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Determining Important Parameters in the Spread of Malaria Through the Sensitivity Analysis of a Mathematical Model

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Abstract We perform sensitivity analyses on a mathematical model of malaria transmission to determine the relative importance of model parameters to disease transmission and prevalence. We compile two sets of baseline parameter values: one for areas of high transmission and one for low transmission. We compute sensitivity indices of the reproductive number (which measures initial disease transmission) and the endemic equilibrium point (which measures disease prevalence) to the parameters at the baseline values. We find that in areas of low transmission, the reproductive number and the equilibrium proportion of infectious humans are most sensitive to the mosquito biting rate. In areas of high transmission, the reproductive number is again most sensitive to the mosquito biting rate, but the equilibrium proportion of infectious humans is most sensitive to the human recovery rate. This suggests strategies that target the mosquito biting rate (such as the use of insecticide-treated bed nets and indoor residual spraying) and those that target the human recovery rate (such as the prompt diagnosis and treatment of infectious individuals) can be successful in controlling malaria.

Keywords Malaria · Epidemic model · Sensitivity analysis · Reproductive number · Endemic equilibria

1. Introduction

Malaria is an infectious disease caused by the *Plasmodium* parasite and transmitted between humans through bites of female *Anopheles* mosquitoes. There are about 300–500 million annual cases of malaria worldwide with 1–3 million deaths (Roll Back Malaria

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Partnership, 2005). About 40% of the world's population live in malaria endemic areas. Although the incidence of malaria had been rising in the last few decades due to increasing parasite drug-resistance and mosquito insecticide-resistance, recently significant resources have been made available to malaria control programs worldwide to reduce malaria incidence and prevalence. Comparative knowledge of the effectiveness and efficacy of different control strategies is necessary to design useful and cost-effective malaria control programs. Mathematical modeling of malaria can play a unique role in comparing the effects of control strategies, used individually or in packages. We begin such a comparison by determining the relative importance of model parameters in malaria transmission and prevalence levels.

The mathematical modeling of malaria transmission has a long history, beginning with Ross (1911) and MacDonald (1957), and continuing through Anderson and May (1991). In a Ph.D. dissertation, Chitnis (2005) described a compartmental model for malaria transmission, based on a model by Ngwa and Shu (2000); defined a reproductive number, R_0, for the expected number of secondary cases that one infected individual would cause through the duration of the infectious period; and showed the existence and stability of disease-free equilibrium points, x_{dfe}, and endemic equilibrium points, x_{ee}. He also computed the sensitivity indices for R_0 and x_{ee} to the parameters in the model. Chitnis et al. (2006) presented a similar bifurcation analysis of an extension to the model in Chitnis (2005), defining R_0 and showing the existence and stability of x_{dfe} and x_{ee}.

Here we extend the model in Chitnis et al. (2006) and evaluate the sensitivity indices of R_0 and x_{ee}. This model is different from previous models in that it generalizes the mosquito biting rate, and includes immigration in a logistic model for the human population with disease-induced mortality. Previous models assumed that mosquitoes have a fixed number of bites per unit time. This model allows the number of mosquito bites on humans to depend on both, the mosquito and human, population sizes. This allows a more realistic modeling of situations where there is a high ratio of mosquitoes to humans, and where human availability to mosquitoes is reduced through vector control interventions. Human migration is common in most parts of the malaria-endemic world and plays an important role in malaria epidemiology. As in Ngwa and Shu (2000), this model also allows humans to be temporarily immune to the disease, while still transmitting malaria to mosquitoes.

We compile two reasonable sets of baseline values for the parameters in the model: one for areas of high transmission, and one for areas of low transmission. For some parameters, we use values published in available literature, while for others, we use realistically feasible values. We then compute the sensitivity indices of R_0 and x_{ee} to both sets of baseline parameter values. As R_0 is related to initial disease transmission and x_{ee} represents equilibrium disease prevalence, an evaluation of these sensitivity indices allows us to determine the relative importance of different parameters in malaria transmission and prevalence. We thus look at the relative importance of the parameters in four different situations:

- The initial rate of disease transmission in areas of low transmission
- The equilibrium disease prevalence in areas of low transmission
- The initial rate of disease transmission in areas of high transmission
- The equilibrium disease prevalence in areas of high transmission

A knowledge of the relative importance of parameters can help guide in developing efficient intervention strategies in malaria-endemic areas where resources are scarce.

We first summarize the model and analysis from Chitnis et al. (2006). We then present the baseline parameter values, the sensitivity indices of R_0 and x_{ee} for these baseline values, and their interpretation. Appendix A contains data from literature and our reasons for choosing the baseline parameter values. The second Appendix describes the methodology of the sensitivity analysis.

