

Supplementary Information

The content of this supplementary information is summarised as:

1. Supplementary Figures

Supplementary Figure S1. Violin plots of the HbS posterior predictive distribution

Supplementary Figure S2. Temporal distribution of the data points

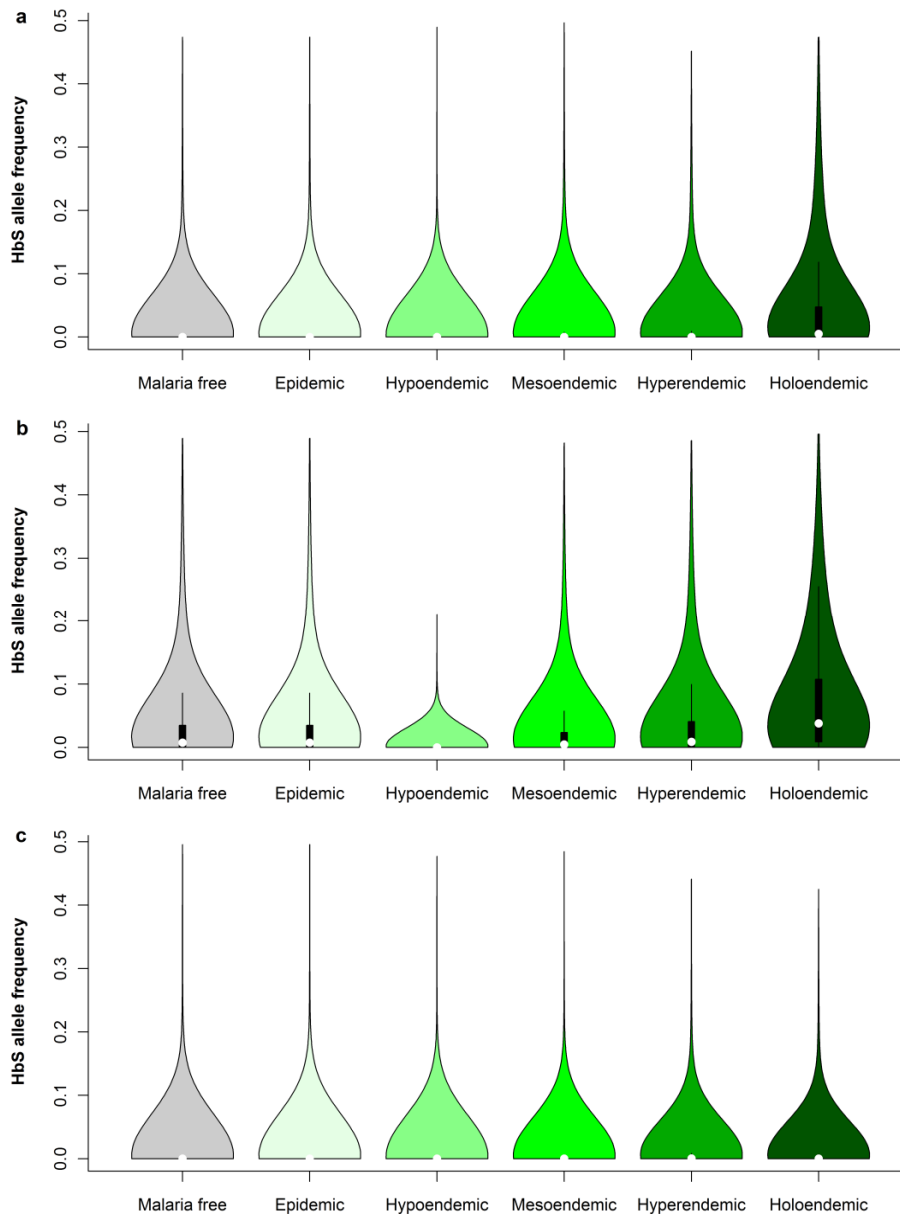
2. Supplementary Methods

The choice of a malaria map

Bayesian model-based geostatistical framework

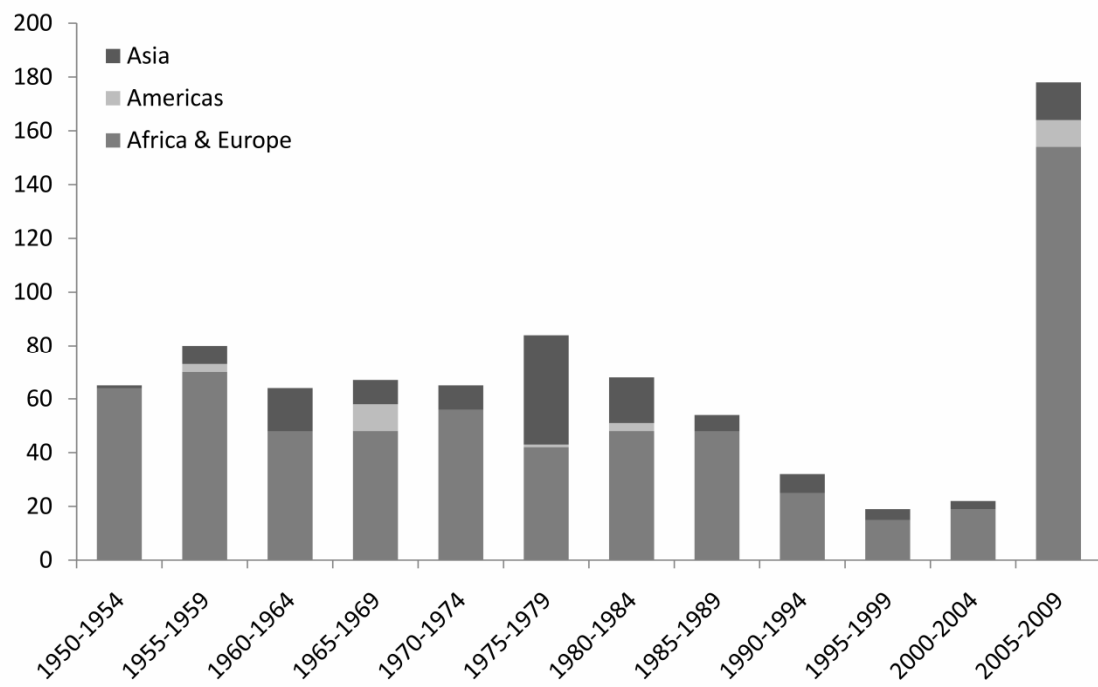
3. Supplementary References

Supplementary Figures



Supplementary Figure S1. Violin plots of the HbS posterior predictive distribution.

Predictive distribution of HbS prevalence at a uniformly-distributed point within each endemicity region for the world (a), Africa-Europe (b), and Asia (c). The green areas match the colours used in the Lysenko map (Fig. 2c) and show a smoothed approximation of the frequency distribution (a kernel density plot) of the predicted allele frequency within each endemicity class. The black central bar indicates the interquartile range and the white circles indicate the median values. The plots have been adjusted to an equal-area projection of the Earth



Supplementary Figure S2. Temporal distribution of the data points. The regional sub-divisions (the Americas in light grey; Africa, including the western part of Saudi Arabia, and Europe in medium grey; and Asia in dark grey), are shown in Figure 2a of the main manuscript.

Supplementary Methods

The choice of a malaria map

The Malaria Atlas Project (MAP, www.map.ox.ac.uk) has recently invested considerable efforts in refining the limits and the malaria endemicity maps for *Plasmodium falciparum*⁴⁶ and *P. vivax*⁴⁷. Despite the quality of such products, these contemporary maps cannot be used to investigate the spatial link between the distribution of haemoglobin S (HbS) and malaria. Here we are interested in the historical spatial relationship between HbS and malaria, not in their contemporary distributions, which have changed considerably over the last 50 years due to human migration (as, for instance, indicated by the prevalence of HbS in African Americans or