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The entomological inoculation rate and *Plasmodium falciparum* infection in African children

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Abstract

Malaria is an important cause of global morbidity and mortality. The fact that some people are bitten more often than others has a large effect on the relationship between risk factors and prevalence of vector-borne diseases[1–3]. Here we develop a mathematical framework that allows us to estimate the heterogeneity of infection rates from the relationship between rates of infectious bites and community prevalence. We apply this framework to a large, published data set that combines malaria measurements from more than 90 communities[4]. We find strong evidence that heterogeneous biting or heterogeneous susceptibility to infection are important and pervasive factors determining the prevalence of infection: 20% of people receive 80% of all infections. We also find that individual infections last about six months on average, per infectious bite, and children who clear infections are not immune to new infections. The results have important implications for public health interventions: the success of malaria control will depend heavily on whether efforts are targeted at those who are most at risk of infection.

Economic, public-health, and medical advances over the past 100 years halved the global geographical extent of malaria[5]. Nonetheless, population growth and failure to prevent infection or manage disease in this reduced extent means that *Plasmodium falciparum* remains a leading cause of global morbidity[6] and mortality[4,7,8]. Central to the future of malaria control is more effective understanding of the relationships between risk factors, the frequency and longevity of infection, and disease outcome[9]. These relationships have been debated extensively in relation to disease control[10,11].

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An important aspect of this debate is the quantitative relationship that inevitably exists between the proportion of people who are infected with *P. falciparum*, (the parasite ratio, PR) and the rate at which people are bitten by infectious mosquitoes (the entomological inoculation rate, EIR). The EIR is rarely recorded in Africa[4], limiting informed debate on the relationship between vector biology, transmission intensity, clinical disease and mortality risks. Conversely, the PR is a widely measured index of infection risk, allowing a more detailed investigation of the interaction between transmission intensity, age, and disease burden. Using mathematical models, we seek here to explore the factors that determine the complex, nonlinear association between EIR and PR, and use these models to highlight key features of the biology of malaria transmission that relate to future disease control.

Ross first developed a mathematical model for the relationship between EIR and PR[12], but his model, as extended by Macdonald, performed poorly in the African Savannah[13]. Since then, several modifications to Ross' original model have been proposed that are now considered important in malaria epidemiology. Informed by a century of theory, we have developed a large set of mathematical models, fitted them to a comprehensive data set, and selected the best of these models to describe the relationship between EIR and PR (Methods).

It was assumed by Ross that human populations were homogeneous, but in fact some people are bitten by mosquitoes more than others because of proximity to larval habitat[14], differential attractiveness to mosquitoes[15], or other reasons. Moreover, some people are more susceptible to infection, per bite. Heterogeneous infection rates have important implications for the dynamics and control of malaria[1–3], and heterogeneity fundamentally changes the relationship between EIR and PR[14]. Those who are infected most play a role in malaria transmission that is analogous to the role of the most sexually active in transmission of sexually transmitted diseases[16]. We assume that relative infection rates follow a Γ distribution, with mean 1 and variance $1/k$.

Ross assumed that infections clear at a constant rate, regardless of subsequent infections. The assumption was challenged by a growing consensus that superinfection with *P. falciparum* would increase the time to clear an infection[17–20]. Let ε denote the annual EIR, b the transmission efficiency (the probability that a bite by an infectious mosquito results in an infection—either a new infection or superinfection) and $1/r$ the expected time to clear each infection. Assuming superinfection and assuming infections clear independently, clearance occurs at the rate $b\varepsilon/(e^{b\varepsilon/r} - 1)$ (refs 17–19); thus, the time to clearance is longer when annual EIR is higher. We also considered immunity to reinfection by comparing SIS to SIRS dynamics (Methods). The full set of candidate models included SIS and SIRS models combined with heterogeneous infection and superinfection.