2. Mathematical model and analysis

The malaria model (Fig. 1) (Chitnis et al., 2006) and the state variables (Table 1) with parameters in Table 2 satisfy,

$$\frac{dS_h}{dt} = \Lambda_h + \psi_h N_h + \rho_h R_h - \lambda_h(t) S_h - f_h(N_h) S_h, \tag{1a}$$

$$\frac{dE_h}{dt} = \lambda_h(t) S_h - \nu_h E_h - f_h(N_h) E_h, \tag{1b}$$

$$\frac{dI_h}{dt} = \nu_h E_h - \gamma_h I_h - f_h(N_h) I_h - \delta_h I_h, \tag{1c}$$

$$\frac{dR_h}{dt} = \gamma_h I_h - \rho_h R_h - f_h(N_h) R_h, \tag{1d}$$

$$\frac{dS_v}{dt} = \psi_v N_v - \lambda_v(t) S_v - f_v(N_v) S_v, \tag{1e}$$

$$\frac{dE_v}{dt} = \lambda_v(t) S_v - \nu_v E_v - f_v(N_v) E_v, \tag{1f}$$

$$\frac{dI_v}{dt} = \nu_v E_v - f_v(N_v) I_v, \tag{1g}$$

where, $N_h = S_h + E_h + I_h + R_h$, $N_v = S_v + E_v + I_v$, and,

$$f_h(N_h) = \mu_{1h} + \mu_{2h} N_h,$$

$$f_v(N_v) = \mu_{1v} + \mu_{2v} N_v,$$

$$\lambda_h = \frac{\sigma_v N_v \sigma_h}{\sigma_v N_v + \sigma_h N_h} \cdot \beta_{hv} \cdot \frac{I_v}{N_v},$$

$$\lambda_v = \frac{\sigma_v \sigma_h N_h}{\sigma_v N_v + \sigma_h N_h} \cdot \left(\beta_{vh} \cdot \frac{I_h}{N_h} + \tilde{\beta}_{vh} \cdot \frac{R_h}{N_h} \right).$$

All parameters are strictly positive with the exception of the disease-induced death rate, δ_h, which is nonnegative. The mosquito birth rate is greater than the density-independent mosquito death rate: $\psi_v > \mu_{1v}$, ensuring that there is a stable positive mosquito population.
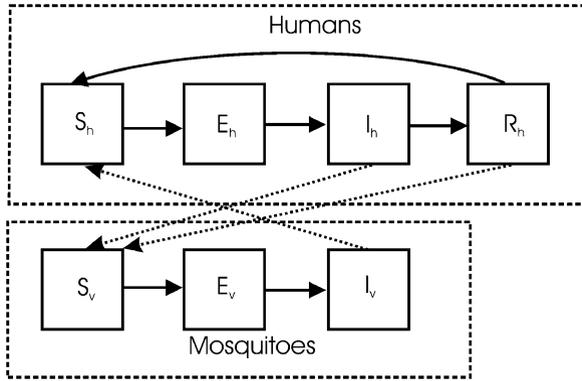
Fig. 1 Susceptible humans, S_h, can be infected when they are bitten by infectious mosquitoes. They then progress through the exposed, E_h, infectious, I_h, and recovered, R_h, classes, before reentering the susceptible class. Susceptible mosquitoes, S_v, can become infected when they bite infectious or recovered humans. The infected mosquitoes then move through the exposed, E_v, and infectious, I_v, classes. Both species follow a logistic population model, with humans having additional immigration and disease-induced death. Birth, death, and migration into and out of the population are not shown in the figure.

Table 1 The state variables for the original malaria model (1) and for the malaria model with scaled population sizes (2)

S_h:	Number of susceptible humans
E_h:	Number of exposed humans
I_h:	Number of infectious humans
R_h:	Number of recovered (immune and asymptomatic, but slightly infectious) humans
S_v:	Number of susceptible mosquitoes
E_v:	Number of exposed mosquitoes
I_v:	Number of infectious mosquitoes
e_h:	Proportion of exposed humans
i_h:	Proportion of infectious humans
r_h:	Proportion of recovered (immune and asymptomatic, but slightly infectious) humans
N_h:	Total human population
e_v:	Proportion of exposed mosquitoes
i_v:	Number of infectious mosquitoes
N_v:	Total mosquito population

We scale the population sizes in each class by the total population sizes to derive,

$$\frac{de_h}{dt} = \left(\frac{\sigma_v \sigma_h N_v \beta_{hv} i_v}{\sigma_v N_v + \sigma_h N_h} \right)(1 - e_h - i_h - r_h) - \left(\nu_h + \psi_h + \frac{\Lambda_h}{N_h} \right) e_h + \delta_h i_h e_h, \quad (2a)$$

$$\frac{di_h}{dt} = \nu_h e_h - \left(\gamma_h + \delta_h + \psi_h + \frac{\Lambda_h}{N_h} \right) i_h + \delta_h i_h^2, \quad (2b)$$

$$\frac{dr_h}{dt} = \gamma_h i_h - \left(\rho_h + \psi_h + \frac{\Lambda_h}{N_h} \right) r_h + \delta_h i_h r_h, \quad (2c)$$

$$\frac{dN_h}{dt} = \Lambda_h + \psi_h N_h - (\mu_{1h} + \mu_{2h} N_h) N_h - \delta_h i_h N_h, \quad (2d)$$