Mediterranean immigrants in North America), epidemiological transition, and human interventions. Amongst numerous global malaria maps^{46, 48-55}, only one^{56,57} provides a reliable global proxy of pre-intervention malaria endemicity. Its main advantages lie in the efforts made by its authors to gather comprehensive information from the literature and from expert opinion, in order to map malaria globally at the peak of its distribution (c.1900).

Bayesian model-based geostatistical framework

The model for HbS allele frequency. The HbS allele frequency s was modelled using a Bayesian spatial generalized linear model (GLM)⁵⁸. The core of the model was a Gaussian process (GP)⁵⁸, denoted f . A GP is a probability distribution for functions, which can be used as a prior for unknown functions in Bayesian statistics^{58,59}. In this model, a Gaussian process prior was assigned to transformed HbS allele frequency. The model form can be defined using the following statements:

$$m \sim \text{Normal}(0, 10000)$$

$$\phi \sim \text{Exponential}(.1)$$

$$\psi \sim \text{Uniform}(0, 1)$$

$$\phi_s = \psi\phi$$

$$\phi_l = (1 - \psi)\phi$$

$$\theta_l \sim \text{Exponential}(.1)$$

$$\theta_s \sim \text{Exponential}(.1)1_{\theta_s < \theta_l}$$

$$\nu \sim \text{Uniform}(.1, 3)$$

$$M(x) = m$$

$$C(x, y) = \phi_s \text{Matern}(d(x, y)/\theta_s; \nu) + \phi_l \exp[-(d(x, y)/\theta_l)^2]$$

$$f \sim \text{GP}(M, C)$$

$$s(x) = \text{logit}^{-1}(f(x))$$

The mean function simply returned constant m , and no covariates were used. We used a

“nested” covariance function consisting of two components: a long-range Gaussian

component and a short-range Matern component⁵⁹. The range parameters of the two

components were θ_l and θ_s , respectively. The overall amplitude parameter ϕ was partitioned between the long-scale and short-scale components with proportions $(1 - \psi)$ and ψ , respectively, to obtain component-specific amplitude parameters ϕ_l and ϕ_s . The degree of differentiability ν of the Matern component was learned from the data alongside the other parameters. A global “nugget variance” V was assumed.

