

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
<input type="checkbox"/>	<input checked="" type="checkbox"/> The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement
<input type="checkbox"/>	<input checked="" type="checkbox"/> A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
<input checked="" type="checkbox"/>	<input type="checkbox"/> The statistical test(s) used AND whether they are one- or two-sided <i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i>
<input checked="" type="checkbox"/>	<input type="checkbox"/> A description of all covariates tested
<input type="checkbox"/>	<input checked="" type="checkbox"/> A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
<input checked="" type="checkbox"/>	<input type="checkbox"/> 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)
<input checked="" type="checkbox"/>	<input type="checkbox"/> For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted <i>Give P values as exact values whenever suitable.</i>
<input type="checkbox"/>	<input checked="" type="checkbox"/> For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
<input checked="" type="checkbox"/>	<input type="checkbox"/> For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
<input checked="" type="checkbox"/>	<input type="checkbox"/> Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), 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	<p>This work uses both simulated output from a computational model and empirical data.</p> <p>The empirical datasets were recently published (Tiedje et al. eLife (2023)) and publicly available. Nonetheless, we are providing a description here. The cleaned DBLα sequences generated from Ghanaian <i>P. falciparum</i> isolates were processed (i.e., cleaned, clustered, and classified) using custom pipelines previously published (He et al. Nat. Comms (2018) and Ruybal-Pesantez et al. Sci. Reports (2017)) and freely available on GitHub. The python code for the (1) DBLαCleaner pipeline is available on GitHub at https://github.com/Unimelb-Day-Lab/DBLαCleaner. The python code for the (2) clusterDBLalpha pipeline is available on GitHub at https://github.com/Unimelb-Day-Lab/clusterDBLalpha. Finally the python code for the (3) classifyDBLalpha pipeline is available on GitHub at https://github.com/Unimelb-Day-Lab/classifyDBLalpha. A dataset to demo this software/code is available on GitHub at https://github.com/Unimelb-Day-Lab/tutorialDBLalpha.</p> <p>The data analyzed that support the findings of this study, specifically the participant age class/groups for the <i>P. falciparum</i> isolates utilized, are not publicly available due to ethical reasons. Data are available upon reasonable request from co-author, Prof. Karen Day (karen.day@unimelb.edu.au; Response timeframe: ~1-2 months), however restrictions apply depending on the participant data required and how this data will be utilized.</p> <p>The agent-based stochastic simulator of malaria dynamics is available on Github at https://github.com/qzhan321/Intervention.</p> <p>The above information has been provided in the manuscript in the Data and Code Availability section.</p>
Data analysis	<p>The analysis scripts for reproducing results reported in this work are available on Github at https://github.com/qzhan321/Intervention. R version 4.0.3 was utilized for all analyses. The base R, along with the R packages RSQLite, dplyr, tidyverse, and stringr were used.</p> <p>This information has been provided in the manuscript in the Code Availability section.</p>

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 sequences utilized in this study are publicly available in GenBank under BioProject Number: PRJNA396962 [<https://www.ncbi.nlm.nih.gov/bioproject/?term=PRJNA396962>]. All additional data associated with this study are available in the main text, the supplementary information, or upon reasonable request to the authors. The data analyzed that support the findings of this study, specifically the participant age class/groups for the *P. falciparum* isolates utilized, are not publicly available due to ethical reasons. Data are available upon reasonable request from co-author, Prof. Karen Day (karen.day@unimelb.edu.au; Response timeframe: ~1-2 months), however restrictions apply depending on the participant data required and how this data will be utilized.

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

We did not collect or analyzed sex or gender information for this study. This information was not relevant to the objectives of the study. For the field surveys, as described below, there were no exclusions based on race, ethnicity, sex or gender. Pregnant women, individuals with disabilities, and individuals presenting with a serious or acute disease (including symptomatic/clinical malaria) on the day the survey was conducted were not eligible for enrollment and were excluded.

Reporting on race, ethnicity, or other socially relevant groupings

Not applicable. No groupings in these categories were considered or relevant to our study.

Population characteristics

This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023), which are referenced in this work. We provide a summary below:
All study participants enrolled were from Bongo District, Ghana and both male and female volunteers >1 year of age were included. This age range was selected so that we could investigate the asymptomatic *P. falciparum* reservoir that exists across all ages in areas of high seasonal malaria transmission, like Ghana.

Recruitment

This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023), which are referenced in this work. We provide a summary below:
During each survey the study team informed the participants by visiting their respective homes and inviting them to participate in the study. Individual informed consent was obtained in the local language from each enrolled participant by signature/thumbprint accompanied by the signature of an independent witness. A parent or guardian provided consent for children under the age of 18 years, and all children between the ages of 12 and 17 years also provided assent.