Table 2 The parameters for the malaria model (2) and their dimensions (Chitnis et al., 2006)

Λ_h:	Immigration rate of humans. Humans $\times$ Time^{-1}
ψ_h:	Per capita birth rate of humans. Time^{-1}
ψ_v:	Per capita birth rate of mosquitoes. Time^{-1}
σ_v:	Number of times one mosquito would want to bite humans per unit time, if humans were freely available. This is a function of the mosquito's gonotrophic cycle (the amount of time a mosquito requires to produce eggs) and its anthropophilic rate (its preference for human blood). Time^{-1}
σ_h:	The maximum number of mosquito bites a human can have per unit time. This is a function of the human's exposed surface area and any vector control interventions used by the human to reduce exposure to mosquitoes. Time^{-1}
β_{hv}:	Probability of transmission of infection from an infectious mosquito to a susceptible human given that a contact between the two occurs. Dimensionless
β_{vh}:	Probability of transmission of infection from an infectious human to a susceptible mosquito given that a contact between the two occurs. Dimensionless
$\tilde{\beta}_{vh}$:	Probability of transmission of infection from a recovered (asymptomatic carrier) human to a susceptible mosquito given that a contact between the two occurs. Dimensionless
ν_h:	Per capita rate of progression of humans from the exposed state to the infectious state. $1/\nu_h$ is the average duration of the latent period. Time^{-1}
ν_v:	Per capita rate of progression of mosquitoes from the exposed state to the infectious state. $1/\nu_v$ is the average duration of the latent period. Time^{-1}
γ_h:	Per capita recovery rate for humans from the infectious state to the recovered state. $1/\gamma_h$ is the average duration of the infectious period. Time^{-1}
δ_h:	Per capita disease-induced death rate for humans. Time^{-1}
ρ_h:	Per capita rate of loss of immunity for humans. $1/\rho_h$ is the average duration of the immune period. Time^{-1}
μ_{1h}:	Density independent part of the death (and emigration) rate for humans. Time^{-1}
μ_{2h}:	Density dependent part of the death (and emigration) rate for humans. Humans^{-1} $\times$ Time^{-1}
μ_{1v}:	Density independent part of the death rate for mosquitoes. Time^{-1}
μ_{2v}:	Density dependent part of the death rate for mosquitoes. Mosquitoes^{-1} $\times$ Time^{-1}

$$\frac{de_v}{dt} = \left(\frac{\sigma_v \sigma_h N_h}{\sigma_v N_v + \sigma_h N_h} \right) (\beta_{vh} i_h + \tilde{\beta}_{vh} r_h)(1 - e_v - i_v) - (\nu_v + \psi_v)e_v, \tag{2e}$$

$$\frac{di_v}{dt} = \nu_v e_v - \psi_v i_v, \tag{2f}$$

$$\frac{dN_v}{dt} = \psi_v N_v - (\mu_{1v} + \mu_{2v} N_v)N_v, \tag{2g}$$

where the new state variables are also described in Table 1.

In this model, σ_v is the rate at which a mosquito would like to bite a human, and σ_h is the maximum number of bites that a human can have per unit time. Then $\sigma_v N_v$ is the total number of bites that the mosquitoes would like to achieve in unit time and $\sigma_h N_h$ is the availability of humans. The total number of mosquito-human contacts is half the harmonic mean of $\sigma_v N_v$ and $\sigma_h N_h$. The exposed classes, e_h and e_v, model the delay before infected humans and mosquitoes become infectious. While in humans, this period is short and its effect on transmission may be ignored, in mosquitoes, this delay is important because it is on the same order as their expected life span. Thus, many infected mosquitoes die before they become infectious.

The model also includes an immigration term into the susceptible class (that is, independent of the total population size). This ignores the immigration of exposed, infectious,

and recovered humans. While the exposed period is short and there would, therefore, be few exposed humans, and sick infectious humans are less likely to travel; the exclusion of immigrating recovered humans is a simplifying assumption.

The recovered class captures the difference between infection and disease in malaria. In hyperendemic areas, most adults are immune in the sense that while they have the malaria parasite in their blood stream and are infectious to mosquitoes, they do not suffer from clinical malaria. In the model, infectious humans move to the recovered class at a constant per capita rate, where they are still infective to mosquitoes (but less infective than infectious humans) and do not suffer from additional disease-induced mortality. The model assumes that the recovered humans move back to the susceptible class at a constant per capita rate. This is a simplifying assumption because immunity in malaria is dependent on the inoculation rate. However, in the case where transmission levels are relatively stable, the inoculation rate would approach a constant value and, therefore, the rate of loss of immunity would also approach a constant value. As we conduct our sensitivity analyses around equilibrium points, this assumption is reasonable.