We identified 119 empirical estimates of EIR matched to coincidental measures of PR in African children under 15 years of age[4]; these data should be regarded with circumspection, as they were collected using different methods and for other purposes. One hundred and nine pairs measured positive EIR and PR. Ninety-one of these pairs also reported the sample sizes for the PR estimate. Two other modifications to these models were considered. First, microscopy errors bias estimates of PR and affect the analysis[21]. As the sensitivity and specificity of microscopy is not known, they were fitted along with the other model parameters. Second, the age ranges of the children sampled differed among studies. This introduces a potential bias if estimated prevalence varied substantially with age. We fitted each model with and without age corrections and microscopy errors (Methods).

Each candidate model was fitted to the data by maximum likelihood using *R* (ref. 22) and compared to a log-linear model[5,23]. Based on these fits, the best overall model was selected using Akaike's information criterion (AIC)[24] (Table 1, Fig 1a). The best overall model was a simple function that incorporated heterogeneous infection rates, with no immunity to reinfection:

$$\mathrm{PR}=1-\left(1+\frac{b\varepsilon}{rk}\right)^{-k} \quad (1)$$

Equation (1) fitted better than the log-linear model (another two-parameter model) and had very strong evidential support over the log-linear model, with ΔAIC of 185 (refs 5, 23). Moreover, equation (1) was selected over the log-linear model in every case when the analysis was repeated on 1,000 bootstrapped data sets.

The model has six fitted parameters, including sensitivity, specificity, age-corrections, k and b/r: b and r are exactly co-linear—the mathematical relationship between EIR and PR in these models depends only on their ratio. For the best overall model, the fitted sensitivity and specificity were 95.8% and 88.4%, respectively. The estimates were different for each model. A sensitivity analysis demonstrates that PR is much more sensitive to changes in k, which determines variance in infection rates, when annual EIR is greater than about 1, but PR is more sensitive to b/r when EIR is lower (Fig. 1b).

A simple summary of heterogeneous infection is the fraction of all infections received by the subpopulation that is infected most frequently; for $1/k = 4.2$, 20% of the population receives 80% of all infections, similar to a single study from Tanzania in which 20% of the population received 80% of all bites[3]. This represents an average across the 91 populations sampled—the distribution of infection rates in a particular population may be more or less heterogeneous, depending on the local ecology[14].

The fitted parameter b/r is the product of transmission efficiency and persistence times; alternatively, it is the expected duration of an infection, per infectious bite. If transmission efficiency were perfect, the best-fit parameter would correspond to a duration of infection of approximately 166 days; if transmission efficiency were approximately 50%, then persistence would be 11 months. These estimates are consistent with estimates of persistence from simple infections induced for malaria therapy[25] and with recent studies of persistence for natural infections[26,27].

Consistent with other studies[28,29] and the notion that immunity to clinical illness develops after repeated infection in early childhood, we found no evidence for immunity to infection among these populations of African children, as reflected in the relationship between EIR and PR. A direct comparison of SIS and SIRS models (Methods; equation (4) versus equations (6) or (7)) demonstrated that mathematical models for malaria infection in children should be SIS and not SIRS because children do not become immune to infection after clearing a single infection, but immunity requires repeated infection or possibly some change in immune function with age.

On the other hand, the analysis did reveal a strong decline in prevalence associated with the maximum age of the sample population. The lower bound for age was associated with a 0.8% increase in prevalence for each year of age, and the upper bound was associated with a 1.6% decrease in prevalence. On closer scrutiny, most of the effect was due to 16 studies for which the maximum age was larger than 12. One likely explanation is that these studies included many children who had become sufficiently immune to control the peripheral parasitaemia. Individuals who control peripheral parasitaemia may clear infections faster, or

they may be more likely to return a false negative microscopy report, an issue that may be resolved with a more sensitive test such as PCR (polymerase chain reaction).

One objection to this analysis is that the heterogeneous composition of the population inevitably biases the study. The inferential perils of cross-level analysis can be avoided if the heterogeneous composition of the population is known in advance and incorporated into the analysis, but this is a practical impossibility. Our approach deals with this problem by assuming that the heterogeneity can be treated statistically. We specify a one-parameter family of distributions and allow a shape parameter to be fitted. This analysis corrects for the bias introduced by heterogeneity, assuming that the distribution is properly chosen, and that heterogeneous infection rates are the main source of bias.

