nature portfolio

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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	Custom code was used to run preliminary Quality Checks on raw immunogenicity data.
Data analysis	Analyses were performed using Stata version 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC) and R v. 4.3.3 R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/. Figures were generated using R v. 4.3.3 and GraphPad Prism (version 10.0.0 for Windows, GraphPad Software, Boston, Massachusetts USA, www.graphpad.com).

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 that support the findings of this study are not openly available due to reasons of sensitivity and the ongoing nature of the trial. They are available from the corresponding author upon reasonable request.

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	Participants in this trial were aged between 5 and 36 months when enrolled. Sex was collected as either self reported by the caregiver or as per the child's medical records. Trial randomization was stratified by sex to ensure balance. The analysis of change in IgG antibody titre over time was stratified by sex (as well as other variables). Summary of IgG antibodies titres was stratified by site and age group as this was thought to be most relevant, dividing the group further by sex would have resulted to very small numbers.
Reporting on race, ethnicity, or other socially relevant groupings	We do not include socially constructed variables in this analysis. We do not report on race, ethnicity or socioeconomic status. We do report on nutritional status as defined by a weight-for-age z-score. This is not used as a proxy for socioeconomic status. Analyses are stratified, or adjusted for, age and study site as differences in IgG antibodies by age and geographical region have been previously documented.
Population characteristics	Age and geographical region are important co-variates for which the analysis presented here is either stratified by or adjusted for. We also look at the impact of prior malaria infection status (immediatley prior to vaccination), and nutritional status, in this paper.
Recruitment	Lists of eligible children were identified from local surveillance databases and community sensitisation. Participants were screened for eligibility. Only children from parents or guardians who consented to participation of their child in this clinical trial were enrolled.
Ethics oversight	The trial was approved by all the local ethics committees and regulatory authorities as well as the ethics committees at the University of Oxford and The London School of Hygiene & Tropical Medicine, with supportive coordination by the African Vaccine Regulatory Forum (AVAREF).

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	The trial planned to enroll 4800 participants, 50% of which would be enrolled into the immunogenicity cohort. 5139 participants were enrolled, 4644 met the modified per-protocol definition and 2308 of these were included in the immunogenicity cohort.
Data exclusions	Data from participants who did not receive vaccinations within the pre-specified window for the modified-per-protocol population were excluded from this analysis. This is detailed in the flow diagram. Data from samples collected outside of the pre-specified window were excluded and data from any immunological samples for which a valid result was not obtained were also not included. This is detailed in Table S1.
Replication	Biological samples were assayed in triplicate at three dilutions by laboratory staff blinded to vaccine group allocation. Plates were deemed to have passed if the seven-point standard curve and three quality control samples all passed in house criteria according to assay validation. Samples were deemed to have passed if triplicate measurements reported equal or less than 20%CV and if the value lay within the linear portion of the standard curve. For the diagnosis of clinical malaria, two blinded, independent microscopists at each sites analysed each blood film and a third adjudicating microscopist was used in case of disagreement.
Randomization	Children aged 5–36 months who fulfilled the eligibility criteria were randomly assigned (2:1) to receive vaccinations with R21/Matrix-M or a licensed rabies vaccine (Abhayrab), respectively. Randomisation was done using an electronic interactive web response system (DiagnoSearch

Life, Thane, India). Randomisation was stratified by trial site, age (5–12 months, 13–24 months, or 25–36 months) and sex (male or female), using block randomisation with variable block sizes. As it was not possible to analyse all immunological samples at each time point, all samples from pre-vaccination and 28 days after 3rd dose were aalysed. After that a random sample were selected for analysis using random number generation by the trial statistician aiming for 50% samples per site from R21 study arm and 20% from controls.

Blinding

The trial was double-blinded: participants, their families, all investigators, the laboratory teams, and the local study team were all masked to treatment.

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

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

NCT04704830

Study protocol

Study protocol is available at appendix to manuscript

Data collection

Recruitment occurred between April 14, 2021, to Jan 12, 2022 from five sites in four African countries. The clinical data on malaria incidence presented in this paper was collected over 12 months after the 3 dose primary vaccine series. Laboratory analysis for collection of IgG antibody data was between February 2022 and May 2024. As well as routine visits in which clinical data and samples for immunological analysis were collected, caregivers were advised to attend their local health facility if their child became ill or had a fever so adverse events could be monitored and a sample taken for blood film analysis.

Outcomes

The primary outcome of the trial was clinical malaria defined as the presence of an axillary temperature (≥37·5°C), or history of fever within the past 24 h, and P falciparum asexual parasite density of more than 5000 parasites per µL of blood using passive case detection.
The secondary outcomes described in this paper is titre of IgG antibodies specific to four vaccine induced antigens (NANP, CTERM, full length R21 and HBsAg), at five time points (pre-vaccination, 28, 180 and 365 days after third vaccine dose and 28 days after first booster dose). We summarise these across different demographic groups, look at the change in titre over time, and the association with the trials primary outcome - clinical malaria.

Plants

Seed stocks

n/a

Novel plant genotypes

n/a

Authentication

n/a