The model (2) is epidemiologically and mathematically well posed in the domain,

$$
\mathcal{D} = \left\{ \begin{pmatrix} e_h \\ i_h \\ r_h \\ N_h \\ e_v \\ i_v \\ N_v \end{pmatrix} \in \mathbb{R}^7 \left| \begin{array}{c} e_h \geq 0, \\ i_h \geq 0, \\ r_h \geq 0, \\ e_h + i_h + r_h \leq 1, \\ N_h > 0, \\ e_v \geq 0, \\ i_v \geq 0, \\ e_v + i_v \leq 1, \\ N_v > 0 \end{array} \right. \right\}.
\tag{3}
$$

We denote points in $\mathcal{D}$ by $x = (e_h, i_h, r_h, N_h, e_v, i_v, N_v)$. This domain is valid epidemiologically as the scaled populations, e_h, i_h, r_h, e_v, and i_v are all nonnegative and have sums over their species type that are less than or equal to 1. The human and mosquito populations, N_h and N_v, are positive. For initial conditions in $\mathcal{D}$, the model (2) has a unique solution that exists and remains in $\mathcal{D}$ for all time $t \geq 0$ (Chitnis et al., 2006, Theorem 2.1).

Disease-free equilibrium points are steady state solutions where there is no disease. We define the "*diseased*" classes as the human or mosquito populations that are either exposed, infectious or recovered; that is, e_h, i_h, r_h, e_v, and i_v. The positive equilibrium human and mosquito population sizes, in the absence of disease, for (2) are

$$
N_h^* = \frac{(\psi_h - \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}}{2\mu_{2h}} \quad \text{and} \quad N_v^* = \frac{\psi_v - \mu_{1v}}{\mu_{2v}}.
\tag{4}
$$

The model (2) has exactly one equilibrium point, $x_{\mathrm{dfe}} = (0, 0, 0, N_h^*, 0, 0, N_v^*)$, with no disease in the population (in the intersection of $\mathcal{D}$ and the boundary of the positive orthant in $\mathbb{R}^7$) (Chitnis et al., 2006, Theorem 3.1).

The reproductive number, R_0, is the expected number of secondary infections that one infectious individual (human or mosquito) would create over the duration of the infectious period provided that all other members of both populations are susceptible,

$$
R_0 = \sqrt{K_{vh}K_{hv}},
\tag{5}
$$

with,

$$K_{hv} = \left(\frac{\nu_v}{\nu_v + \mu_{1v} + \mu_{2v} N_v^*} \right) \cdot \frac{\sigma_v \sigma_h N_h^*}{\sigma_v N_v^* + \sigma_h N_h^*} \cdot \beta_{hv} \cdot \left(\frac{1}{\mu_{1v} + \mu_{2v} N_v^*} \right), \tag{6a}$$

$$K_{vh} = \left(\frac{\nu_h}{\nu_h + \mu_{1h} + \mu_{2h} N_h^*} \right) \cdot \frac{\sigma_v N_v^* \sigma_h}{\sigma_v N_v^* + \sigma_h N_h^*} \cdot \left(\frac{1}{\gamma_h + \delta_h + \mu_{1h} + \mu_{2h} N_h^*} \right)$$

$$\times \left[\beta_{vh} + \tilde{\beta}_{vh} \cdot \left(\frac{\gamma_h}{\rho_h + \mu_{1h} + \mu_{2h} N_h^*} \right) \right]. \tag{6b}$$

The disease-free equilibrium point, x_{dfe}, is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$ (Chitnis et al., 2006), Theorem 3.3. Note that the number of new infections in humans that one human causes through his/her infectious period is R_0^2, not R_0. Because this definition of R_0 (5) is based on the next generation operator approach (Diekmann et al., 1990), it counts the number of new infections from one generation to the next. That is, the number of new infections in mosquitoes counts as one generation.

Endemic equilibrium points are steady state solutions where the disease persists in the population (all state variables are positive). Theorems 4.1 and 4.2 in Chitnis et al. (2006) state that there is a transcritical bifurcation at $R_0 = 1$, and there exists at least one endemic equilibrium point for all values of $R_0 > 1$. Typically in epidemiological models, bifurcations at $R_0 = 1$ tend to be supercritical (i.e., positive endemic equilibria exist for $R_0 > 1$ near the bifurcation point). Theorem 4.3 in Chitnis et al. (2006) states that in the absence of disease-induced death ($\delta_h = 0$), the transcritical bifurcation at $R_0 = 1$ is supercritical (forward). However, this model (2) can exhibit a subcritical bifurcation (i.e., positive endemic equilibria exist for $R_0 < 1$ near the bifurcation point) for some positive values of δ_h.