The distance function d gave the great-circle distance between x and y , unless x was in

the Americas and y was in Eurasia or Africa, in which case it returned ∞ . This modification prevented data in Africa from unduly influencing the east coast of South America. This method was preferred to a regional covariate which would influence the mean and covariance within each region.

Likelihoods. We assumed that Hardy-Weinberg^{60,61} assumptions applied in all sampled

populations, so newborns were in proportions:

$$\begin{aligned} AA_0 &= a_0^2 \\ AS_0 &= 2a_0s_0 \\ SS_0 &= s_0^2. \end{aligned}$$

where AA corresponds to the normal homozygous individuals, AS to the heterozygous carriers of HbS, and SS to the homozygous individuals with sickle cell anaemia. The “0” subscript denotes newborns. However, we assumed that all SS individuals died before reaching the age of reproduction, so to preserve equilibrium the reproductive population would be in proportions:

$$\begin{aligned} AA : \quad & \frac{a_0^2}{a_0^2 + 2ka_0s_0} = 1 - 2s \\ AS : \quad & \frac{2ka_0s_0}{a_0^2 + 2ka_0s_0} = 2s \\ SS : \quad & 0 \end{aligned}$$

where the coefficient k can be determined from s and from the fact that allele frequencies in newborns have to match allele frequencies in reproductive individuals. We assumed that the observed frequencies more closely matched those of the reproductive population than of the newborn population. Accordingly, we discarded the few SS records in the database.

A binomial sampling model was assumed for the number n_{AS} of heterozygous individuals observed at each data location x , given the number n sampled and the allele frequency s .

$$n_{AS}(x) \sim \text{Binomial}(n(x), 2s(x))$$

This likelihood specification completes the Bayesian probability model in the previous section.

A sensitivity analysis (not presented here) revealed that, for the small SS prevalences observed, the likelihood functions did not change substantially when the SS individuals were incorporated and Hardy-Weinberg frequencies were assumed.

Implementation. The model was implemented in the Python (<http://www.python.org>) programming language. The code is available from the MAP's code repository (<http://github.com/malaria-atlas-project/ibd-world>). It was fitted with the Markov chain Monte Carlo algorithm⁶² using the open-source Bayesian analysis package PyMC⁶³. All

scalar parameters in the model were updated using the standard one-at-a-time Metropolis algorithm with a normal transition density⁶². The evaluation of f at the data locations, which has a multivariate normal full conditional distribution, was updated using Gibbs steps⁶². Dynamic traces⁶² are available upon request. Maps were generated using Python and Fortran code available from the MAP's code repository (<http://github.com/malaria-atlas-project/generic-mbg>).

Map Uncertainty. Bayesian geostatistical analysis⁵⁸ makes it possible to estimate the uncertainty associated with model predictions. In comparison, when using traditional uncertainty measures (such as the kriging standard deviation) it is not possible to determine the probability of finding a value within a certain range (e.g. the probability of finding an allele frequency of between 10% and 15% in one location) or to find the range of values most likely to be found in an area where no data is available. High uncertainties are typically associated with a high heterogeneity of variables in an area (e.g. presence of both high and low allele frequencies separated by short distances in Africa) or with the absence of data over a large area (e.g. in Mauritania, Niger, Libya and Iran within the sickle cell area, in western parts of Russia and China outside the sickle cell area). Non-zero uncertainty predicted in parts of Oceania represent a local artefact of the model due to the very low density of data points in that part of the world. In the Americas, a similar effect was prevented by the higher number of data points showing absences and the artificially increased distance across the Atlantic, to avoid HbS AF from Western Africa influencing the prediction in Brazil. See Figure 3.

Validation metrics. In order to estimate the predictive skill of our geostatistical model, a 10% semi-random sample of the data was held out. A minimum distance of 100 km between points was imposed during the random sampling process to insure a good coverage of the hold out sample. The model was run with the thinned 90% of the data, allowing a comparison between the model's predictions and the observed allele frequencies of the 10% of the data which had been held out, and allowing the calculation of the prediction's mean error and mean absolute error. The mean error is the average distance between the actual data points and the predicted values. The

absolute mean error is a measure of the average magnitude of the errors in the predicted values. They provide a measure of the model's overall bias and overall accuracy, respectively.

Probabilities of categorical increases. The difference in the mean values of $s(x)$ between Lysenko⁵⁶ regions 1 (malaria free) and 2 (epidemic) is:

$$E[s(X_1) - s(X_2)]$$

where the random variable X_1 is a location uniformly distributed within Lysenko region 1, and likewise for X_2 . This figure can be approximated using n independent realizations $\{x_1^1, \dots, x_n^1\}$ of X_1 and a corresponding set of realizations for X_2 :

$$E[L(X_1) - L(X_2)] = \frac{1}{n} \sum_{i=1}^n L(x_i^1) - L(x_i^2).$$

This procedure was conducted using $n = 100$ and 5% of the parameter samples in the dynamic trace, selected at random. To assess the Monte Carlo standard error of the approximation, the procedure was repeated to compute the standard deviation using 100 different realizations of X_1 and X_2 and subsets of the dynamic trace (see Figure 5 and Supplementary Figure S2).

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