MATHEMATICAL MODELING OF THE IMPACT OF MALARIA VACCINES ON THE CLINICAL EPIDEMIOLOGY AND NATURAL HISTORY OF *PLASMODIUM FALCIPARUM* MALARIA: OVERVIEW

THOMAS SMITH,* GERRY F. KILLEEN, NICOLAS MAIRE, AMANDA ROSS, LOUIS MOLINEAUX,
FABRIZIO TEDIOSI, GUY HUTTON, JÜRG UTZINGER, KLAUS DIETZ, AND MARCEL TANNER

Swiss Tropical Institute, Basel, Switzerland; Ifakara Health Research and Development Center, Ifakara, Tanzania; World Health Organization, Geneva, Switzerland; University of Tübingen, Tübingen, Germany

Abstract. We report a major project to develop integrated mathematical models for predicting the epidemiologic and economic effects of malaria vaccines both at the individual and population level. The project has developed models of the within-host dynamics of *Plasmodium falciparum* that have been fitted to parasite density profiles from malariatherapy patients, and simulations of *P. falciparum* epidemiology fitted to field malariologic datasets from a large ensemble of settings across Africa. The models provide a unique platform for predicting both the short- and long-term effects of malaria vaccines on the burden of disease, allowing for the temporal dynamics of effects on immunity and transmission. We discuss how the models can be used to obtain robust cost-effectiveness estimates for a wide range of malaria vaccines and vaccination delivery strategies in different eco-epidemiologic settings. This paper outlines for a non-mathematical audience the approach we have taken and its underlying rationale.

INTRODUCTION

Despite considerable efforts over the last three decades, and millions of dollars spent, there is still no registered vaccine against *Plasmodium falciparum* malaria. Several candidate malaria vaccines are now in phase I or phase II clinical trials or have entered pre-clinical testing. There is a need for rational approaches to decide how to prioritize different malaria vaccine development programs and to plan for the deployment of the vaccine(s) once efficacy has been established.

Mathematical models have been valuable decision-making tools for vaccination strategies against infectious diseases, in particular for those covered by the Expanded Program on Immunization (EPI).[1] Compared with other organisms that cause infectious diseases, *P. falciparum* has a complex life cycle, expressing many different potential targets for vaccines and various candidate vaccines targeting different stages of the parasite are in clinical development.[2] The history of ineffective or partially effective control of malaria and failed vaccination attempts has led to the assumption that the efficacy of a malaria vaccine is unlikely to approach 100%, but since *P. falciparum* is one of the most frequent causes of morbidity and mortality in areas where it is endemic,[3–5] even a partially protective vaccine may be highly cost-effective and a critically important public health tool. However, it is not obvious what minimum level of efficacy must be achieved before major investments in vaccine production can be justified. The issue arises that if a number of partially effective candidates with different profiles become available, how should their development be prioritized?

In this context, mathematical models of both the natural history and epidemiology of malaria are needed to guide the process of malaria vaccine development. Malaria models have several roles that transcend their obvious limitations in making precise predictions.[6] They offer the possibility of systematically comparing the likely benefits of alternative types of vaccines and vaccine delivery scenarios, of predicting likely cost-effectiveness, and of identifying the role of vaccination within integrated control approaches. In addition, they provide a means of identifying current gaps in knowledge that need to be filled for rational planning of vaccine development strategies.

Plasmodium falciparum malaria was one of the first pathogens to be described by a mathematical model.[7] Subsequent developments, i.e., the Ross-Macdonald models and the malaria model of the Garki project[8,9] have played seminal roles in the design of malaria control policies and the global malaria eradication campaign carried out in the 1950s and 1960s.[10,11] However, these malaria models were not designed to predict the likely impact of malaria vaccination.

We now describe the challenges that a model must address if it is to provide useful predictions of the potential impact and cost-effectiveness of malaria vaccines, and then outline our malaria modeling project that aims to meet this objective. The accompanying articles describe the different components of our models, and the conclusions we have so far been able to draw from them.

REQUIREMENTS OF A PREDICTIVE MODEL FOR THE EFFECTS OF MALARIA VACCINES

Characteristics of individual *P. falciparum* infections. A model for use in predicting the population impact of a vaccine must embed within it a relevant description of the course of individual infections. For many infectious diseases, the necessary description is quite simple. For instance measles, pertussis, rubella, and varicella have well-defined latent periods, followed by acute episodes of morbidity and infectiousness, making it realistic to use a common modeling approach to address all of them. In contrast, the course of a single infection of *P. falciparum*, such as that shown in Figure 1, is far more complex, with infectiousness and the risks of acute morbidity and mortality varying as consequences of erratic temporal patterns of parasite densities. A number of recent models have analyzed how these patterns depend on clonal antigenic variation of the parasite[12–14] or on erythrocyte dynamics.[15,16]

A complete population model of *P. falciparum* dynamics with sub-models of clonal antigenic variation and erythrocyte