3. Baseline parameter values

We show baseline values and ranges in Table 3 for the parameters described in Table 2. We include two sets of baseline values: one for areas of high transmission and one for low transmission (as measured by R_0). In Appendix A, we describe our reasons for using these values and give references where available. We estimate some parameter values from published studies and country-wide data. For location specific parameters, such as migration rates, we pick realistically feasible values. For parameters concerning human populations, we pick values representing villages, small towns, or small regions. We assume high transmission occurs in parts of Africa and low transmission occurs in Asia and the Americas. We use two significant figure accuracy for all the parameters.

3.1. Low transmission

For the baseline parameters at low malaria transmission in Table 3, $R_0 = 1.1$ (corresponding to 1.3 new infections in humans from one infected human through the duration of the infectious (and recovered) period). There is only one locally asymptotically stable endemic equilibrium point in $\mathcal{D}$,

$$x_{\text{ee}} = (0.0029, 0.080, 0.10, 578, 0.024, 0.016, 2425). \tag{7}$$

Figure 2 shows graphs of a typical solution of the model (1) in the original variables.

Table 3 Baseline values and ranges for parameters for the malaria model (2). Descriptions of the parameters are in Table 2 and explanations for the values are in Appendix A

	Dimension	Baseline high	Baseline low	Range
Λ_h	Humans $\times$ Days^{-1}	0.033	0.041	0.0027–0.27
ψ_h	Days^{-1}	1.1×10^{-4}	5.5×10^{-5}	2.7×10^{-5}–1.4×10^{-4}
ψ_v	Days^{-1}	0.13	0.13	0.020–0.27
σ_v	Days^{-1}	0.50	0.33	0.10–1.0
σ_h	Days^{-1}	19	4.3	0.10–50
β_{hv}	1	0.022	0.022	0.010–0.27
β_{vh}	1	0.48	0.24	0.072–0.64
$\tilde{\beta}_{vh}$	1	0.048	0.024	0.0072–0.64
ν_h	Days^{-1}	0.10	0.10	0.067–0.20
ν_v	Days^{-1}	0.091	0.083	0.029–0.33
γ_h	Days^{-1}	0.0035	0.0035	0.0014–0.017
δ_h	Days^{-1}	9.0×10^{-5}	1.8×10^{-5}	0–4.1×10^{-4}
ρ_h	Days^{-1}	5.5×10^{-4}	2.7×10^{-3}	1.1×10^{-2}–5.5×10^{-5}
μ_{1h}	Days^{-1}	1.6×10^{-5}	8.8×10^{-6}	1.0×10^{-6}–1.0×10^{-3}
μ_{2h}	Humans^{-1} $\times$ Days^{-1}	3.0×10^{-7}	2.0×10^{-7}	1.0×10^{-8}–1.0×10^{-6}
μ_{1v}	Days^{-1}	0.033	0.033	0.0010–0.10
μ_{2v}	Mosquitoes^{-1} $\times$ Days^{-1}	2.0×10^{-5}	4.0×10^{-5}	1.0×10^{-6}–1.0×10^{-3}

3.2. High transmission

For the baseline parameters at high malaria transmission in Table 3, $R_0 = 4.4$ (corresponding to 20 new infections in humans from one infected human through the duration of the infectious (and recovered) period). There is only one locally asymptotically stable endemic equilibrium point in $\mathcal{D}$,

$$x_{\text{ee}} = (0.0059, 0.16, 0.77, 490, 0.15, 0.11, 4850). \tag{8}$$

Figure 3 shows graphs of a typical solution of the model (1) in the original variables.

