

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- | | |
|-------------------------------------|--|
| n/a | Confirmed |
| ☐ | ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☒ | ☐ A description of all covariates tested |
| ☐ | ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ For null hypothesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ Estimates of effect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

Data collection Flow cytometry data were acquired using SpectroFlo v.2.2 and SQS v.1.18.

Data analysis Flow cytometry data were analyzed using FlowJo v10 and Prism v9. ELISA, ELISpot, and neutralization data were analyzed using Prism v9. Sequence data were analyzed using Cell Ranger v.6.0.1, SCANPY v.1.7.2, pRESTO v0.6.2, IgBLAST v1.17.1, IMG/GENE-DB release 202113-2, Change-O v1.0.2, Alakazam v1.1.0, TIGER v1.0.0, circize v0.4.13, and SHazAM v1.0.2. VSV chimera neutralization data were analyzed using IN Cell Analyzer 1000 Workstation Software v3.7.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

Antibody sequences are deposited on GenBank under the following accession numbers: OQ634308 - OQ635939, available from GenBank/EMBL/DDBJ. Newly reported raw sequencing data and transcriptomics count matrix are deposited at the Sequence Read Archive and Gene Expression Omnibus under BioProject PRJNA800176. Processed transcriptomics and BCR data are deposited at Zenodo (<https://doi.org/10.5281/zenodo.7719030>). Previously reported BCR data used in

this study were deposited under BioProjects PRJNA731610, PRJNA741267, and PRJNA777934. The IMGT/V-QUEST database is accessible at http://www.imgt.org/IMGT_vquest/. Materials are available upon request, through an interinstitutional materials transfer agreement.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see [nature.com/documents/nr-reporting-summary-flat.pdf](https://www.nature.com/documents/nr-reporting-summary-flat.pdf)

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to determine sample size. 54 healthy participants were enrolled based on recruitment, of whom 54 provided peripheral blood, 25 provided axillary lymph node samples and 14 provided bone marrow samples. These numbers were sufficient to detect statistically significant differences in the effect sizes of interest.
Data exclusions	No data were excluded
Replication	Human samples were collected from 43 participants. ELISA and neutralization tests were performed once with two technical replicates. Affinity analysis via biolayer interferometry was performed at least two technical replicates according to the fitting-curve. ELISpot and flow cytometry experiments were performed once for each sample at each time point due to insufficient specimens. All attempts at replication were successful.
Randomization	Participants were from a sub-study of NCT04927065, which allocated them to different vaccine cohorts per its requirements. No other allocations to groups were made.
Blinding	No blinding was done for convenience; subjective measurements were not made.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	total Ig (goat polyclonal, Jackson ImmunoResearch 109-005-064), IgG-HRP (goat polyclonal, Jackson ImmunoResearch 109-035-088), murine anti-S mAbs: SARS2-2, SARS2-11, SARS2-16, SARS2-31, SARS2-38, SARS2-57, and SARS2-71, SARS2-08, -09, -10, -13, -14, -17, -20, -26, -27, -28, -31, -41, -42, -44, -49, -62, -64, -65, and -67 (Diamond laboratory, Washington University School of Medicine), IgG (Sigma 12-349), IgG-BV480 (goat polyclonal, Jackson ImmunoResearch 109-685-098), PD-1-BB515 (EH12.1, BD Horizon 564494), IgA-FITC (M24A, Millipore CBL114F), CD45-AS32 (HI30, Thermo 58-0459-42), Bcl6-PE (K112-91, 561522, BD Pharmingen), CD38-BB700 (HIT2, 566445, BD Horizon), Blimp1-PE (646702, IC36081P R&D), CD16 (3G8, 302002), CD32 (FUN-2, 303202), CD64 (10.1, 566178), CD19-BV421 (HIB19, 302234), FoxP3-BV421 (206D, 320129), CD20-Pacific Blue (2H7, 302320), CD27-BV510 (O323, 302836), CD8-BV570 (RPA-T8, 301038), IgM-BV-605 (MHM-88, 314524), HLA-DR-BV650 (L243, 307650), Ki-67-BV711 (Ki-67, 350516), CD19-BV750 (HIB19, 302262), CD3-FITC (HIT3a, 300306), CD71-FITC (CY1G4, 334104), IgD-PE (IA6-2, 348204), CD71-PE (CY1G4, 334106), CXCR5-PE-Dazzle 594 (J252D4, 356928), IgD-BV785 (IA6-2, 348242), CD4-PerCP (OKT4, 317432), CD14-PerCP (HCD14, 325632), IgD-PerCP-Cy5.5 (IA6-2, 348208), CD38-PE-Cy7 (HIT2, 303516), CD71-PE-Cy7 (CY1G4, 334112), CD19-APC (HIB19, 302212), CD4-Spark 685 (SK3, 344658), CD20-APC-Fire750 (2H7, 302358), CD3-APC-Fire810 (SK7, 344858); all Biolegend.
Validation	All commercial antibodies were validated by their manufacturers as detailed in their product information and titrated in the lab for the indicated assay by serial dilution. We validated mAbs generated in our lab in preliminary ELISAs and multiplex bead array to SARS-CoV-2 spike, bovine serum albumin, and anti-Ig. Influenza B/HA-specificity of mAb 321-05 6F05 was previously published (Turner, J. S. et al. Nature 586, 127–132 (2020)). E484-specificity of mAb mu 2B04 was previously published (Alsoussi, W. B. et al. J. Immunol. 205,

