-cancer therapy indicated treatment was tested for patients who received the treatment vs patients not receiving that treatment. BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cell; HSCT – Haematopoetic stem cell transplant.

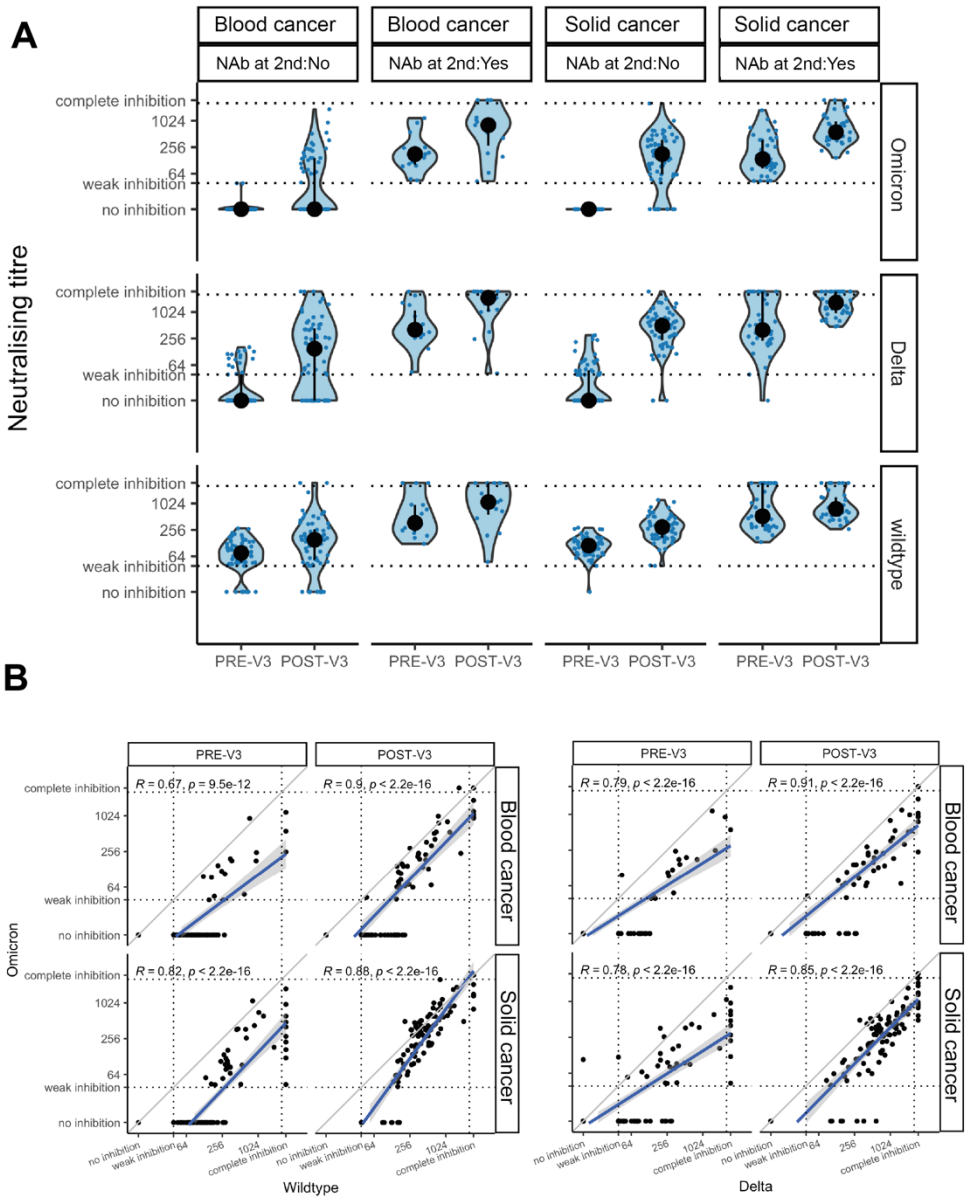

Figure S1: NAb responses against Omicron in patients after three COVID-19 vaccine doses

A) NAbT against Delta and Omicron before (PRE-V3, n=179) or after three vaccine doses (POST-V3, n=199). Samples were further split as having detectable or undetectable NAbT against Omicron after the second dose. Horizontal lines denote the upper and lower limit of detection. Violin plots denote data density, Pointrange denotes the median and the 25th and 75th percentile. Data points represent individual samples. NAb against Delta and WT were reported previously and were added for comparison (1). Scatterplot of NAbT against Omicron vs NAbT against wildtype and Delta respectively (PRE-V3, n=179; POST-V3, n=199). Each data point represents an individual sample. Horizontal lines denote the upper and lower limit of detection. The linear regression line is blue with 95% CI in grey. Spearman's rank correlation coefficients and corresponding p-values are denoted in the panel for each group. Blood cancer: patients with blood cancer; Solid cancer: patients with solid cancer.