4. Sensitivity analysis

In determining how best to reduce human mortality and morbidity due to malaria, it is necessary to know the relative importance of the different factors responsible for its transmission and prevalence. Initial disease transmission is directly related to R_0, and disease prevalence is directly related to the endemic equilibrium point, specifically to the magnitudes of e_h, i_h, r_h, e_v, and i_v. These variables are relevant to the individuals (humans and mosquitoes) who have some life stage of *Plasmodium* in their bodies. The proportion of infectious humans, i_h, is especially important because it represents the people who may be clinically ill, and is directly related to the total number of malarial deaths. We calculate the sensitivity indices of the reproductive number, R_0, and the endemic equilibrium point, x_{ee}, to the parameters in the model. These indices tell us how crucial each parameter is to disease transmission and prevalence. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values (since there are usually errors in data collection and presumed parameter values). Here we use it to discover parameters that have a high impact on R_0 and x_{ee}, and should be targeted by intervention strategies.
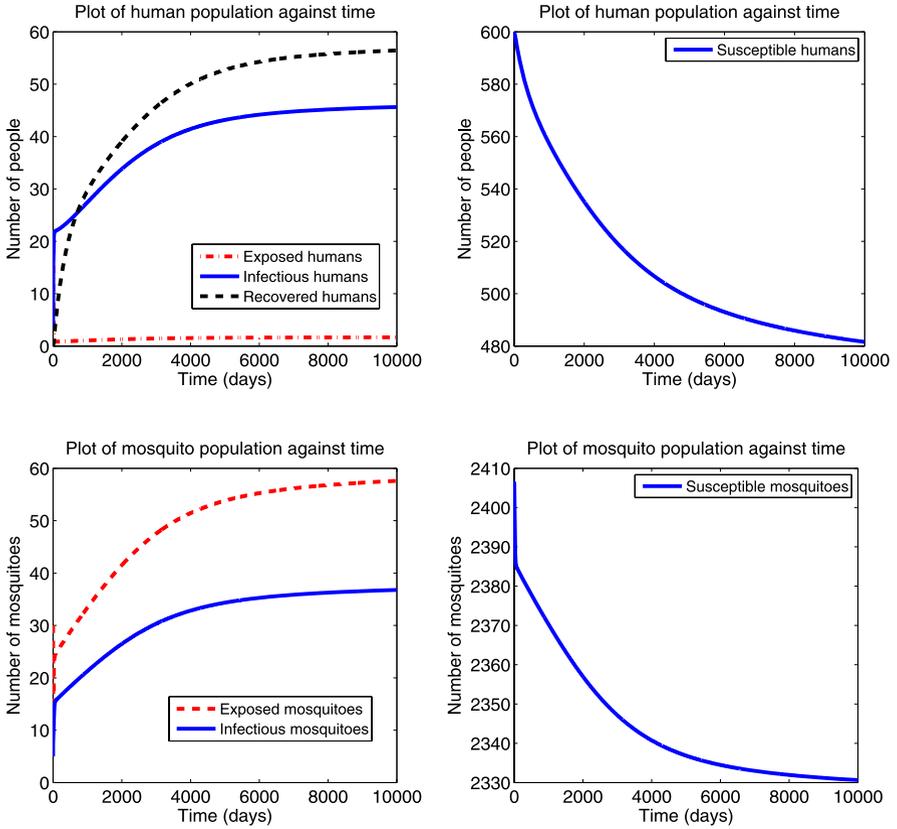
Fig. 2 Solution of the malaria model (1) with baseline parameter values defined in Table 3 for areas of low transmission. These parameters correspond to $R_0 = 1.1$. The initial condition is $S_h = 600$, $E_h = 20$, $I_h = 3$, $R_h = 0$, $S_v = 2400$, $E_v = 30$, and $I_v = 5$. The system approaches the endemic equilibrium point (7).

4.1. Description of sensitivity analysis

Sensitivity indices allow us to measure the relative change in a state variable when a parameter changes. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

Definition. The normalized forward sensitivity index of a variable, u, that depends differentiably on a parameter, p, is defined as:

$$\Upsilon_p^u := \frac{\partial u}{\partial p} \times \frac{p}{u}. \tag{9}$$
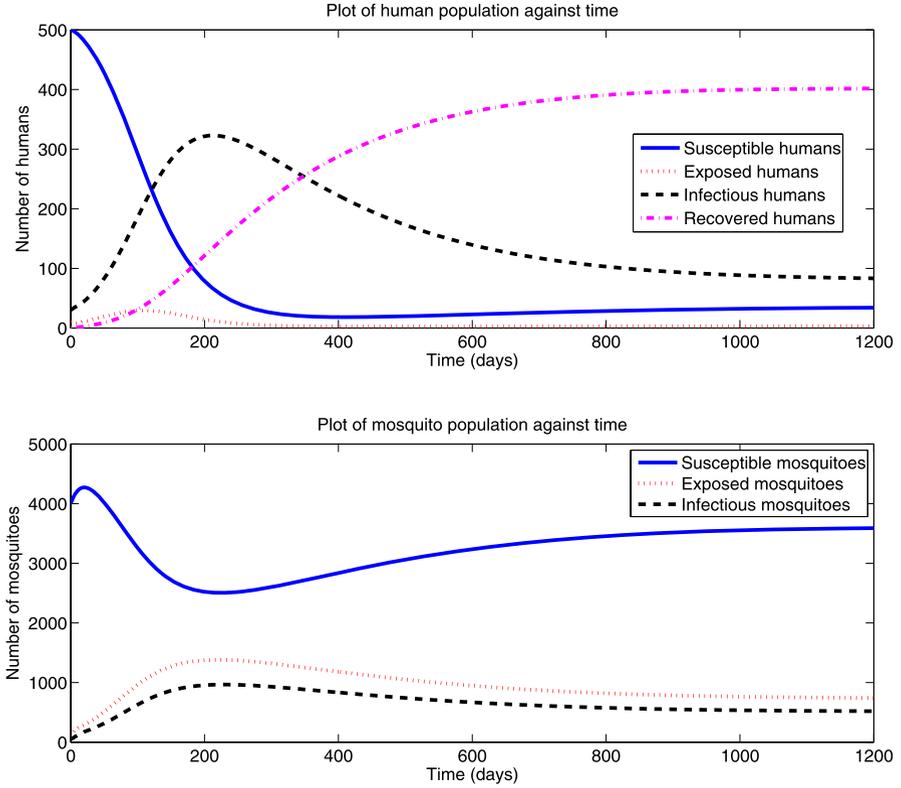
Fig. 3 Solution of the malaria model (1) with baseline parameter values defined in Table 3 for areas of high transmission. These parameters correspond to $R_0 = 4.4$. The initial condition is $S_h = 500$, $E_h = 10$, $I_h = 30$, $R_h = 0$, $S_v = 4000$, $E_v = 100$, and $I_v = 50$. The system approaches the endemic equilibrium point (8).

