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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	Filemaker Pro v10
Data analysis	SAS v9, JMP v14 and Amira v2019.2

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

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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	Both cohort studies were based on open enrolment of participants living in the malaria endemic villages under study.
Data exclusions	no data was excluded
Replication	two independent cohorts were assessed. For in vitro experiments, multiple independent replicates were performed and all were successful.
Randomization	no formal randomization was performed
Blinding	slide readers (enumeration of parasitemia) were blind to treatment status for human blood films, in vitro assays, and the monkey vaccine experiments.

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

Antibodies Catalog no. Clone Lot no. Company
F(ab')2-Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 A-11070 853487 Invitrogen Molecular Probes
Goat anti-Mouse IgG (H+L) Highly Cross-Adsorbed Secondary Antibody, Alexa Fluor 594 A-11032 1985396 Invitrogen Molecular Probes
Goat anti-Rat IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor 488 A-A11006 1423045 Invitrogen Molecular Probes
F(ab')2-Goat anti-Mouse IgG, IgM (H+L) Secondary Antibody, Alexa Fluor 488 A10684 891190 Invitrogen Molecular Probes
Goat anti-Rabbit IgG (H+L) Secondary Antibody, Alexa Fluor 488-5 nm colloidal gold A31565 764359 Invitrogen Molecular Probes
IRDye 800CW Goat anti-Rabbit IgG (H + L) Secondary Antibody 926-32211 C30829-02 ODYSSEY imaging system 926-68070 C30723-04 ODYSSEY imaging system
FITC anti-human CD235a (Glycophorin A) Antibody 349103 HI264 B138023 BioLegend Inc.
Biotin Mouse anti-human IgG 555784 5288794 BD Biosciences
APC anti-human CD235a (Glycophorin A), 349113 Clone-HI 264 B262669 Biolegend Inc.
V5-Tag Monoclonal antibody R960-25 1937181 Thermo Fisher Scientific

Validation

manufacturer validated each antibody for the intended application

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	NIH repository (MR4)
Authentication	none
Mycoplasma contamination	not tested

Commonly misidentified lines (See ICLAC register)	none used

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Mice BALB/cJ both male and female mice (The Jackson Laboratory). Ages 20-26 weeks. Monkey Aotus nancymaae Both male and female (MD Anderson Cancer Center). Adults, age unknown.
Wild animals	none
Field-collected samples	none
Ethics oversight	Animal studies approved by IACUC of Brown University, Rhode Island Hospital and the NIH

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

Human research participants

Policy information about studies involving human research participants

Population characteristics	Tanzanian Birth cohort (age 0 to 4 years) Kenyan Cohort, males only, ages 12-35 Further details can be found in the MS as well as ref #19 (Kenyan cohort) and ref #2 (Tanzanian cohort)
Recruitment	Kenyan cohort: Open recruitment in the designated malaria endemic villages. Details provided in ref#19 Tanzanian Cohort: Open recruitment at delivery facilities. Details provided in Ref #2.
Ethics oversight	Ethical clearance was obtained from the IRBs of SBRI and Rhode Island Hospital, the Medical Research Coordinating Committee of the National Institute for Medical Research, Tanzania, and the Kenyan Medical Research Institute.

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	This is not a clinical trial.
Study protocol	*Note where the full trial protocol can be accessed OR if not available, explain why.*
Data collection	*Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.*
Outcomes	*Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.*

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	After treatment in culture, the infected RBCs were harvested and washed two times with PBS. After thorough washing, RBCs were appropriately stained and suspended in PBS before acquisition and analysis by using flow cytometer.
Instrument	BD LSR II Flow Cytometer was used for data collection

Software	BD FACS Diva 6.1.1 was used for data collection Flowjo vX.0.7 was used for data analysis
Cell population abundance	No sorting was done in the study; Infected RBCs were identified and gated using standard markers
Gating strategy	Single cells were gated using SSC-H and SSC-A; Normal and Infected RBCs were identified and gated by using Hoechst 33342 and APC conjugated anti-human Glycophorin A antibody. Infected RBCs were identified as cells which were positive for both Glycophorin A and Hoechst 33342. Normal RBCs were identified as cells which were positive for Glycophorin A but negative for Hoechst 33342. Among the infected RBCs, the cells, which were positive for JC-1 red high, represent live parasites and cells, which were JC-1, red low, represent dead parasites. Gating strategy provided in the main Figure 3 H and I.

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