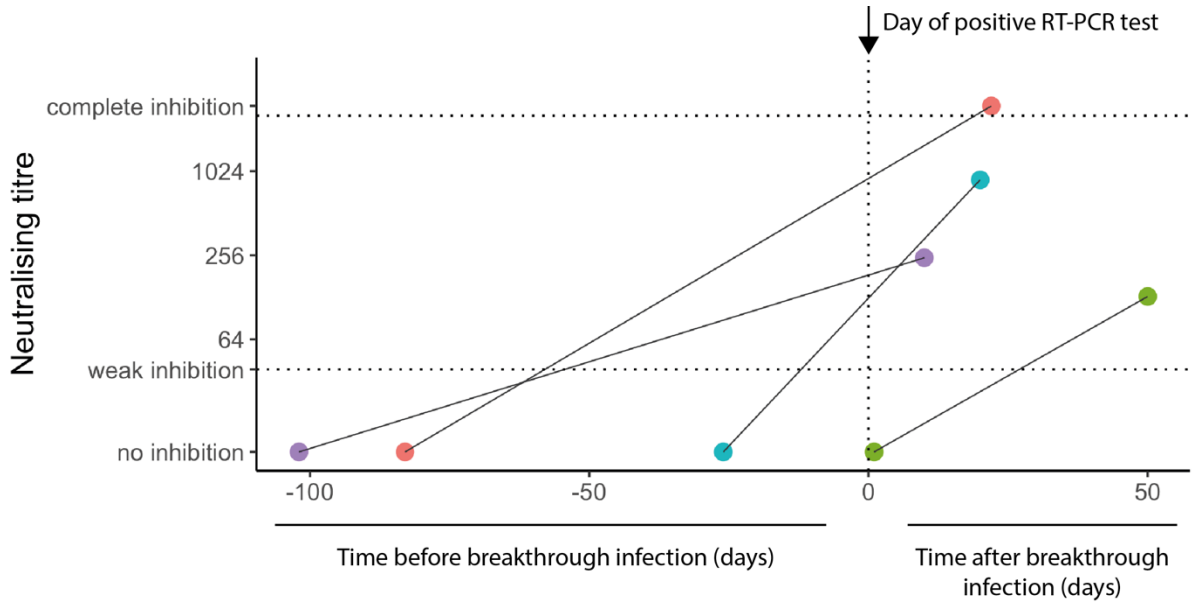

Figure S2: NAb against Omicron in patients with breakthrough Delta infection after two vaccine doses

NAbT against Omicron were measured at varying time points before and after infection in four patients whith breakthrough Delta infections after two vaccine doses. Vertical line denotes the day SARS-CoV-2 infection was confirmed by RT-PCR; horizontal lines indicate the upper and lower limit of NAbT detection. Different colours represent individual patients, and time points are connected. NAb, Neutralising antibody; NAbT, Neutralising antibody titres.

Methods

Study design

CAPTURE (NCT03226886) is a prospective, longitudinal cohort study that commenced recruitment in May 2020 and continues to enrol patients at the Royal Marsden NHS Foundation Trust. The study design has been previously published (1). In brief, adult patients with a current diagnosis or history of invasive cancer are eligible for enrolment. Inclusion criteria are intentionally broad, and patients were recruited irrespective of cancer type, stage, or treatment. Patients recruited to the CAPTURE study who had received two COVID-19 vaccine doses, and subsequently a third dose regardless of prior SARS-CoV-2 infection status, were included in this analysis. The primary endpoint of the CAPTURE vaccine was the seroconversion rate in cancer patients at 14-28 days following the second dose of vaccine (2). Exploratory endpoints include evaluation of neutralising responses to SARS-CoV-2 variants of concern (VOC). When considering the neutralising response to Omicron VOC, there was no prior published data in cancer patients in this setting, and the sample size was determined by the number of eligible patienst recruited at the time of evaluation. The most precise estimate of NAb responses in cancer patients would be achieved by recruiting as many patients as possible in the time period.

CAPTURE received ethical approval as a substudy of the TRACERx Renal Study (NCT03226886). TRACERx Renal was initially approved by the NRES Committee London, Fulham, on January 17, 2012 (11/LO/1996). The CAPTURE protocol was part of Substantial Amendment 9 and received approval by the Health Research Authority on April 30, 2020, and the NRES Committee London, Fulham on May 1, 2020CAPTURE is conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice and applicable regulatory requirements. All patients provided written, informed consent to participate. The Chief Investigator, Samra Turajic is responsible for the oversight of all aspects of study conduct and governance.