* Address correspondence to Thomas Smith, Swiss Tropical Insitute, Socinstrasse 57, PO Box CH-4002, Basel, Switzerland. E-mail: Thomas-A.Smith@unibas.ch
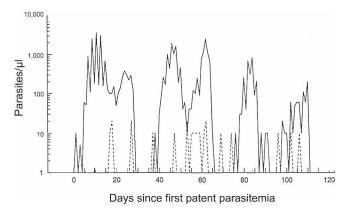
FIGURE 1. Course of a single infection of *Plasmodium falciparum*. Data of a characteristic malariatherapy patient (Patient S-1044).[85] Dashed line = gametocytes; solid line = asexual parasites. (Reproduced with permission of the American Society of Tropical Medicine and Hygiene).

dynamics embedded within it is possible in principle, but there is currently no consensus on how such a model should be formulated. For the purpose of making epidemiologic predictions, such an approach would introduce an undesirable level of complexity. However, an adequate model for the population impact of a vaccine must contain a description of a malaria infection that is not at variance with the biology and must also contain representations of those processes that may be modified by vaccination.

Short-term effects on the vaccinated individual. The effects on morbidity and mortality of a partially protective vaccine are likely to be more complex than the effects on primary infections in the non-immune host.[17] Even if the effect of the vaccine is simply to reduce the force of infection, the short-term consequences in terms of morbidity and mortality risks are not simply proportional to the reduction in infection rate. Pre-existing immunity and heterogeneity in the efficacy of a vaccine both lead to reduction in the effectiveness in preventing infection.[18] The efficacy of vaccination against post-infection outcomes such as morbidity and mortality may be very different from that against infection.[19] A model to predict population impact of a vaccine needs to include these processes that modulate the impact of infection.

Long-term effects on the vaccinated individual. Field trials of malaria vaccines carried out thus far consider only impacts that can be measured during the 6–18 months follow-up periods.[20,21] Unfortunately, the longer-term consequences of a vaccination program cannot simply be extrapolated from the results of such trials. For example, some benefits of vaccination may take an extended period to become evident. This will be particularly the case if there is natural boosting or if there are effects on transmission dynamics. Conversely, vaccination may result merely in delay of morbidity and mortality in some individuals, in which case field trials may suggest a greater benefit than will be observed during implementation and scaling up of malaria vaccine programs.

The introduction of insecticide-treated nets for malaria control has been accompanied by extensive debate about possible long-term effects. Related issues arise with regard to vaccines. Since reduction in exposure to the parasite will delay the acquisition of immunity, it has been conjectured that other factors being equal, long-term transmission control might only delay severe disease or even death.[22–24] Supported by data from long-term follow-up of transmission control projects,[25–28] others have contended that the benefits will outweigh any such potential effects.[29–32] Such possible delays in acquisition of immunity need to be considered in appraisals of the cost-effectiveness of malaria interventions, including vaccination.[33]

Some of the long-term effects of malaria control are extremely difficult to predict. These include effects on children's attendance rates and performance at school, higher education achievements, aspirations and forgone opportunities to enter competitive job markets, general well-being, and equity.[34] On the macroeconomic scale, malaria has measured effects on foreign direct investment, population mobility, tourism, and international trade, but the causal relationships of how malaria delays social and economic advancement of whole societies remain elusive.[35,36]

Interdependence of hosts. An epidemiologic model for the effects of a vaccination program must consider the dependence between events in different individuals. All malaria vaccine field trials done so far have been designed with the objective of directly protecting the vaccinated individuals either from infection or from consequent morbidity and mortality, and have not considered broader effects on transmission. Evaluations of transmission effects do not form part of standard methods for evaluating vaccines against pre-erythrocytic or asexual blood stages of malaria.[37]

The importance for mathematical models of the dependence between events in different individuals was already recognized by Ronald Ross some 90 years ago,[38] and has been the core of most subsequent malaria modeling exercises. This is the key element that distinguishes infectious disease modeling from that of non-infectious diseases.[39] The analysis of this dependence has been the objective of most previous models for vaccination against malaria,[40–43] which have concentrated on identifying the conditions for controlling or interrupting transmission.

The current burden of malaria morbidity and mortality, particularly in sub-Saharan Africa, is so large[3–5,44] that even a vaccine that modifies the course of infection in only a proportion of recipients without any effects on transmission may be worth pursuing. Transmission effects should not be ignored, but need to be just one part of a model that includes also the independent effects.

Cost-effectiveness analysis (CEA). This has become increasingly important for evidence-based decision-making in health care in resource-constrained settings. There is now consensus among economists about the main points of CEA methodology,[45,46] although there continues to be important advances in techniques related to CEA such as modeling uncertainty.[47] Little work has been done on the cost-effectiveness of malaria vaccination,[48] and this has not considered the potential savings in health care costs or productivity of workers. However, CEA of malaria interventions, even when based on careful costing,[33,49–51] have generally not taken into account either the transmission effects or the dynamics of the long-term impact. An adequate model for CEA of malaria vaccines needs to consider these elements.