We show a detailed example of evaluating these sensitivity indices in Appendix B.1.

4.2. Sensitivity indices of R_0

As we have an explicit formula for R_0 (5), we derive an analytical expression for the sensitivity of R_0, $\Upsilon_p^{R_0} = \partial R_0 / \partial p \times p / R_0$, to each of the seventeen different parameters described in Table 2. For example, the sensitivity index of R_0 with respect to β_{hv},

$$\Upsilon_{\beta_{vh}}^{R_0} = \frac{\partial R_0}{\partial \beta_{vh}} \times \frac{\beta_{vh}}{R_0} = \frac{1}{2},$$

does not depend on any parameter values. Two important indices that also have an obvious structure are:

$$\Upsilon_{\sigma_v}^{R_0} = \frac{\sigma_h N_h^*}{\sigma_v N_v^* + \sigma_h N_h^*} \quad \text{and} \quad \Upsilon_{\sigma_h}^{R_0} = \frac{\sigma_v N_v^*}{\sigma_v N_v^* + \sigma_h N_h^*}. \tag{10}$$

Table 4 Sensitivity indices of R_0 (5) to parameters for the malaria model, evaluated at the baseline parameter values given in Table 3. The parameters are ordered from most sensitive to least. In both cases, of high and low transmission, the most sensitive parameter is the mosquito biting rate, σ_v, and the least sensitive parameter is the human rate of progression from the latent period, ν_h

Low transmission			High transmission		
	Parameter	Sensitivity index		Parameter	Sensitivity index
1	σ_v	+0.76	1	σ_v	+0.80
2	β_{hv}	+0.50	2	β_{hv}	+0.50
3	ψ_v	−0.46	3	ψ_v	−0.39
4	β_{vh}	+0.44	4	β_{vh}	+0.34
5	γ_h	−0.43	5	μ_{2v}	−0.30
6	ν_v	+0.31	6	γ_h	−0.30
7	μ_{2v}	−0.26	7	ν_v	+0.29
8	σ_h	+0.24	8	μ_{2h}	+0.20
9	μ_{2h}	+0.15	9	σ_h	+0.20
10	Λ_h	−0.10	10	ψ_h	−0.18
11	μ_{1v}	−0.088	11	$\tilde{\beta}_{vh}$	+0.16
12	ψ_h	−0.081	12	ρ_h	−0.12
13	$\tilde{\beta}_{vh}$	+0.055	13	Λ_h	−0.10
14	ρ_h	−0.053	14	μ_{1v}	−0.10
15	μ_{1h}	+0.012	15	μ_{1h}	+0.020
16	δ_h	−0.0025	16	δ_h	−0.012
17	ν_h	+0.00063	17	ν_h	+0.00086

However, most of the expressions for the sensitivity indices are complex with little obvious structure. We, therefore, evaluate the sensitivity indices at the baseline parameter values given in Table 3. The resulting sensitivity indices of R_0 to the seventeen different parameters in the model for areas of high and low transmission are shown in Table 4.

We replace σ_v and σ_h by the parameters,

$$\zeta = \frac{\sigma_v \sigma_h}{\sigma_v N_v^* + \sigma_h N_h^*} \quad \text{and} \quad \theta = \frac{\sigma_h}{\sigma_v}. \tag{11}$$

The parameter ζ is an intrinsic measure of the number of mosquito bites on humans. By definition, it is the number of mosquito bites on humans, per human, per mosquito, at the disease-free equilibrium population sizes, per unit time. We can measure the sensitivity of R_0 with respect to ζ, keeping θ fixed, that is, allowing both σ_v and σ_h to vary while keeping the ratio between them fixed. We find

$$\Upsilon_\zeta^{R_0} = \Upsilon_{\sigma_v}^{R_0} + \Upsilon_{\sigma_h}^{R_0} = 1. \tag{12}$$

In both cases of high and low transmission, the most sensitive parameter is the mosquito biting rate, σ_v. Other important parameters include the probability of disease transmission from infectious mosquitoes to susceptible humans, β_{hv}, the mosquito birth rate, ψ_v, and the human to mosquito disease transmission probability, β_{vh}. Since $\Upsilon_{\sigma_v}^{R_0} = +0.76$ in areas of low transmission, decreasing (or increasing) σ_v by 10% decreases (or increases) R_0 by 7.6%. Similarly, in either high or low transmission, as $\Upsilon_{\beta_{hv}}^{R_0} = +0.5$, increasing (or decreasing) β_{hv} by 10% increases (or decreases) R_0 by 5%.