Ethics oversight

This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023), which are referenced in this work. We provide a summary below:
The study was reviewed/approved by the ethics committees at the Navrongo Health Research Centre (Ghana), Noguchi Memorial Institute for Medical Research (Ghana), University of Melbourne (Australia), and the University of Chicago (United States).

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

This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023), which are referenced in this work. We provide a summary below:
In June 2012, an enumeration/demographic survey was completed in Bongo District, Ghana. This enumeration/demographic data was used to establish the villages, sections, and compounds in two catchment areas selected in Bongo District. Age-stratified sampling was completed based on these demographic data to reflect the underlying age characteristics of the population. At the time the study was designed in 2012, age-specific malaria prevalence data was not available for Bongo District. Consequently malaria prevalence data from neighboring Kassena-Nankana District, Ghana was used. Based on these data an estimated risk ratio of 3.0 during the dry season for malaria prevalence between

the catchments areas was used to calculate the survey samples sizes. Therefore at a 95% confidence level, 80% power and sample ratio of 1:1 between the catchment areas the estimated sample size per catchment area was 865, allowing for a 15% nonresponse rate. Based on these numbers, ~1,000 participants per catchment area were recruited with ~2,000 participants being enrolled during each survey. Data obtained from each participant sample represents an independent experiment.

Data exclusions	This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023), which are referenced in this work. We provide a summary below: There were no exclusions based on race, ethnicity, or sex. Pregnant women, individuals with disabilities, and individuals presenting with a serious or acute disease (including symptomatic/clinical malaria) on the day the survey was conducted were not eligible for enrollment and were excluded. Participants who had a positive rapid diagnostic test for <i>P. falciparum</i> and were febrile (i.e., axillary temperature $\geq 37.5^{\circ}\text{C}$) on the day the survey was conducted were considered to be symptomatic for malaria and excluded as they failed to meet the study's case definition for an asymptomatic <i>P. falciparum</i> infection. Var genotyping was completed on all 1,783 participants with confirmed microscopic <i>P. falciparum</i> infections (i.e., isolates), and no participant isolates were excluded.
Replication	This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023), which are referenced in this work. We provide a summary below: The population was sampled three times (i.e., pre-, during, and immediately post-IRS). The surveys were undertaken at the end of the wet/high-transmission season, i.e., in October of 2012, 2014, and 2015 respectively. DNA was extracted from the dried blood spots for all participants with a confirmed microscopic asymptomatic <i>P. falciparum</i> infection. Var genotyping (PCR and sequencing) was completed for all isolates and only those isolates that gave no sequencing data on their first attempt were repeated.
Randomization	This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023), which are referenced in this work. We provide a summary below: Based on the average enumeration data of 5.6 persons per compound, a total of 500 index compounds were randomly selected for the enrollment of study participants. From the index compounds, an equal number of participants in each of the age-stratified categories (1–5, 6–10, 11–20, 21–39, 40+ years) were selected and enrolled into the study. Equal numbers of male and female participants were recruited sequentially into each of the age-stratified categories until the required enrollment numbers for each catchment area (i.e., ~1,000 participants/catchment area) was reached. Where necessary, participants were randomly recruited from nearby compounds in order of proximity to the index compounds to reach the enrollment numbers required for each catchment area. All participants enrolled during the first survey were invited for each of the subsequent surveys, with additional participants be recruited as required from the index compounds to maintain an age-stratified sample.
Blinding	This information has been previously provided in Tiedje et al. AJTMH (2017), Tiedje et al. PLOS Glob. Public Health (2022), and Tiedje et al. eLife (2023)), which are referenced in this work. We provide a summary below: Blinding was not suitable for the analyses performed in this study.

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
<input checked="" type="checkbox"/>	<input type="checkbox"/> Antibodies
<input checked="" type="checkbox"/>	<input type="checkbox"/> Eukaryotic cell lines
<input checked="" type="checkbox"/>	<input type="checkbox"/> Palaeontology and archaeology
<input checked="" type="checkbox"/>	<input type="checkbox"/> Animals and other organisms
<input checked="" type="checkbox"/>	<input type="checkbox"/> Clinical data
<input checked="" type="checkbox"/>	<input type="checkbox"/> Dual use research of concern
<input checked="" type="checkbox"/>	<input type="checkbox"/> Plants

Methods

n/a	Involved in the study
<input checked="" type="checkbox"/>	<input type="checkbox"/> ChIP-seq
<input checked="" type="checkbox"/>	<input type="checkbox"/> Flow cytometry
<input checked="" type="checkbox"/>	<input type="checkbox"/> MRI-based neuroimaging

Plants

Seed stocks	n/a
Novel plant genotypes	n/a
Authentication	n/a