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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 *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	Sequences and metadata were obtained from GISAID (https://www.epicov.org/). Both metadata and fasta files of all sequences annotated with the BA.1 lineage were downloaded on 20DEC2021 at 8.30pm PST. SPR binding data were collected using Biacore T200 Control Software, v. 2.0.2
Data analysis	As detailed in the materials and methods, "collection date" and "country" fields were extracted from the metadata file. Spike protein sequences were extracted from the genome fasta files and aligned to the Wuhan-1 reference spike protein. The prevalence of mutations present in the BA.1 lineage was extracted in R (4.0.2, https://www.R-project.org/), considering only un-ambiguous residues in both nominator and denominator. Sequence counts per country and/or per week were extracted in R and plotted with ggplot2 3.3.2 (https://ggplot2.tidyverse.org) and sf 0.9-7 (https://doi.org/10.32614/RJ-2018-009) packages. BioPharma Finder 3.2 and GPMAW 285 10.10 software were used for analysis by LC/MS of intact protein mass. Neutralization assays were analyzed using GraphPad Prism (Version 9.1.0) as described in Methods. Biacore T200 Evaluation Software, v. 3.1, was used to fit models to the ACE2 binding data.

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

Materials generated in this study will be made available on request and may require a material transfer agreement. GISAID (www.gisaid.org) data access requires registration. Note: after consulting with the local Ethical authority, due to health and data protection laws relating to the demographic and clinical information contained in the manuscript, we will not be able to fully comply with the requirement to share demographic and clinical data of individual patients/ donors in this study.

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	N/A. Sample size for samples from covalescent/vaccinated individuals was chosen according to or exceeding standards in the field, and in most cases exceeded 10 samples per group.
Data exclusions	monoclonal antibodies that did not show a reliable neutralization curve with SARS-CoV-2 Wuhan S VSV pseudotypes were excluded from the analysis.
Replication	Experimental assays were performed at least in two independent replicates. Each replicate was performed with 2, 3, or more technical repeats or was done in biological triplicate according to or exceeding standards in the field. We conducted all neutralization and antibody functional assays in biological duplicate, triplicate, or more, as indicated in relevant figure legends. In all cases, representative figure displays were appropriately indicated.
Randomization	Randomization was not a relevant feature as we were applying a uniform set of techniques across a panel of sera/plasma or monoclonal antibodies.
Blinding	Blinding was not a relevant feature as we were applying a uniform set of techniques across a panel of sera/plasma or monoclonal antibodies and tests were repeated two or more times by different individuals.

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	Sotrovimab and NTD- and RBD-specific antibodies discovered at VIR Biotechnology were produced as recombinant IgG1 in mammalian cells as described in material and methods, see details in Extended Data Table 2. As to the other therapeutic mAbs were cloned and produced according to publicly available sequences: VH and VL sequences for mAbs COV2-2130 (PDB ID 7L7E),

	COV2-2196 (PDB ID 7L7E, 7L7D), REGN10933 (PDB ID 6XDG), REGN10987 (PDB ID 6XDG) and ADI-58125 (PCT application WO2021207597, seq. IDs 22301 and 22311), LY-CoV555 (PDB ID 7KMG), LY-CoV016 (PDB ID 7C01), and CT-P59 (PDB ID 7CM4) All the commercial antibodies used in the study have been indicted with supplier name, catalog number.
Validation	The identity of the produced monoclonal antibodies (produced recombinantly as human IgG1) was confirmed by LC-MS analysis.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Cell lines used in this study were obtained from ATCC (HEK293T and Vero E6), ThermoFisher Scientific (Expi CHO cells, FreeStyle™ 293-F cells and Expi293F™ cells) Lenti-X 293T cells (Takara) or generated in-house (Vero E6/TMPRSS2)
Authentication	None of the cell lines used were authenticated
Mycoplasma contamination	Cell lines were not tested for mycoplasma contamination
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell lines were used in the study

Human research participants

Policy information about studies involving human research participants

Population characteristics	Samples were collected 14-28 days after symptoms onset and 14-28 days after vaccination (with the exception of individuals vaccinated with Ad26.COV2.S where samples were collected 1-19 weeks affter 1st vaccine dose). Details on patients demographics is provided in Extended Data Table 1
Recruitment	Patients were recruited on the basis of prior SARS-CoV-2 infection or vaccination in the hospital or outpatient setting. Patients were healthy volunteers who donated blood after being informed about the study. The only exclusion criteria used were HIV or other debilitating disease, but other information about diagnosis and treatment was not collected. Convalescent plasma, Ad26.COV2.S, mRNA-1273 and BNT162b2 samples were obtained from the HAARVI study approved by the University of Washington Human Subjects Division Institutional Review Board (STUDY00000959). AZD1222 samples were obtained from INGM, Ospedale Maggio Policlinico of Milan and approved by the local review board Study Polimmune. Sputnik V samples were obtained from healthcare workers at the hospital de Clínicas "José de San Martín", Buenos Aires, Argentina. Sinopharm vaccinated individuals were enrolled from Aga Khan University under IRB of UWARN study.
Ethics oversight	Study protocols for antibody isolation were approved by the local Institutional Review Board (Canton Ticino Ethics Committee, Switzerland), and all donors provided written informed consent for the use of blood and blood components. Study protocols for serological assays were approved by the local Institutional Review Boards relevant for each of three cohorts of samples (Canton Ticino Ethics Committee, Switzerland, the Ethical Committee of Luigi Sacco Hospital, Milan, Italy, and University of Washington Human Subjects Division Institutional Review Board. All donors provided written informed consent for the use of blood and blood components (such as PBMCs, sera or plasma) and were recruited at hospitals or as outpatients.

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