STRUCTURE OF THIS PROJECT

None of the existing malaria models satisfies all of the requirements articulated above, so we have been able to make

only limited use of them in developing new models to make quantitative predictions of the potential impact of vaccination against *P. falciparum* malaria.

The main component of the project is a stochastic simulation model for the epidemiology of *P. falciparum* that incorporates insights from the within-host models, but is implemented independently of them.[49–55] We have used this epidemiologic model to simulate the results[56] from the recently completed trials of the malaria vaccine RTS,S/AS02 carried out in adult men in The Gambia[57] and in children 1–5 years of age in Mozambique.[21] The model has also been used to predict the potential epidemiologic impact of such a vaccine,[58] and the cost-effectiveness of introducing it via the EPI.[59] To make these predictions, we incorporated costing data[59,60] and a model for the health system currently in place in a low-income country context, based largely on data from Tanzania.[61]

In addition, we have also made progress on developing models of within-host dynamics of malaria.[62] This work is intended to complement earlier within-host models,[13,63] specifically with a view to providing insights relevant to modeling vaccination, useful for informing the epidemiologic models. The within-host models have been fitted to data from malariatherapy patients and lead to conclusions that are particularly relevant to the modeling of asexual blood-stage vaccination.

STRATEGY OF EPIDEMIOLOGIC MODELING

Processes modeled. To give reasonable predictions, our models need to simulate the processes that may be affected by vaccination, and also to capture the relationships between these processes and outcomes of public health importance. Figure 2 gives a simplified illustration of how these processes and outcomes relate to the malaria transmission cycle. For our model, we use as input the seasonal pattern of transmission (measured by the entomologic inoculation rate [EIR]), and make predictions of the consequent infection rate of humans.[54] We then consider how this relationship may be modified by naturally acquired immunity[54] or by vaccination.[56]

We embed an empirical description of within-host asexual parasite densities in the model for the infection process to give stochastic predictions of parasite densities as a function of the age of a malaria infection, and model the effect of immunity to asexual blood stages by considering how the distribution of parasite densities is modified in the semi-immune host.[50] This model for immunity provides a straightforward basis for analyzing possible effects of asexual blood stage vaccines, which can be simulated by a function that reduces parasite densities.

We analyze the relationship between asexual parasite densities and infectivity to the vector in malariatherapy patients to derive a model for the transmission to the mosquito vector.[53] This relationship is used to simulate the transmission-blocking effects of vaccines. This makes use of the simulated population distribution of parasite densities to predict the human infectious reservoir for *P. falciparum*.[49]

Acute episodes of clinical malaria are predicted to occur as a consequence of high parasite densities.[55] A further stochastic sub-model is used to specify when these lead to severe disease or malaria-related mortality.[51,52]

An important simplification in our strategy is to avoid predicting those intermediate variables whose quantitative relationships with epidemiologic outcomes are very uncertain. We do not dissect protection during the pre-erythrocytic stages of infection into that against sporozoites and that against liver stages because effects on these different pre-erythrocytic stages cannot be distinguished in large-scale field studies. We do not model levels of immune effector molecules, such as antibodies or cytokines. We consider levels of gametocytemia only as part of the validation of the sub-model for infectiousness because the quantitative relationships between gametocytemia and infectiousness to mosquitoes are problematic.[53,64] These simplifications do not compromise the ability of our models to make predictions of the effectiveness and cost-effectiveness of vaccines.

Stochastic simulation. We use individual-based simulations with five-day time steps to implement our models of *P. falciparum* epidemiology. This approach makes it possible to model populations of hosts and infections, each characterized by a set of continuous and state variables (parasite densities, infection durations, and immune status variables for individual hosts). This approach can allow more realistic consideration of the stochastic interactions between individual hosts
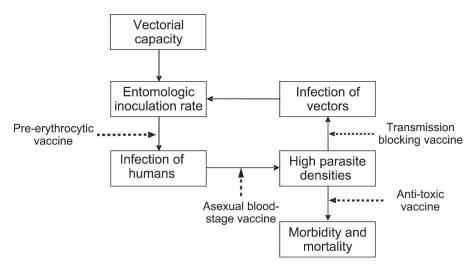

FIGURE 2. Simplified diagram of the malaria transmission cycle. Dashed arrows indicate the points at which vaccines are intended to act.

and pathogens than the use of compartment models.[64] It provides estimates of distributions of outcomes, rather than only predicting averages. A disadvantage is that it is computationally more intensive than the deterministic alternatives. All modules shown in Figure 3 (except that to predict the prevalence of anemia) were implemented using the FORTRAN programming language using numerical and statistical libraries provided by the Numerical Algorithms Group (http://www.nag.co.uk/). These core components were wrapped in a application written in Java (http://sun.java.com) and accessed via the Java Native Interface (http://java.sun.com/j2se/1.4.2/docs/guide/jni)[65] for three reasons. First, implementation of data-holding components, which provide the input data for the core model and store the generated results, is easier with a programming language that supports object-oriented programming. Second, we developed a graphical user interface to simplify the process of defining simulation scenarios and to facilitate exploratory analysis of model predictions. Third, the use of the Java Remote Method Invocation (http://java.sun.com/products/jdk/rmi/)[66] allowed us to distribute the computation to a large number of computers and thereby cope with the considerable computational requirements posed by the data fitting process. The model for prediction of anemia was implemented as part of the analysis module in Java.