Study schedule and follow-up

We previously reported results following two COVID-19 vaccine doses (3) where clinical data and samples collection was performed at baseline (pre-first dose vaccine or within 14 days of first dose vaccine), at timepoints follow-up 1 (FU1; 2-4 weeks post-first dose vaccine); FU2 (within 14 days before the second vaccine); FU3 (2-4 weeks post-second dose vaccine). Patients eligible for a third vaccine dose were invited to receive the vaccine in our institution. Samples were collected before the third vaccine dose (Pre-V3; 0-28 days before the third dose) and following the third vaccine dose (Post-V3; 14-28 days post third vaccination).

Patient data and sample sources

Demographic, epidemiological and clinical data (e.g. cancer type, cancer stage, treatment history) were collected from the internal electronic patient record, and pseudonymised data was entered into a cloud-based electronic database (Ninox Software, Berlin, Germany). Regarding systemic-anticancer therapy (SACT), we deemed chemotherapy, targeted therapy (small molecule inhibitors or monoclonal antibodies) or endocrine therapy to be current if given within 28 days of vaccination. Treatment with immune checkpoint inhibitors (CPI) within six months was considered significant given the prolonged receptor occupancy reported with these agents (3). Treatment with ant-CD20 monoclonal antibodies within 12 months was considered. Concomitant medications were recorded for: corticosteroids (considered significant if >10mg prednisolone equivalent given for at least seven days); GCSF when delivered within 48 hours of vaccination or five days in the case of pegylated preparation; and other immunosuppressive drugs taken within 48 hours of vaccination.

Patients were grouped by cancer diagnosis (solid vs blood cancer). Where two independent diagnoses of cancer were identified in the same patient, the case was reviewed by two clinicians (STCS & AMS), and the highest stage and/or cancer receiving active treatment was used for classification. Patients with haematological malignancies were grouped by conventional subtypes.

Detailed sampling schedule and methodology were described previously (1). Study biospecimens included per-protocol blood samples, oropharyngeal swabs and cryostored serum from routine clinical investigations. Collected data and study samples were de-identified and stored with only the study-specific study identification number.

Definition of breakthrough SARS-CoV-2 infection

We considered patients to have had a breakthrough SARS-CoV-2 infection if they had SARS-CoV-2 positive RT-PCR (tests conducted as part of routine clinical care) at least seven days following the second COVID-19 vaccine dose.

WHO classification of severity of COVID-19

We classified the severity of COVID-19 according to the WHO clinical progression scale (4). Uninfected: uninfected, no viral RNA detected – 0; Asymptomatic: viral RNA and/or S1-reactive IgG detected – 1; mild (ambulatory): symptomatic, independent – 2; symptomatic, assistance needed - 3; moderate (hospitalised): no oxygen therapy (if hospitalised for isolation only, record status as for ambulatory patient) – 4; oxygen by mask or nasal prongs - 5; severe (hospitalised): oxygen by non-invasive

ventilation or high flow – 6; intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ – 7; mechanical ventilation, $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors – 8; mechanical ventilation, $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or extracorporeal membrane oxygenation - 9; Dead - 10.

Handling of whole blood samples

All blood samples and isolated products were handled in a CL2 laboratory inside a biosafety cabinet using appropriate personal protective equipment and safety measures, which were in accordance with a risk assessment and standard operating procedure approved by the safety, health and sustainability committee of the Francis Crick Institute. For indicated experiments, serum or plasma samples were heat-inactivated at 56ºC for 30 minutes prior to use after which they were used in a CL1 laboratory.

Serum isolation

Whole blood was collected in serum coagulation tubes (Vacuette CAT tubes, Greiner) for serum isolation and stored at 4ºC until processing. All samples were processed within 24 hrs. Time of blood draw, processing, and freezing was recorded for each sample. Tubes were centrifuged for 10 minutes at 2000g at 4ºC. Serum was separated from the clotted portion, aliquoted and stored at -80ºC.