We have found a simple approximating model for the relationship between EIR and PR. Our analysis suggests that heterogeneous biting or susceptibility to infection plays an important role in determining PR, that immunity to infection in early childhood does not, and that persistence times for malaria are at least six months, and possibly much longer.

Our findings have broad implications for malaria dynamics. Clearly, PR declines in adults[28,29] owing to some kind of immunity that reduces infection, increases clearance, or that reduces apparent PR by lowering the parasite densities in peripheral parasitaemia and decreasing sensitivity by microscopy. The distinction between immunity to clinical disease, immunity to infection, transmission blocking immunity, and the ability of individuals to manage peripheral parasitaemia has been confusing in mathematical models; the epidemiological state often called ‘recovered and immune’ acts as a reservoir of *P. falciparum* in some models but not in others. A critical evaluation of the mathematical models of malaria is warranted.

The results here are consistent with earlier views of malaria epidemiology; very substantial reductions in EIR will be necessary to achieve modest reductions in PR throughout Africa. In quantitative terms, reducing EIR from 200 to 100 and then to 50 would reduce PR by 4% and then by an additional 5%. A corollary is that the effort required to reduce the disease burden in Africa would be enormous. Such findings have substantial implications for (1) the prospects of control with imperfect vaccines, (2) the development and persistence of anti-malarial drug resistance, and (3) public health interventions that aim to reduce disease without reducing PR. In particular, heterogeneous infection implies that malaria will be substantially more difficult to control if control measures are applied uniformly. Conversely, targeting malaria control at those who are bitten most, where practical, may provide a disproportionate impact and wider community benefits by reducing the frequency of asymptomatic infections, the sporozoite rate in the mosquito population and overall transmission[1–3].

METHODS

Models

Ross’s population dynamic model describes the temporal relationship between EIR and PR, as well as the relationship at equilibrium[12]. Let x denote PR in a population as a function of time or age. Initially, we assume people become susceptible to infections after clearing an infection. Assuming EIR remains constant, PR changes according to the following equation:

$$\dot{x} = b\varepsilon(1 - x) - rx \quad (2)$$

Ross's relationship between EIR and PR is found by setting $\dot{x}=0$ and solving for x (Table 1). The model is called SIS, because those who are infected (I) become susceptible (S) again after clearing an infection.

For super-infection, PR is the equilibrium of the equation:

$$\dot{x}=b\varepsilon(1-x)-f(b\varepsilon,r)\,x \quad (3)$$

where $f(\Lambda, r) = \Lambda/(e^{\Lambda/r} - 1)$. We call this an SI°S model, where I° implies the per capita time to clearance (that is, from I to S) is given by f.

In heterogeneous populations, let s index the population with expected infection rate $bs\varepsilon$, and let $x(s)$ denote the proportion of humans in that class that are infected. To describe the distribution of infection rates in the population, let $g(s)$ denote the fraction of the population in class s, and without loss of generality, let $g(s)$ denote a probability distribution function with mean 1. Thus, $g(s)$ affects the distribution of infection rates without changing the mean; $b\varepsilon$ describes average infection rates, but individual expectations can vary substantially. The dynamics are described by the equation:

$$\dot{x}(s)=bs\varepsilon(1-x(s))-f(bs\varepsilon,r)\,x(s) \quad (4)$$

The population prevalence is found by solving for the equilibrium in equation (4), denoted $\bar{x}(s)$, and integrating:

$$\int_0^\infty \bar{x}(s)\,g(s)\,ds \quad (5)$$

Here, we let $g(s, k)$ denote a Γ distribution, with mean 1 and variance $1/k$. Thus, the average rate of infection in the population is $b\varepsilon$ and the variance of the infection rate is $b^2\varepsilon^2/k$;$1/k$ is the coefficient of variation of the population infection rate. For this distribution, equation (5) has the closed form solution given by equation (1). This model is called ∫SI°S.