Fitting to real data. The uncertainty inherent in complex models needs to be minimized by ensuring that all elements of the model conform as much as possible to reality. There have been only limited efforts to optimize complex dynamic models of malaria by formal fitting to field data.[9,67–69] Even these studies optimized only a limited number of parameters. Most previous malaria models have at best been only superficially validated against field observations.

In contrast, we have fitted different components of our model to a wealth of datasets from many different ecologic and epidemiologic settings. We then validated them by comparing our predictions with further field data. Stochastic simulations are more difficult to fit to data than are deterministic models. Our approach leads to implicit statistical models requiring many repeated simulations to make approximate parameter estimates.[70] We were able to fit these using a simulated annealing algorithm,[71,72] distributing simulations across our local computer network.

Modular structure. Since the computational demands and complexity of the fitting process meant that it was not feasible to fit our overall model to all the relevant data simultaneously, different sub-models were fitted separately. The analyses described in subsequent reports[49–55,73] contributed sub-models to the overall model of malaria epidemiology (Figure 3).
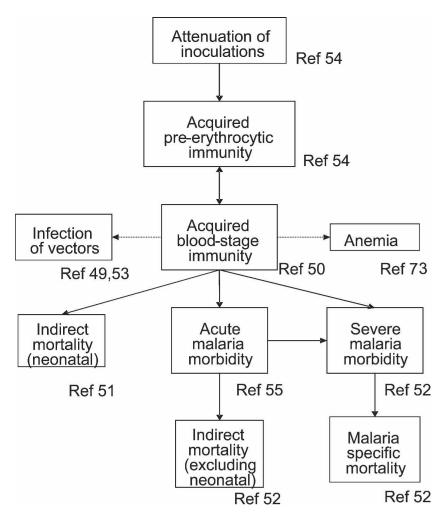

FIGURE 3.   Key processes and relationships simulated by the dynamic models of *Plasmodium falciparum* transmission and morbidity.

Our model for how infection rates are related to the EIR in the naive host[54] was fitted to data from The Gambia[74] and Kenya.[75] The core (parasitologic) model for infection and parasite densities[50,54] was jointly fitted to datasets from Ghana, Nigeria, and Tanzania. The sub-model to predict clinical episodes[55] was fitted to data from Senegal conditional on the parasitologic model and uses the same point estimates of the parameters of the parasitologic model. Similarly, the sub-model for severe malaria[52] is conditional on both the parasitologic and clinical sub-models. Those for mortality[52] depend on the parasitologic, clinical, and severe malaria sub-models (Figure 3) and, like the model for severe malaria, were fitted to rates from multiple African settings.

These sub-models were fitted to field data quantifying the relationship between malaria transmission and the outcome of interest. Each sub-model was thus fitted conditionally on the parameter estimates made at earlier stages in the fitting process (i.e., on the sub-models higher up in Figure 3). This approach made it possible for us to allow for the dynamic effects of the treatment of clinical episodes, an important consideration when we use the model to predict the impact of interventions.

The sub-models for the infection of the vector[49,53] and for anemia[73] were fitted to independent datasets. To make predictions of vector infection rates and of anemia prevalence we apply the estimated functions to the outputs of the parasitologic sub-model.

Equations. The equations of the epidemiologic model are summarized in Appendix 1. In view of the modular structure of the project, they are grouped around six main components: infection of the human host, characteristics of the simulated infections, infectivity to mosquitoes, acute morbidity, mortality, and anemia.

STRENGTHS AND LIMITATIONS OF OUR MODELING APPROACH

Strengths. It may be unrealistic to expect any model to deliver quantitative predictions of the cost-effectiveness of malaria vaccination with any degree of confidence. However our models can certainly suggest where to look for possible counter-intuitive impacts of vaccination. At each stage in our modeling approach, we have examined what are the main uncertainties that could impinge on the estimates of outcomes, and thus explored what are the important gaps in knowledge of malaria epidemiology. We also compare the fit of competing models, and thus choose between alternative model formulations. Although each component of the project is linked (Figure 3), each paper leads to its own conclusions. Many of these conclusions have bearing on vaccine development strategies independently of their consequences for quantitative predictions of vaccine impact.

