nature research

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Last updated by author(s): Feb 1st, 2021

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 Authors & Referees 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	IRIS by iMedRIS version 11.01 for clinical data collection and management; BD FACSDiva Software Version 8.0.2 for flow sorting; Glomax Navigator Promega V.3 for neutralization assays; Omega 5.11 by BMG Labtech was used for Elisa Assays, Illumina Miseq, SerialEM automated image acquisition software version 3.7.
Data analysis	FlowJo 10.6.2 for FACS analysis; GraphPad Prism 8.4; Microsoft Excel 16.36; MacVector 17.5.4 for sequence analysis; Omega MARS V2.10 by BMG Labtech for luminometer; Glomax Navigator V.3 from Promega, Adobe Illustrator 2020, Geneious Prime (Version 2020.1.2), cryoSPARC v2.15 and UCSF chimera version 1.13.1 for EM analysis; BBDuk for sequencing read processing, scripts and the data used to process antibody sequences are available on GitHub (https://github.com/stratust/igpipeline).

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/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

Data are provided in SI Table 3-5 and 7. The raw sequencing data and computer scripts associated with Figure 2 has been deposited at Github (https://github.com/stratust/igpipeline). This study also uses data from "A Public Database of Memory and Naive B-Cell Receptor Sequences" (https://doi.org/10.5061/dryad.35ks2), PDB (6VYB and 6NB6) and from "High frequency of shared clonotypes in human B cell receptor repertoires" (https://doi.org/10.1038/s41586-019-0934-8). Cryo-EM maps associated with data reported in this manuscript will be deposited in the Electron Microscopy Data Bank (EMDB: https://www.ebi.ac.uk/pdbe/emdb/) under accession codes EMD-23393 (C601-S), EMD-23394 (C603-S), EMD-23395 (C643-S), EMD-23396 (C663-S), EMD-23397 (C666-S), EMD-23398 (C669-S), and

EMD-23399 (C670-S).

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	Sample size of 20 individuals was based on succesful recruitment of volunteers who received two doses of the Moderna or Pfizer mRNA vaccines between 19 October 2020 and 15 January 2021.
Data exclusions	No data were excluded from the analysis.
Replication	All experiments successfully repeated at least twice.
Randomization	This is not relevant as this is an observational study.
Blinding	This is not relevant as this is an observational study.

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
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data

Methods

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

Antibodies

Antibodies used	Mouse anti-human CD20-PECy7 (BD Biosciences, 335793), clone L27 Mouse anti-human CD3-APC-eFluro 780 (Invitrogen, 47-0037-41), clone OKT3 Mouse anti-human CD8-APC-421eFluro 780 (Invitrogen, 47-0086-42), clone OKT8 Mouse anti-human CD16-APC-eFluro 780 (Invitrogen, 47-0168-41), clone eBioCB16 Mouse anti-human CD14-APC-eFluro 780 (Invitrogen, 47-0149-4), clone 61D3 Zombie NIR (Biolegend, 423105) Peroxidase Goat anti-Human lgG Jackson Immuno Research 109-036-088 Peroxidase Goat anti-Human lgM Jackson Immuno Research 109-035-129 Peroxidase Goat anti-Human lgA Sigma A0295
Validation	No validation statements for the antibodies that are commercially available.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	293T (ATCC CRL-11268) 293T / ACE2.cl22 HT1080/ACE2.cl14 (Schmidt, F. et al. J Exp Med 217, doi:10.1084/jem.20201181)
Authentication	Not authenticated after purchase from ATCC.

Mycoplasma contamination	The cells were checked for mycoplasma contamination by Hoechst staining.
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	A cohort of 20 individuals that participated in either the Moderna or Pfizer phase 3 vaccine clinical trial was recruited at the NIH Blood Center and the Rockefeller University Hospital for blood donation. Eligible participants included adults, at least 18 years of age with no known heart, lung, kidney disease or bleeding disorders, no history of HIV-1 or malaria infection. All participants were asymptomatic at the time of the study visit and had received a complete 2 dose regimen of either mRNA vaccine. Informed consent was obtained from all participants and the study was conducted in accordance with Good Clinical Practice. The study visits and blood draws were reviewed and approved under the National Institutes of Health's Federalwide Assurance (FWA00005897), in accordance with Federal regulations 45 CFR 46 and 21 CFR 5 by the NIH Intramural Research Program IRB committee (IRB# 99CC0168, Collection and Distribution of Blood Components from Healthy Donors for In Vitro Research Use) and by the Institutional Review Board of the Rockefeller University (IRB# DRO-1006, Peripheral Blood of Coronavirus Survivors to Identify Virus-Neutralizing Antibodies).
Recruitment	Between 19 October 2020 and 15 January 2021, 20 volunteers who received two doses of the Moderna (n=14) or Pfizer mRNA (n=6) vaccines were recruited for blood donation and analyzed. Ages of the analyzed volunteers ranged from 29-69 years (median 43); 12 (60%) were male and 8 (40%) female. 16 participants identified as Caucasian, 2 as Hispanic, and 1 as African American or Asian, respectively. The time from the second vaccination to sample collection varied between 3-14 weeks with an average of 8 weeks. None of the volunteers had a history of prior SARS-CoV-2 infection and none reported serious adverse events after vaccination
Ethics oversight	NIH Intramural Research Program IRB committee (IRB# 99CC0168, Collection and Distribution of Blood Components from Healthy Donors for In Vitro Research Use) and by the Institutional Review Board of the Rockefeller University (IRB# DRO-1006, Peripheral Blood of Coronavirus Survivors to Identify Virus-Neutralizing Antibodies)

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	Whole blood samples were obtained from study participants recruited through NIH or Rockefeller University Hospital. Peripheral blood mononuclear cells (PBMCs) were separated by Ficoll gradient centrifugation. Prior to sorting, PBMCs were enriched for B cells using a Miltenyi Biotech pan B cell isolation kit (cat. no. 130-101-638) and LS columns (cat. no. 130-042-401).
Instrument	FACS Aria III (Becton Dickinson)
Software	BD FACSDiva Software Version 8.0.2 and FlowJo 10.6.2
Cell population abundance	Sorting efficiency ranged from 24% to 77%. This is calculated based on the number of IgG-specific antibody sequences that could be PCR-amplified successfully from single sorted cells from each donor.
Gating strategy	Cells were first gated for lymphocytes in FSC-A (x-axis) versus SSC-A (y-axis). We identify single cells in FSC-A versus FSC-H, and then SSC-A versus SSC-W. We then select for CD20+ Dump- B Cells in dump (anti-CD3-eFluro 780, anti-CD16-eFluro 780, anti-CD8-eFluro 780, anti-CD14-eFluro 780, Zombie NIR) versus CD20 (anti-CD20-PE-Cy7); dump-negative was considered to be signal less than 250, and CD20-positive was taken to be signal greater than 100. We then gate for Ova- B cells in FSC-A versus Ova-BV711; Ova-negative was considered to be all cells with signal less than 100. Select for Sars-CoV-2 RBD double positive cells in RBD PE versus RBD Alexa Fluor 647; this gate was made along the 45 diagonal, above 103 on both axes.

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