Ross's model, the heterogeneous infection model, and the superinfection model are closely related. As expected, the functional relationship with super-infection is the limit of a heterogeneous infection model as the variance in expected infection rates approaches 0. Curiously, Ross's original function is a special case of a heterogeneous infection model (equation (1)) with $k = 1$. A longer closed form expression can be derived for the model ∫SIS, the heterogeneous model with Ross's assumption about clearance (not shown). The best fit model ∫SI°S is virtually identical to the Ross analogue of the best fit model ∫SIS but with a very different interpretation (results not shown). Thus, the super-infection clearance assumption does little, *per se*, to improve the model fit. On the other hand, it may provide a more accurate estimate of the time to clear an infection[19].

For immunity to infection, let y denote the proportion of a population that has cleared *P. falciparum* infections and is immune to re-infection. Let ϕ denote the average duration of immunity to re-infection. The dynamics are described by the equations:

$$\begin{aligned}\dot{x}&=b\varepsilon(1-x-y)-f(b\varepsilon,r)\,x\\ \dot{y}&=f(b\varepsilon,r)\,x-y/\phi\end{aligned} \quad (6)$$

Note that the fitted parameter is actually $\phi' = b\phi$ (see Table 1). This model is called SI°RS, where R means recovered and immune.

For a heterogeneous population model with immunity to infection, let $y(s)$ denote the proportion of recovered and immune hosts. The dynamics are described by the equations:

$$\begin{aligned} \dot{x}(s) &= bs\varepsilon(1 - x(s) - y(s)) - f(bs\varepsilon, r)\, x(s) \\ \dot{y}(s) &= f(bs\varepsilon, r)\, x(s) - y(s)/\phi \end{aligned} \quad (7)$$

We could not find a closed-form expression, so we fitted the function shown in Table 1; numerical integration was performed by *R*. This model is called ∫SI°RS. **Age, microscopy errors and likelihood**. Let α denote the sensitivity of microscopy and $1 - \beta$ the specificity. The estimated PR, Y, is related to the true PR by the formula $Y = \alpha X + \beta(1 - X)$; it is biased upwards at low prevalence by false positives (β) and downwards at high prevalence by false negatives (α).

Similarly, the differences in the age distribution of children sampled is a potential source of bias. As we have no information about the age distribution of children actually sampled, we use the bounds for bias correction.

Let L_i and U_i be the lower and upper ages of the children from the ith study, and let $\hat{L}$ and $\hat{U}$ denote the mean lower and bounds from all the studies. The predicted PR in the ith sample, given the estimated EIR, is $X_i = f(\varepsilon_i) + a(L_i - \hat{L}) + b(U_i - \hat{U})$. The predicted estimate of PR in the ith sample, given the estimated *EIR* is $Y_i = \alpha X_i + \beta(1 - X_i)$. The log likelihood of the data, given the model, was:

$$\sum_{i=1}^{91} P_i \log(Y_i) + N_i \log(1 - Y_i) \quad (8)$$

where P_i was the number of humans that tested positive and N_i the number that tested negative in the ith study. For each underlying function f, we verified that the full model was in fact the best model by backwards fitting (that is, we redid the analysis setting α, β, a and b to zero, one by one, then in combinations).

We have reported the fitted sensitivity and specificity, but we also repeated the analysis assuming a constant sensitivity and specificity for all models. The results and model ranking are similar to those reported here if the assumed values of sensitivity and specificity are high, close to their fitted values. In contrast, when sensitivity and specificity are much lower, the log-linear model is strongly favoured. As the lowest PR that could be measured is β, and as the PR in several studies was close to zero, specificity must be fairly high, at least when PR is low. Some of this information is captured by fitting α and β.

Uncertainty in EIR

The studies used different methods to estimate EIR, so we were uncertain how to estimate the study precision. Moreover, only 38 studies reported sample sizes for their estimates of the human biting rate and the sporozoite rate. To evaluate whether uncertainty in EIR would affect our analysis, we repeated the analysis 1,000 times using equation (1) and the log-linear model. In each instance, we multiplied the estimated EIR by 2^{ξ}, where ξ was a uniform random variable drawn from the interval (−1, 1). The average best-fit parameter estimates changed, but equation (1) was selected as the best model in 98.8% of these trials. We repeated the analysis again multiplying EIR by 4^{ξ} with similar results.