Limitations. With all models of biology, there is a trade-off between parsimony and the fitting of details to what is know about the dynamics being modeled. A model is only useful if it represents a simplification, indicating which elements of the processes being analyzed are important. However, the better the fit to reality, the more likely are the predictions to be accurate. In the case of malaria the need for accurate models required simulation of many different processes. The requirement for a good fit to field data has thus committed us to developing a model with many different components and pa-

rameters. At present, some of the processes we modeled are ill-understood or lack relevant data, leading to uncertainties that cannot be captured by statistical measures of imprecision.

One role of modeling is to identify such gaps in knowledge. There are also other simplifications that limit the extent to which our models should be applied uncritically. The models developed so far do not address the issue of differences between ethnic groups in their response to infection, although such differences are known to exist within the savannah zone of West Africa,[76,77] the source of many of the data available to us, and are likely to be even more important in extensions of the model outside Africa. Our models do not consider effects of micro-heterogeneity in transmission within the human population.[78] This limits their applicability as a tool for estimating the basic reproductive number, and thus for predicting the conditions for elimination.

Our models do not capture all the epidemiologic phenomena that are relevant to immunity to malaria. In endemic areas, chronic asymptomatic infection appears to play a role in effective clinical immunity[79] and may be necessary for long-term maintenance of immune memory.[80] These phenomena, sometimes referred to as premunition, very likely involve several distinct immunologic mechanisms. In our models concomitant infections induce clinical immunity mainly by increasing the threshold level of parasitemia necessary for an acute malaria episode.[55] A further element is innate immunity to hepatic stages which could be stimulated by either hepatic or erythrocytic stages of *P. falciparum.* We allow for this implicitly by including density-dependent regulation of the infection process, but have so far not been able to explicitly model effects of erythrocytic infections on the control of hepatic stages.[54] We do not make any allowance for decay of either pre-erythrocytic or blood stage immunity because we have no good quantitative data from which to estimate rates of decay. The limited field data that do exist suggest that even exposure many years in the past provides important clinical protection.[81]

In the long-term, vaccines are likely to exert selective effects on parasite populations, and selection in favor of non-vaccine parasite genotypes has already been demonstrated in one phase IIb trial carried out in Papua New Guinea.[82] Selection of other parasite traits, such as virulence[83] is also possible but we contend that an adequate epidemiologic model is a pre-requisite for convincing models of such effects.[84]

CONCLUSION

In this introductory paper, we have provided a succinct overview of our approach for developing a dynamic mathematical model for prediction of the epidemiologic and economic impact of a malaria vaccine. An important strength of this framework is that it ties together an ensemble of interconnected sub-models validated against actual field data from various settings across Africa. In view of the complex malaria life cycle and gaps in our current knowledge, there are inherent limitations attached to some of these components, which in turn influence the overall model outcomes. However we are confident that the material presented in the remaining 14 papers provides a sound foundation on which improved models can be built. To the best of our knowledge, this is the most comprehensive population-based simulation of malaria yet

developed. It represents a major new tool for rational planning of malaria vaccine development, and can readily be adapted to assess efficacy and cost-effectiveness of other malaria control interventions used singly or in combination. This makes it possible to integrate epidemiologic and economic considerations in rational formulation of policy to reduce the intolerable burden of malaria.

Authors' addresses: Thomas Smith, Nicolas Maire, Amanda Ross, Fabrizio Tediosi, Guy Hutton, Jürg Utzinger, and Marcel Tanner, Swiss Tropical Institute, Socinstrasse 57, PO Box, CH-4002, Basel, Switzerland, Telephone: 41-61-284-8273, Fax: 41-61-284-8105, E-mails: Thomas-A.Smith@unibas.ch, nicolas.maire@unibas.ch, amanda.ross@unibas.ch, fabrizio.tediosi@unibas.ch, guy.hutton@ unibas.ch, juerg.utzinger@unibas.ch, and marcel.tanner@unibas.ch. Gerry F. Killeen, Ifakara Health Research and Development Centre, Ifakara, Kilombero District, Tanzania, Telephone: 255-748-477-118, Fax: 255-23-262-5312, E-mail: gkilleen@ihrdc.or.tz. Louis Molineaux, Peney-Dessus, CH-1242 Satigny, Geneva, Switzerland. Klaus Dietz, Department of Medical Biometry, University of Tübingen, Westbahnhofstrasse 55, 72070 Tübingen, Germany, Telephone: 49-7071-29-78253, Fax: 49-7071-29-5075, E-mail: klaus.dietz@ uni-tuebingen.de.

Reprint requests: Thomas Smith, Swiss Tropical Institute, Socinstrasse 57, PO Box, CH-4002, Basel, Switzerland.