915–922 (2020)). S2-specificity of mAb 368-22 1B08 was previously published (Turner, J. S. et al. Nature 596, 109–113 (2021)).

Eukaryotic cell lines

Policy information about [cell lines](#)

Cell line source(s)	Expi293F (Thermo), Vero E6 (ATCC), Vero-TMPRSS2 (Diamond Laboratory)
Authentication	The cell lines were not authenticated.
Mycoplasma contamination	Vero-TMPRSS2 lines are routinely tested each month and were negative for mycoplasma. Other cell lines were not tested for mycoplasma contamination. Growth rates were consistent with manufacturer's published data.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used.

Human research participants

Policy information about [studies involving human research participants](#)

Population characteristics	Study participants demographics are detailed in Extended Data Table 1.
Recruitment	Study participants were recruited from the St. Louis metropolitan area by the Washington University Clinical Trials Unit. Potential self-selection and recruiting biases are unlikely to affect the parameters we measured.
Ethics oversight	The WU382 study was reviewed and approved by the Washington University Institutional Review Board (approval no. 202109021)

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	NCT04927065
Study protocol	Details of protocol elements can be accessed from clinicaltrials.gov and Chalkias, S. et al. Nat. Med. 28, 2388–2397 (2022).
Data collection	Data for NCT04927065 from the subset of participants reported here were collected at the Washington University Infectious Disease Clinical Research Unit.
Outcomes	In this report of a subset of participants in the clinical trial, the following study primary endpoints are presented: Number of Participants with Solicited Local and Systemic Reactogenicity Adverse Reactions (Time Frame: 7 days post-vaccination, as recorded daily by participants). Number of Participants with Unsolicited Adverse Events (Time Frame: Up to 28 days post-vaccination).

Flow Cytometry

Plots

Confirm that:

- ☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☒ All plots are contour plots with outliers or pseudocolor plots.
- ☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Fine needle aspirates of axillary LNs were flushed from needles with 3 mL of RPMI supplemented with 10% FBS and 100 U/mL penicillin/streptomycin, followed by three 1 mL rinses. Red blood cells were lysed with ammonium chloride buffer, washed twice with PBS supplemented with 2% FBS, 2mM EDTA and immediately used or cryopreserved in 10% DMSO in FBS. Blood samples were collected in EDTA tubes, and peripheral blood mononuclear cells (PBMCs) were enriched by density gradient centrifugation over Ficoll 1077 (GE) or Lymphopure (BioLegend). The residual red blood cells were lysed with ammonium chloride lysis buffer, and cells were immediately used or cryopreserved in 10% dimethylsulfoxide in FBS.
Instrument	Cytek Aurora

Software

Flow cytometry data was acquired using Cytex SpectroFlo and analyzed using FlowJo (Treestar) v10.

Cell population abundance

Bulk sorts directly into lysis buffer were not amenable to post-sort purity analysis.

Gating strategy

Gating strategies are shown in Figures 1 and 4 and Extended Data Figures 1, 2, and 3

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.