Virus variants & culture

The B.1.617.2 (“Delta”) isolate was MS066352H (GISAID accession number EPI_ISL_1731019), which carries the T19R, K77R, G142D, Δ156-157/R158G, A222V, L452R, T478K, D614G, P681R, D950N, and was kindly provided by Prof. Wendy Barclay, Imperial College London, London, UK through the Genotype-to-Phenotype National Virology Consortium (G2P-UK). The BA.1 (“Omicron”) isolate was M21021166, which carries the A67V, Δ69-70, T95I, Δ142-144, Y145D, Δ211, L212I, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, A701V, N764K, D796Y, N856K, Q954H, N969K, and L981F mutations in Spike. It was kindly provided by Prof. Gavin Screaton, University of Oxford, Oxford, UK through the Genotype-to-Phenotype National Virology Consortium (G2P-UK). All viral isolates were propagated in Vero E6 cells. Briefly, 50% confluent monolayers of Vero E6 cells were infected with the given SARS CoV-2 strains at an MOI of approx. 0.001. Cells were washed once with DMEM (Sigma; D6429), then 5 ml virus inoculum made up in DMEM was added to each T175 flask and incubated at room temperature for 30 minutes. DMEM + 1% FCS (Biosera; FB-1001/500) was added to each flask.

Cells were incubated at 37° C, 5% CO^2 for four days until the extensive cytopathogenic effect was observed. The supernatant was harvested and clarified by centrifugation at 2000 rpm for 10 minutes in a benchtop centrifuge. The supernatant was aliquoted and frozen at -80°C.

Virus PCR and sequencing

All virus stocks generated for use in neutralisation assays were sequence-validated before use. To confirm the identity of cultured VoC samples, 8ul of viral RNA was prepared for sequencing by the ARTIC method (https://www.protocols.io/view/ncov-2019-sequencingprotocol-v3-locost-bh42j8ye) and sequenced on the ONT GridION platform to >30k reads/sample. The data was demultiplexed and processed using the viralrecon pipeline (https://github.com/nf-core/viralrecon).

High-throughput live virus micro-neutralisation assay

High-throughput live virus micro-neutralisation assays were performed as described previously (5). Briefly, Vero E6 cells (Institut Pasteur) at 90-100% confluency in 384-well format were first titrated with varying MOI of each SARS-CoV-2 variant and varying concentrations of a control monoclonal nanobody in order to normalise for possible replicative differences between variants and select conditions equivalent to wild-type virus. Following this calibration, cells were infected in the presence of serial dilutions of patient serum samples. After infection (24 hrs Vero E6 Pasteur), cells were fixed with 4% final Formaldehyde, permeabilised with 0.2% TritonX-100, 3% BSA in PBS (v/v), and stained for SARS-CoV-2 N protein using Alexa488-labelled-CR3009 antibody produced in-house and cellular DNA using DAPI (6). Whole-well imaging at 5x was carried out using an Opera Phenix (Perkin Elmer) and fluorescent areas and intensity calculated using the Phenix-associated software Harmony 9 (Perkin Elmer). Inhibition was estimated from the measured area of infected cells/total area occupied by all cells. The inhibitory profile of each serum sample was estimated by fitting a 4-parameter dose-response curve executed in SciPy. Neutralising antibody titres are reported as the fold-dilution of serum required to inhibit 50% of viral replication (IC_{50}). They are further annotated if they lie above the quantitative (complete inhibition) range, below the quantitative range but still within the qualitative range (i.e. partial inhibition is observed, but a dose-response curve cannot be fit because it does not sufficiently span the IC_{50}), or if they show no inhibition at all. IC_{50} values above the quantitative limit of detection of the assay (>2560) were recoded as 3000; IC_{50} values below the quantitative limit of the assay (< 40) but within the qualitative range were recoded as 39 and data below the qualitative range (i.e. no response observed) were recoded as 10.

Quantification and statistical analysis

Data and statistical analysis were done in R v3.6.1 in R studio v1.2.1335. McNemar, Chi2, Mann-Whitney U tests were used to evaluate statistical significance. A p-value <0.05 was considered significant. All tests were performed two-sided. Statistical details for each experiment are provided in the figure legends. The ggplot2 package in R was used for data visualisation. Data are plotted as single data points and violin plots on a logarithmic scale. PointRange in violin plots denotes median and upper and lower quartiles. Multivariable binary logistic regression analysis was performed using the glm function within the stats package in R, OR and 95% CI were generated using the coef and confint function within the stats package in R. Covariates included in the model were selected based on previously reported effects (3, 8, 9) on NAb responses after two or three doses of COVID-19 vaccine. The reference was chosen for covariates with multiple categories to reflect the group with the least expected effect on NAb response. Anti-CD20 and BTKi treatments were combined in a single covariate based on their similar effect on B cell levels. HSCT and CAR-T were combined based on the similar effect on immune responses, particularly on T follicular helper cell suppression and reduced B cell subset number and function.

Supplemental References

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