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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	For the Meso Scale Discovery Electrochemiluminescence Immunoassay (MSD-ECLIA), the Discovery Workbench software (version 4.0.13) was used. For RT-qPCR the QIAcube HT (version 1.1.0.39) and QuantStudio 6 Flex System (version 1.7.1), both from Applied BioSystems were used. For PsVNA GloMax Navigator (version 3.2.3) from Promega was used. For micro neutralization assays Gen5 (version 3.09.07) from Agilent was used .
Data analysis	All data analysis was done in R (version 4, [analyses were done over several years using specific versions 4.0.0-4.5.2]). All R code is embedded in R markdown files and the files and the data are available at github.com/michaelpfay/NHP_SARS-CoV2_Vaccines.

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

The data are available at github.com/michaelpfay/NHP_SARS-CoV2_Vaccines

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	*Use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Indicate if findings apply to only one sex or gender; describe whether sex and gender were considered in study design; whether sex and/or gender was determined based on self-reporting or assigned and methods used.* *Provide in the source data disaggregated sex and gender data, where this information has been collected, and if consent has been obtained for sharing of individual-level data; provide overall numbers in this Reporting Summary. Please state if this information has not been collected.* *Report sex- and gender-based analyses where performed, justify reasons for lack of sex- and gender-based analysis.*
Reporting on race, ethnicity, or other socially relevant groupings	*Please specify the socially constructed or socially relevant categorization variable(s) used in your manuscript and explain why they were used. Please note that such variables should not be used as proxies for other socially constructed/relevant variables (for example, race or ethnicity should not be used as a proxy for socioeconomic status).* *Provide clear definitions of the relevant terms used, how they were provided (by the participants/respondents, the researchers, or third parties), and the method(s) used to classify people into the different categories (e.g. self-report, census or administrative data, social media data, etc.)* *Please provide details about how you controlled for confounding variables in your analyses.*
Population characteristics	*Describe the covariate-relevant population characteristics of the human research participants (e.g. age, genotypic information, past and current diagnosis and treatment categories). If you filled out the behavioural & social sciences study design questions and have nothing to add here, write "See above."*
Recruitment	*Describe how participants were recruited. Outline any potential self-selection bias or other biases that may be present and how these are likely to impact results.*
Ethics oversight	*Identify the organization(s) that approved the study protocol.*

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

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	There were 126 rhesus macaques used, divided in 4 active vaccine groups, each of those divided into 5 or 6 dose groups, and a control group. That works out to between 4-6 animals per dose group for the active vaccines and 16 animals for the controls. In order to generate data which can be used to explore immune correlates of protection, a range of immune responses are expected to result in varying levels of protection from infection over the vaccine dose groups for each vaccine manufacturer. The protocol statistical analysis will compare body weights, RT-qPCR endpoints, TCID50, MNA, MSD-ECLIA, and PSVNA endpoints between vaccinated and control animals and among the vaccinated groups for each vaccine manufacturer (note: comparisons between vaccine manufacturers will not be performed). Placebo controls (Group 5A) will be combined for analysis over all 8 challenge days for a total of 16 placebo control animals. For normally distributed, continuous endpoints, the study provides greater than 80% power for comparisons between vaccinated and control groups when the difference in group means is at least 1.5 times the standard deviation for groups of 6 vaccinated animals, or 1.7 times the standard deviation for groups of 4 vaccinated animals. For comparisons between groups of vaccinated animals, the study provides greater than 80% power when the group means differ by at least 2.1 times the standard deviation (2.1xSD) when comparing groups of 4 and 6 vaccinated animals, 1.8xSD when comparing groups of 6, and 2.4xSD when comparing groups of 4. Power calculations were performed using SAS (SAS Institute, version 9.4) Proc Power for two-sided, two sample t-tests. T-tests were used for the

	power analysis for simplicity, as the expected means and variances are unknown.
Data exclusions	There were no data exclusions. However, there was other data measured from this study that will be reported in two separate papers.
Replication	This was one large study, so the measures of reproducibility are implicit in the statistical analyses and the fact that n=126 animals were used.
Randomization	Animals were randomized to vaccine arm/dose group/challenge day stratified by body weight and sex, so that about equal numbers of both sexes were in each vaccine/dose/challenge day group.
Blinding	No blinding of investigators was done, except the lung tissue and slides were evaluated in a blinded fashion by the veterinary pathologist.

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
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

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

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	n=126 rhesus macaque (Macaca mulatta) of Chinese origin, all greater than 2.5 years of age. Challenge was SARS-CoV-2 (USA-WA1/2020 strain.
Wild animals	Study did not involve wild animals.
Reporting on sex	By design, randomization was stratified by sex such that within each vaccine/dose/challenge day group there was about equal numbers of animals. Because of this balanced design and because there was no prespecified concern about sex effects, we did not do sex specific analyses.
Field-collected samples	Study did not involve samples collected from the field.
Ethics oversight	The study was performed at Battelle. Battelle is a Public Health Service (PHS) Animal Welfare Assurance approved facility. The study protocol was approved by the Battelle Institutional Animal Care and Use Committee (IACUC) and the study performed at Battelle was conducted under United States Food and Drug Administration's (FDA) Good Laboratory Practice (GLP) Regulations (21 CFR Part 58).

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

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*