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Reporting Summary

Nature Research 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 Research 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 *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	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 *Give P values as exact values whenever suitable.*
☒	☐	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	No software was used in this study to collect data
Data analysis	Prism 8.0 was used to perform all statistical analysis. BWA4 v0.7.17-r1188 (http://bio-bwa.sourceforge.net). DeepVariant4 v1.1.0 (https://github.com/google/deepvariant) was used to call variants with an allele frequency >= 50%. Variants were annotated using SNPEff4 5.0c (https://sourceforge.net/projects/snpeff/). FlowJo software (v9) was used for analysis of flow cytometry

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 Research 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 list of figures that have associated raw data
- A description of any restrictions on data availability

All data supporting the findings of this study are available within the paper and are available from the corresponding author upon request. Deep sequencing datasets of viral stocks are available at NCBI BioProject PRJNA698378 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA698378).

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

Life sciences study design

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

Sample size	No sample sizes were chosen a priori, as samples were used based on availability. Notwithstanding this point, each serum analysis has n =10 to 24 samples, which allows us to reliably detect 2-fold differences in potency.
Data exclusions	No data was excluded.
Replication	All experiments with monoclonal antibodies were performed at least two independent times each with two technical replicate per experiment. Serum studies were performed as one independent experiment with two technical replicates.
Randomization	No randomization was performed as we obtained available samples that were deidentified
Blinding	Blinding was not performed for convenience. However, data was scanned and analyzed by a separate investigator who did not perform the experiment.

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	Human mAbs (all generated by the Crowe, Ellebedy, Corti and Screaton laboratiries as part of this study): COV2-2196, COV2-2072, COV2-2050, COV2-2381, COV2-2130, COVOX-384, COVOX-40, 1B07, S309, S2E12, S2H58, and S2X259; Mouse mAbs (all generated by the Diamond laboratory): SARS2-2, SARS2-11, SARS2-16, SARS2-31, SARS2-38, SARS2-57, and SARS2-71; HRP-conjugated goat anti-mouse IgG (Sigma 12-349), anti-V5 antibody (Thermo Fisher 2F11F7), anti-TMPRSS2 mAb (Abnova, Clone 2F4), APC-conjugated goat anti-mouse IgG (BioLegend, 405308), Goat anti-human IgG-HRP (Jackson ImmunoResearch, 115-035-003)
Validation	All primary anti-SARS-2 CoV-2-S mAbs were validated using purified SARS-CoV-2 RBD or S proteins using ELISA or BLI assays. All secondary antibodies were validated by each respective manufacturer per their associated DataSheets.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Vero E6 (CRL-1586, American Type Culture Collection (ATCC), Vero-TMPRSS2, Diamond laboratory; Vero-hACE2-TMPRSS2, Graham laboratory, VRC/NIH; Expi-CHO (ThermoFisher, A29127), 293T/17 (ATCC CRL-11268)
Authentication	These were obtained from ATCC or other academic laboratories and grew and performed as expected (or stained positively for antigens (TMPRSS2 and hACE2) by flow cytometry). No additional specific authentification was performed.
Mycoplasma contamination	All cell lines are routinely tested each month and were negative for mycoplasma.

Commonly misidentified lines (See ICLAC register)	This study did not involve any commonly misidentified cell lines.

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	BALB/c mice (both sexes, 4 months); Syrian Golden hamsters (both sexes, 1 year), Rhesus macaques (male 4 years): these were used in previous studies. In this study, only banked sera was used
Wild animals	N/A
Field-collected samples	N/A
Ethics oversight	All experiments were conducted with approval of the Institutional Animal Care and Use Committee at the Washington University School of Medicine (Assurance number A3381-01) - [prior studies, as current one did not have active animal work]

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	The convalescent patients were recruited from the St. Louis metropolitan area who experienced mild SARS-CoV-2 infection. None of those patients required intubation. Human subjects information: (a) Convalescent subjects: Median age = 50 (21-69); Gender = Females (57%); Race = White (95%); (b) Vaccinated subjects: Median age = 45 (26-64); Gender = Females (64%); Race = White (94%).
Recruitment	Convalescent plasma donors were recruited from the St. Louis metropolitan area by the Washington University Infectious Diseases Clinical Trials Unit. Vaccinated individuals were health care workers at Washington University School of Medicine and Barnes and Jewish hospital. Potential self-selection and recruiting biases are unlikely to affect the parameters we measured.
Ethics oversight	Washington University School of Medicine Institutional Review Board. IRB approval numbers: 202003186 (WU353), 202012081 (WU368) and 202012084 (COVaRiPAD)

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

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	Expi-CHO cells were transiently transfected with SARS-CoV-2-S expression vectors. Two days later, intact cells were collected for immunostaining with mAbs.
Instrument	ZE5 Cell Analyzer (Biorard)
Software	FlowJo software (v9, TreeStar)
Cell population abundance	N/A
Gating strategy	Gating on live cells was performed using FSC and SSC

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