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APPENDIX 1
EQUATIONS OF THE EPIDEMIOLOGIC MODEL
INFECTION OF THE HUMAN HOST[54]

$E_a(i,t)$, the age-adjusted entomologic inoculation rate (EIR) for individual i at time t, is given by

$$E_a(i,t) = E_{max}(t) \frac{A(a(i,t))}{A_{max}} \quad (1)$$

where, $A(a(i,t))$ is the average body surface area estimated for an individual of age $a(i,t)$ and A_{max} is the average surface area of people ≥ 20 years of age in the same population. $E_{max}(t)$ refers to the usual measure of the EIR computed from human bait collections. The force of infection is then

$$\lambda(i,t) = E_a(i,t) \left(S_{\infty} + \frac{1 - S_{\infty}}{1 + \frac{E_a(i,t)}{E^*}} \right) \left(S_{imm} + \frac{1 - S_{imm}}{1 + \left(\frac{X_p(i,t)}{X_p^*} \right)^{\gamma_p}} \right) \quad (2)$$

where $S_{imm}, X_p^*, E^*, \gamma_p, S_{\infty}$ are constants (Table 1) and:

$$X_p(i,t) = \int_{t-a(i,t)}^{t} E_a(i,\tau) d\tau. \quad (3)$$

The number of infections $h(i,t)$ introduced in time step t, is distributed as

$$h(i,t) \sim \text{Poisson}(\lambda(i,t)) \quad (4)$$

TABLE 1
Model parameter values

Parameter	Description	Units/dimension	Value
S_{∞}	Lower limit of success probability of inoculations at high $E_a(i,t)$	Proportion	0.049
E^*	Critical value of $E_a(i,t)$	Inoculations/person-night	0.032
S_{imm}	Lower limit of success probability of inoculations in immune individuals	Proportion	0.14
γ_p	Steepness of relationship between success of inoculation and $X_p(i,t)$	Dimensionless constant	2.04
X_p^*	Critical value of cumulative number of entomologic inoculations	Inoculations	1514.4
X_h^*	Critical value of cumulative number of infections	Infections	97.3
X_y^*	Critical value of cumulative number of parasite days	Parasite-days/μL $\times 10^{-7}$	3.5
X_v^*	Critical value of cumulative number of infections for variance in parasite densities	Infections	0.92
α_m	Maternal protection at birth	Dimensionless	0.90
a_m^*	Decay of maternal protection	Per year	2.53
D_x	Effect of concurrent co-infections	Infections	0
β_1	Effect of asexual density (lag 10 days) on expected gametocytemia (fixed)	Dimensionless	1
β_2	Effect of asexual density (lag 15 days) on expected gametocytemia	Dimensionless	0.46
β_3	Effect of asexual density (lag 20 days) on expected gametocytemia	Dimensionless	0.17
ρ	Location parameter for the distribution of the ratio of gametocytes to asexual parasites	Dimensionless	0.00031
η	Scale factor for probability that a mosquito becomes infected at any feed	Dimensionless	0.56
σ_0^2	Fixed variance component for densities	[ln(density)]^2	0.66
σ_g	Standard deviation of the distribution of the ratio of gametocytes to asexual paraistes	Dimensionless	3.91
α	Factor determining increase in $Y^*(i,t)$	Parasites^2 μL^{-2}day^{-1}	143,000
ϖ	Decay rate of pyrogenic threshold	Year^{-1}	2.5
Y_0^*	Pyrogenic threshold at birth	Parasites/μL	296.3
Y_1^*	Critical value of parasite density in determining increase in Y^*	Parasites/μL	0.60
Y_2^*	Critical value of $Y^*(i,t)$ in determining increase in $Y^*(i,t)$	Parasites/μL	6502.3
$Y_{B_1}^*$	Parasitemia threshold for severe episodes type B_1	Parasites/μL	784,000
F_0	Prevalence of co-morbidity/susceptibility at birth relevant to severe episodes (B_2)	Proportion	0.092
a_F^*	Critical age for co-morbidity	Years	0.117
φ_1	Case fatality for severe episodes in the community compared to hospital	Odds ratio	2.09
Q_n	Non-malaria intercept for infant mortality rate	Deaths/1,000 livebirths	49.5
Q_D	Co-morbidity intercept relevant to indirect mortality	Proportion	0.019
x_{MG}^*	Critical value of the simulated prevalence for ages 20–25 years	Proportion	0.19
μ_{max}	Upper limit of risk of neonatal mortality in primigravidae	Proportion	0.011
x_{PG}^*	Critical value of prevalence for neonatal mortality risk	Proportion	0.25
β_0	Intercept in anemia submodel	Log odds	−6.13
β_P	Effect of parasite prevalence	Log odds	12.5
p^*	Critical value of parasite prevalence	Proportion	2.84
β_{a1}	Magnitude of age effect	Per year	3.14
a^*	Critical age	Years	3.66
β_1	Age-prevalence interaction effect	Log odds	−0.75

CHARACTERISTICS OF THE SIMULATED INFECTIONS[50]

Each new infection j, initiated in individual i at time t_0 is assigned a duration of t_{max}, sampled from

$$\ln(\tau_{max}(i,j)) \sim \text{Normal}(5.13, 0.80) \quad (5)$$

The log density in the absence of previous exposure at each time point, $\tau = 0,1,\ldots,\tau_{max}(i,j)$ of the infection j in host i is then normally distributed with expectation

$$\ln(y_0(i, j, \tau)) = \ln d(i) + \ln(y_G(\tau, \tau_{max})) \quad (6)$$

where $y_G(\tau,\tau_{max})$ is an empirical description of malariatherapy patients from the Georgia hospital and $d(i)$ represents between-host variation drawn from a log-normal distribution with variance σ_i^2.

