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Corresponding author(s): Davide Robbiani, Paul Bieniasz, Marina Caskey, Pamela Bjorkman, Michel Nussenzweig

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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	IRIS by iMedRIS version 11.01 for clinical data collection and management; BD FACSDiva Software Version 8.0.2 for flow sorting; Omega version 5.11 by BMG Labtech for luminometer; Modulus II Microplate Reader User interface version 2.1.0 by TURNER BioSystems; MetaXpress V 6.1.2071 by Molecular Devices; SerialEM automated image acquisition software version 3.7.
Data analysis	FlowJo 10.6.2 for FACS analysis; GraphPad Prism 8.4.2; Microsoft Excel 16.36; MacVector 17.5.4 for sequence analysis; Omega MARS V2.10 by BMG Labtech for luminometer; Fortebio Octet Data Analysis Software 8.0; cryoSPARC v2.15 and UCSF chimera version 1.13.1 for EM analysis; code for sequence analysis can be obtained at 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 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

Data are provided in SI Tables 1, 3, 4, 5 and 6; and Figure 3 has associated raw sequencing data (https://github.com/stratust/igpipeline).
Databases used in this study include A Public Database of Memory and Naive B-Cell Receptor Sequences (https://datadryad.org/stash/dataset/doi:10.5061/dryad.35ks2), PDB datasets 6VYB and 6NB6 and Sequence Read Archive SRP010970.

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 157 individuals was based on how many we were able to recruit for blood donation between April 1 and May 8, 2020.
Data exclusions	8 contacts (i.e. exposed to SARS-CoV-2 confirmed infected individuals, but themselves not tested by RT-PCR) that did not develop symptoms were excluded from further analyses as it is possible that they were not infected. Exclusion criteria were not pre-established.
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 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

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
Peroxidase Goat Anti-Human IgG Jackson Immuno Research 109-036-088
Peroxidase Goat Anti-Human IgM Jackson Immuno Research 109-035-129
Rabbit polyclonal anti-SARS-CoV-2 nucleocapsid antibody (catalog no. GTX135357; GeneTex)
Goat anti-rabbit AlexaFluor 594 (catalog no. A-11012; Life Technologies)
Anti-Zika virus monoclonal antibody Z021 (Robbiani et al, Cell 2017) used as isotype control

Validation

The human monoclonal antibody Z021, which binds to the Envelope Domain III of the Zika virus, was previously reported and validated (PMID: 31413072). No validation statements for the other antibodies that are commercially available.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

293T (ATCC CRL-11268)
293TAce2 (derived from 293T); new cell line generated in this study
VeroE6 (ATCC CRL-1586)
Expi293F (ThermoFisher cat. A14527)

	Huh 7.5 (a derivative of Huh 7) was generated in the Laboratory of Virology and Infectious Disease, Rockefeller University (Dr. Charles Rice)
Authentication	Not authenticated after purchase, with the exception of the Huh 7.5 cells (authenticated by Genetica Cell Line Testing)
Mycoplasma contamination	The cells were checked for mycoplasma contamination by Hoechst staining or MycoAlert Kit from Lonza.
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	We enrolled 83 males and 66 females with an average age of 45 and 42, respectively. Eligible participants were adults aged 18-76 years who were either diagnosed with SARS-CoV-2 infection by RT-PCR and were free of symptoms of COVID-19 for at least 14 days (cases), or who were close contacts (e.g., household, co-workers, members of same religious community) with someone who had been diagnosed with SARS-CoV-2 infection by RT-PCR and were free of symptoms suggestive of COVID-19 for at least 14 days (contacts). Exclusion criteria included presence of symptoms suggestive of active SARS-CoV-2 infection, or hemoglobin < 12 g/dL for males and < 11 g/dL for females.
Recruitment	Study participants were recruited at the Rockefeller University Hospital in New York from April 1 through May 8, 2020. Most study participants were residents of the Greater New York City tri-state region and were enrolled sequentially according to eligibility criteria. Participants were first interviewed by phone to collect information on their clinical presentation, and subsequently presented to the Rockefeller University Hospital for a single blood sample collection. The requirement for participants to be free of symptoms for at least 14 days might have favoured enrollment of participants that developed mild COVID-19 courses of infection during the first weeks of recruitment.
Ethics oversight	The Rockefeller University Institutional Review Board (1230 York Avenue, box 330, New York, NY 10065). Protocol DRO-1006 approved on February 6, 2020.

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 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 40% to 66%. 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 102. Select for TBEV double-positive cells in TBEV EDIII PE versus TBEV EDIII AlexaFluor 647; this gate was made along the 45° diagonal, above 103 on both axes. See also Extended Data Figure 6.

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