nature portfolio

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# 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<br>*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<br>*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 | N/A |
| Data analysis | Prism 9 (GraphPad) |

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

Datasets (raw data) underlying the figures have been provided as Source Data. No custom code was used in this study. Complete genome sequences for the viral isolates cultured from nasal swabs (B.1.351 and B.1.1.529) were deposited to GISAID. The mutations included in the recombinant proteins are listed in the manuscript and source data are provided.

# 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 | At least N=10 samples per group were included (males and females combined). The number of samples was determined based on an amount that allowed to perform robust statistical analyses, the number of donors and ability to process samples. |
| Data exclusions | No data were excluded. One data point from Figure 2A and D is missing due to a technical issue with the assay (as described in the figure legend). |
| Replication | RBD binding ELISAs were performed twice with the same results. All other assays were performed once. |
| Randomization | Samples were assigned to different groups based on the previous history of SARS-CoV-2 infection and vaccination. |
| Blinding | No blinding was performed. |

# 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 | IgG (Fab-specific) horseradish peroxidase (HRP) antibody (produced in goat; Sigma-Aldrich, Cat#A0293, RRID: AB_257875)<br>mAb 1C7C7 Center for Therapeutic Antibody Development at The Icahn School of Medicine at Mount Sinai ISMMS (Millipore Sigma, Cat# ZMS1075)<br>HRP-conjugated streptavidin (Thermo Fisher Scientific, Cat# N100) |
| Validation | All commercial antibodies were validated by their manufacturers and were titrated in the lab to determine optimal concentration for experimentation. In-house biotinylated 1C7C7 monoclonal antibody was validated in cells infected with WT SARS-CoV-2, B.1.351 and B.1.1.529 viral isolates. MAb concentrations were standardized based on the assay and starting concentration is described in methods section. |

## Eukaryotic cell lines

Policy information about cell lines

| | |
|---|---|
| Cell line source(s) | Vero-E6-TMPRSS2 Cells (BPS Biosciences, catalog #78081)<br>Expi293F™ Cells (Gibco, #A14527) |
| Authentication | Cell lines were authenticated by supplier. No other authentication at the lab level was performed. |
| Mycoplasma contamination | Mycoplasma free. |

| | |
|---|---|
| Commonly misidentified lines (See ICLAC register) | No commonly misidentified cell lines were used in this study. |

## Human research participants

Policy information about studies involving human research participants

| | |
|---|---|
| Population characteristics | 85 serum samples from 54 participants were selected. 20/54 participants were seronegative prior to vaccination while 34/54 had COVID-19 prior to vaccination (see Supplemental Tables 1 and 2 for demographics and vaccine information). All participants with pre-vaccination immunity were infected in 2020 when only ancestral SARS-CoV-2 strains circulated in the New York metropolitan area. Convalescent samples (N=15) were obtained within three months of SARS-CoV-2 infection (average: 58 days, range: 23-87 days) while the post vaccinations samples were collected, on average, 23 days (range: 14-39 days) after the second dose (N= 40, 20 Pfizer 2x and 20 Moderna 2x) or 19 days (range: 14-33 days) after the third booster (N= 30, 20 Pfizer 3x and 10 Moderna 3x) vaccine dose. |
| Recruitment | Sera were collected from participants in the longitudinal observational PARIS (Protection Associated with Rapid Immunity to SARS-CoV-2) study. This cohort follows health care workers longitudinally since April 2020. All participants signed written consent forms prior to sample and data collection. All participants provided permission for sample banking and sharing. |
| Ethics oversight | The study was reviewed and approved by the Mount Sinai Hospital Institutional Review Board (IRB-20-03374). |

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