We measure exposure to asexual blood stages with

$$X_y(i, j, t) = \int_{t-a}^{t} Y(i,\tau)\, d\tau - \int_{t0,j}^{t} y(i, j, \tau)\, d\tau \quad (7)$$

where $Y(i,\tau)$ is the total parasite density of individual i at time τ and $y(i,j,\tau,)$ is the density in individual i for infection j at time τ, and

$$X_h(i,t) = \int_{t-a}^{t} h(i,\tau)\, d\tau - 1. \quad (8)$$

the expected log density for each concurrent infection is then

$$E(\ln(y(i, j, \tau))) = D_y D_h D_m \cdot \ln(y_0(i, j, \tau)) + \ln\left(\frac{D_x}{M(t)} + 1 - D_x\right) \quad (9)$$

where $M(t)$ is the total multiplicity of infection and

$$D_y = \frac{1}{1 + \dfrac{X_y(i, j, t)}{X_y^*}}, \quad (10)$$

$$D_h = \frac{1}{1 + \dfrac{X_y(i,t)}{X_h^*}}, \quad (11)$$

$$D_m = 1 - \alpha_m \exp\left(-\frac{0.693a}{a_m^*}\right) \quad (12)$$

and X_y^*, X_h^*, D_x, a_m^*, and α_m, are further constants.

Variation within individual hosts is quantified by a term $\sigma_y^2(i,j,\tau)$, where

$$\sigma_y^2(i, j, \tau) = \frac{\sigma_0^2}{1 + \dfrac{X_h(i, t)}{X_v^*}} \quad (13)$$

and σ_0^2 and X_v^* are constants (Table 1). The simulated densities are specified using:

$$\ln(y(i, j, \tau)) \sim \text{Normal}(E(\ln(y(i, j, \tau))), \sigma_y^2(i, j, \tau)) \quad (14)$$

The total density at time t in host i is then the sum of the densities of the various co-infections j i.e.

$$Y(i,t) = \sum_j y(i, j, \tau(i, j)) \quad (15)$$

MODEL FOR INFECTIVITY OF THE HUMAN HOST[49,53]

Let

$$\Upsilon(i,t) = \beta_1 Y(i,t-2) + \beta_2 Y(i,t-3) + \beta_3 Y(i,t-4) \quad (16)$$

where t is in 5-day units, and

$$\ln(y_g(i,t)) \sim \text{Normal}(\ln(\rho\Upsilon(i,t)), \sigma_g^2) \quad (17)$$

where $\beta_1,\beta_2,\beta_3,\rho,\sigma_g^2$ are constants (Table 1). Define

$$\Pr(y_g(i,t) > y_g^*) = \Phi\left[\frac{\ln(\rho\Upsilon(i,t)) - \ln(y_g^*)}{\sigma_g}\right] = \Phi\left[\frac{\ln(\Upsilon(i,t))}{\sigma_g} + \rho^*\right] \quad (18)$$

where Φ is the cumulative normal distribution, y_g^* is the density of female gametocytes necessary for infection of the mosquito, and $\rho^* = (\ln(\rho) - \ln(y_g^*))/\sigma_g$. Then the proportion of mosquitoes that are infected feeding on individual i at time t is

$$I_m(i,t) = [\Pr(y_g(i,t) > y_g^*)]^2 \quad (19)$$

and the probability that a mosquito becomes infected at any feed is:

$$\kappa_u(t) = \eta \frac{\sum_i (A(a(i,t)) I_m(i,t))}{\sum_i A(a(i,t))} \quad (20)$$

where η is a constant scale factor.

Define $\kappa_u^{(0)}(t)$ as the value of $\kappa_u(t)$ in the simulation of an equilibrium scenario to which an intervention has been applied. Let $E_{max}^{(0)}(t + l_v)$ be the corresponding entomologic inoculation rate. $\kappa_u^{(1)}(t)$ and $E_{max}^{(1)}(t + l_v)$ are the corresponding values for the intervention scenario. Then

$$E_{max}^{(1)}(t + l_v) = \frac{E_{max}^{(0)}(t + l_v)\, \kappa_u^{(1)}(t)}{\kappa_u^{(0)}(t)} \quad (21)$$

where l_v corresponds to the duration of the sporogonic cycle in the vector, which we approximate with two time steps (10 days). ($E_{max}^{(0)}(t + l_v)/\kappa_u^{(0)}(t)$ is the total vectorial capacity).