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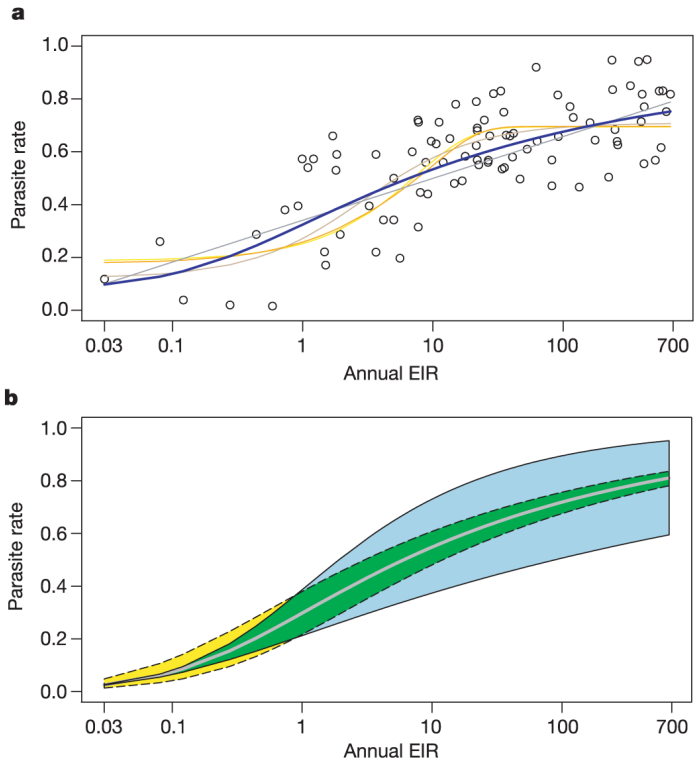

Figure 1. The data and fitted functions and a sensitivity analysis for the best overall model

a, The best fit for SIS (tan), SI°S (yellow), SI°RS (orange), the log-linear model (grey), and the best-overall model ∫SI°S (blue). The best-fit ∫SI°RS model was not visually different from the ∫SI°S model with heterogeneity. **b**, In ∫SI°S, PR is more sensitive to the variance in infection rates (that is, doubling or halving *k*) at high EIR (solid lines, blue and green), and more sensitive to variability in recovery (doubling or halving *r*) for low EIR (dashed lines, yellow and green). Models are defined in Methods.

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Table 1

The models and fitted parameters

PR	ΔAIC	b/r	1/k	$b\phi$	α	β	a	b	Name
$1-\left(1+\frac{be}{rk}\right)^{-k}$	0	0.45	4.2		96%	12%	0.008	−0.0016	∫ *SI°S*
$\int_0^\infty\left(\frac{1-e^{-se/r}}{1+b\phi e e^{-se/r}}\right)g\left(s\right)\mathrm{d}s$	2	0.45	4.2	0	96%	12%	0.008	−0.016	∫ *SI°RS*
$\frac{be}{be+r}$	213	0.16			78%	16%	0.01	−0.026	*SIS*
$\frac{1-e^{-se/r}}{1+b\phi e e^{-se/r}}$	557	0.1		0.05	76%	21%	0.012	−0.028	*SI°RS*
$1-e^{-e/r}$	612	0.077			75%	21%	0.01	−0.03	*SI°S*
		c	*d*						
c log*e* +*d*	185	0.084	0.32				0.008	−0.012	*Log-linear*

Models are ranked by AIC. The analysis found strong evidential support for the model ∫*SI°S* described by equation (1), a model with heterogeneous infection rates (the symbol ∫ denotes heterogeneous infection) and superinfection (the default assumption is constant clearance; *I°* implies superinfection). The models that lacked heterogeneous infection, *SIS*, *SI°S*, *SI°RS*, and the log-linear model fit poorly, as judged by AIC. (We report the ΔAIC values.) Moreover, the parameters for the model ∫*SI°S* are biologically meaningful, unlike those for the log-linear model. Finally, the model ∫*SI°RS* fitted no better than ∫*SI°S*, and the fitted duration of immunity to infection was zero.