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Corresponding author(s): Tulio de Oliveira and Alex Sigal

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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 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	Metamorph 7.7.11.0 software for image acquisition of foci. Libraries were sequenced using a 500-cycle v2 MiSeq Reagent Kit on the Illumina MiSeq instrument. Paired-end fastq reads assembled using Genome Detective 1.126.
Data analysis	Matlab 2019b custom scripts for image analysis, fitting, statistics, and graphing. Python and R custom pipeline for sequence analysis, phylogenetic tree generation and visualization. Matlab custom scripts available at https://github.com/sigallab/NatureMarch2021. Pyton and R pipeline available at https://github.com/nextstrain/ncov.

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

GISAID accession numbers for deposited sequences are: EPI_ISL_602622; EPI_ISL_678615; EPI_ISL_602623; EPI_ISL_660167; EPI_ISL_602629; EPI_ISL_602631; EPI_ISL_602624; EPI_ISL_660170; EPI_ISL_660174; EPI_ISL_660172; EPI_ISL_660173; EPI_ISL_660176; EPISL_660180; EPI_ISL_660181; EPI_ISL_660185; EPI_ISL_1229368; EPI_ISL_1229367.

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 was chosen based on availability of plasma where the SARS-CoV-2 variant eliciting the immune response was sequenced (plasma samples from the first South African infection wave) or availability of plasma (second South African infection wave).
Data exclusions	We have predetermined that no plasma which does not neutralize the matched variant (ie, first South African wave variant for first wave plasma, 501Y.V2 virus for second wave plasma) will not be used. On this basis, we excluded 1 first wave plasma and 2 second wave plasma samples.
Replication	All data was replicated in multiple experiments and for multiple plasma donors. The exception is plasma from a participant elicited by virus with the E484K mutation only, as we only identified one such participant. Nevertheless, we included the E484K data as speculative, with the hypothesis that this mutation leads to an effective cross-neutralizing antibody response to be confirmed or rejected by data from other groups. Other plasma donors were grouped into two groups: 1) Those infected in the first South African SARS-CoV-2 infection wave (no 501Y.V2 defining mutations and infected before November 1, 2020). There were samples from n=14 different participants for this group; 2) those infected in the second South African SARS-CoV-2 infection wave (501Y.V2 defining mutations and infected after November 1, 2020). There were samples from n=6 different participants for this group. For plasma from participants 039-13-0037, 039-13-0038, 039-13-0060, 039-13-0103, 039-02-0030, 039-02-0031, 039-02-0033, we performed 4 independent neutralization experiments. For all other participants, we performed 3 independent experiments. All attempts at replication were successful.
Randomization	Participants allocated based on whether they were infected with the 501Y.V2 or earlier variants circulating in South Africa.
Blinding	Blinding was not possible as participant plasma from the second South African infection wave was received midway during the study after some plasma from the first South African wave was already tested.

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	Genscript A02051 as positive control for neutralization. GenScript A02058 for staining of infected cells. Abcam ab205718 Goat anti-Rabbit HRP conjugated antibody was the secondary antibody for HRP based visualization of infection foci. The anti-spike RBD CR3022 antibody (A gift from Aaron Schmidt, Ragon Institute) was used in ELISA.
Validation	A02051 was validated by titration. A02058 was validated by positive and negative infection controls. More information can be found at: https://www.genscript.com/antibody/A02051-MonoRab_SARS_CoV_2_Neutralizing_Antibody_BS_R2B2_mAb_Rabbit.html?position_no=1&sensors=search%20product%20box. ab205718 validation can be found at https://www.abcam.com/goat-rabbit-igg-hl-hrp-ab205718.html. CR3022 binding to spike RBD is described in https://www.abcam.com/sars-cov-2-spike-glycoprotein-s1-antibody-cr3022-ab273073.html.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	H1299: ATCC (CRL-5803). HEK-293: ATCC (CRL-1573). Vero E6: Cellonex (http://cellonex.azurewebsites.net/) expansion of ATCC CRL-1586.
Authentication	None of the cell lines were authenticated
Mycoplasma contamination	Confirmed mycoplasma negative
Commonly misidentified lines (See ICLAC register)	None

Human research participants

Policy information about studies involving human research participants

Population characteristics	The study population for plasma donors was adults hospitalized with PCR-confirmed COVID-19, regardless of age, severity of disease, and HIV status, which are recorded in Table S1. Time from symptom onset or initial diagnosis (if asymptomatic) and blood draw from plasma was approximately 1 month.
Recruitment	Nasopharyngeal/oropharyngeal swab samples and plasma samples were obtained from 20 hospitalized adults with PCR confirmed SARS-CoV-2 infection enrolled in a prospective cohort study. Potential source of bias are: 1) Bias against severe cases of COVID-19 disease due to difficulty in recruitment due to challenges filing out questionnaire while in poor clinical state; 2) bias to increased enrollment of females because of higher linkage to care of this group in the South African context. Bias 1 is not likely to influence results since severe disease is not representative of the population. 40% male participants were recruited despite bias 2 and these were in similar frequencies across the two groups, so this bias is not expected to affect results.
Ethics oversight	Combined sampling of COVID-19 participants through blood draw and swab was approved by the Biomedical Research Ethics Committee (BREC) at the University of KwaZulu-Natal (reference BREC/00001275/2020). The 501Y.V2 variant was obtained from residual swab samples used for diagnostic testing by the National Health Laboratory Service (BREC approval reference BREC/00001510/2020).

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

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	N/A, observational prospective cohort study
Study protocol	Study protocol is available upon request.
Data collection	Patients hospitalized in three Durban facilities (Inkosi Albert Luthuli Central Hospital, King Edward Hospital, and Clairwood Hospital) with confirmed SARS-CoV-2 infection by qPCR were eligible for enrollment. Clinical data including symptoms, requirement for supplemental oxygen, BMI, and other parameters were collected at enrollment and at weekly intervals thereafter. Accredited tests were performed with a service laboratory to determine HIV status and HIV viral load.
Outcomes	N/A, non-interventional.