ACUTE MORBIDITY[52,55]

An episode of acute morbidity occurs in individual i, at time t, with probability

$$P_m(i,t) = \frac{Y_{max}(i,t)}{Y^*(i,t) + Y_{max}(i,t)} \quad (22)$$

where Y^* is the pyrogenic threshold and Y_{max} is the maximum density of five daily densities sampled during the five-day time interval t. The pyrogenic threshold evolves over time via:

$$\frac{dY^*(i,t)}{dt} = \frac{\alpha Y(i,t)}{(Y_1^* + Y(i,t))(Y_2^* + Y^*(i,t))} - \varpi Y^*(i,t) \quad (23)$$

with the initial condition $Y^*(i, 0) = Y_0^*$ at the birth of the host and α, ϖ, Y_1^*, and Y_2^* are constants.

We consider two different classes of severe episodes, B_1 and B_2. P_{B1} (i,t) is the probability that an acute episode (A) is a class B_1 severe episode and is specified using

$$P_{B_1}(i,t) = \mathrm{Pr}(H(i,t) \in B_1 | H(i,t) \in A) = \frac{Y_{\max}(i,t)}{Y^*_{B_1} + Y_{\max}(i,t)} \tag{24}$$

where $Y^*_{B_1}$ is a constant and $H(i,t)$ is the clinical status.

The second subset of severe malaria episodes (B_2) occur when an otherwise uncomplicated malaria episode happens to coincide with some other insult, which occurs with risk

$$F(a(i,t)) = \frac{F_0}{1 + \left(\frac{a(i,t)}{a^*_F}\right)} \tag{25}$$

where F_0 is the limiting value of $F(a(i,t))$ at birth, and a^*_F is the age at which it is halved.

The probability that an episode belonging to class B_2 occurs at time t, conditional on there being a clinical episode at that time is P_{B2} (i,t) where

$$P_{B_2}(i,t) = \mathrm{Pr}(H(i,t) \in B_2 | H(i,t) \in A) = F(a(i,t)) \tag{26}$$

The age and time specific risk of severe malaria morbidity conditional on a clinical episode is then given by

$$P_B(i,t) = P_{B_1}(i,t) + P_{B_2}(i,t) - P_{B_1}(i,t)P_{B_2}(i,t), \tag{27}$$

MORTALITY[52]

Malaria deaths in hospital are a random sample of those severe malaria cases deemed to be admitted, with age-dependent sampling fraction $Q_h(a)$, the hospital case fatality rate, derived from the data of Reyburn and others.[86]

We estimate the severe malaria case fatality in the community, $Q_c(a)$ for age group a with

$$Q_c(a) = \frac{Q_h(a)\varphi_1}{1 - Q_h(a) + Q_h(a)\varphi_1}, \tag{28}$$

where φ_1, the estimated odds ratio for death in the community compared to death in in-patients, is an age-independent constant and $Q_h(a)$ is the hospital case fatality rate. Malaria mortality is the sum of the hospital and community malaria deaths.

The risk of neonatal mortality attributable to malaria (death in class D_1) in first pregnancies is set equal to $0.3\mu_{PG}$ where μ_{PG} is given by

$$\mu_{PG} = \mu_{\max}\left[1 - \exp\left(-\frac{x_{PG}}{x^*_{PG}}\right)\right], \tag{29}$$

where x_{PG} is related to x_{MG}, the prevalence in simulated individuals 20–24 years of age via

$$x_{PG} = 1 - \frac{1}{1 + \left(\frac{x_{MG}}{x^*_{MG}}\right)} \tag{30}$$

and x^*_{MG} and x^*_{PG} are constants (Table 1).

An indirect death in class D_2 is provoked at time t, conditional on there being a clinical episode at that time, with probability P_{D2} (i,t) where
$P_{D_2}(i,t) = \mathrm{Pr}(H(i,t)\in D_2 | H(i,t)\in A)$ and

$$P_{D_2}(i,t) = \frac{Q_D}{1 + \left(\frac{a(i,t)}{a^*_F}\right)} \tag{31}$$

where Q_D is limiting value of P_{D2} (i,t) at birth and a^*_F is a constant. Deaths in class D_2 occur 30 days (six time steps) after the provoking episodes.

ANEMIA[73]

The prevalence of anemia, $p_A(a,t)$, in age group with mid-age a, at time t is specified by

$$\mathrm{logit}(p_A(a,t)) = \beta_0 + \frac{\beta_{a1}a^*}{a^* + a} + \frac{\beta_P p_P(a,t)}{p^* + p_P(a,t)} + \beta_1 p_P(a,t)\log(a) \tag{32}$$

where $p_P(a,t)$ is the prevalence of patent parasitemia in the age group and $\beta_0, \beta_P, p^*, \beta_{a1}, a^*, \beta_1$ are constants.