We see from (10) that both, $\Upsilon_{\sigma_v}^{R_0}$ and $\Upsilon_{\sigma_h}^{R_0}$ depend on the human and mosquito demographic parameters. Changing the equilibrium population size of either humans or

mosquitoes would affect the sensitivity indices for the human and mosquito biting rates. Thus, to estimate the importance of the human or mosquito biting rates, we would need good knowledge of the population demographic parameters. However, $\Upsilon_\zeta^{R_0}$ does not depend on the equilibrium population sizes and provides a good estimate of the impact of the mosquito-human biting rates. When ζ is considered as a parameter (with θ constant), $\Upsilon_\zeta^{R_0}$ is the largest sensitivity index. Thus, reducing the number of contacts between humans and mosquitoes, through a reduction in either or both, the frequency of mosquito blood meals, and the number of bites that a human will tolerate would have the largest effect on disease transmission.[1]

For almost all parameters, the sign of the sensitivity indices of R_0 (i.e., whether R_0 increases or decreases when a parameter increases) agrees with an intuitive expectation. The only possible exception is the mosquito birth rate, ψ_v. For both, high and low transmission, the reproductive number decreases substantially as the mosquito birth rate increases. We would expect R_0 to increase because increasing ψ_v increases the number of mosquitoes. Our explanation for this counterintuitive result is as follows. The mosquito death rate is assumed to be density dependent. As the birth rate increases and the number of mosquitoes increases, the death rate also increases because the environment can only support a certain number of mosquitoes (given food restrictions and so on). Therefore, the average lifespan of the mosquito also decreases. Mathematically, at equilibrium population size, the per capita birth rate, ψ_v, is equal to the per capita death rate, $\mu_{1v} + \mu_{2v} N_v^*$. Thus, at equilibrium, ψ_v is also the per capita death rate, and with an exponential distribution for the death rate, $1/\psi_v$ is the expected lifespan of the mosquitoes. As the latent period of *Plasmodium* in mosquitoes is about the same as the lifespan of the mosquitoes, shortening the lifespan of the mosquito reduces the reproductive number because more infected mosquitoes die before they become infectious.

In summary, we see that any changes in ψ_v have two opposite effects. On the one hand, increasing ψ_v increases the number of mosquitoes which tends to increase R_0. On the other hand, increasing ψ_v also decreases the mosquito lifespan which tends to reduce R_0. The values of the other parameters help determine which of these two effects is stronger. In both lists of baseline parameters that we use, the effect of the reduction of the mosquito lifespan is stronger and R_0 decreases for an increase in ψ_v.

Also, as the equilibrium mosquito population size changes, the total number of mosquito bites on humans changes. Whether this change increases or decreases R_0 depends on the values of the mosquito and human equilibrium population sizes, and σ_v and σ_h.

We should expect, however, that for other parameter values, it is possible for R_0 to increase when ψ_v increases. For one such example, we evaluate the sensitivity indices for R_0 with parameter values exactly as in Table 3 for low transmission, except for $\mu_{1v} = 0.123$ (instead of $\mu_{1v} = 0.033$). The equilibrium mosquito population for these parameters is $N_v^* = 175$ and the most sensitive parameters are: $\Upsilon_{\mu_{1v}}^{R_0} = -8.4$, $\Upsilon_{\psi_v}^{R_0} = +8.1$, and $\Upsilon_{\sigma_v}^{R_0} = +0.98$. Thus, when there are few mosquitoes, R_0 increases when ψ_v increases. Note that in models where the mosquito death rate is assumed to be constant, any decrease in the emergence of mosquitoes would tend to reduce R_0.

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[1]Although it is not feasible to directly impact the mosquito's gonotrophic cycle, control strategies that reduce the human-biting rate, σ_h, would also reduce the mosquito's chances of feeding successfully, forcing it to search for another blood meal, thereby reducing the mosquito-biting rate, σ_v.

4.3. Sensitivity indices of x_{ee}

Since we do not have an explicit expression for the endemic equilibrium, x_{ee}, we cannot derive analytical expressions for the sensitivity indices. However, we numerically calculate the sensitivity indices at the parameter values given in Table 3 as shown in Appendix B. In a similar manner, we also calculate the sensitivity indices of x_{ee} with respect to ζ (11) while keeping θ constant. We show the resulting sensitivity indices of the state variables at the endemic equilibrium point, x_{ee}, to the parameters for areas of low and high transmission in Tables 5 and 6, respectively. All sensitivity indices, except for some for N_v, are shown to two significant figures because that was the accuracy of the parameters. The sensitivity indices for N_v can be calculated analytically as we have an explicit expression for the equilibrium value of the number of mosquitoes. We show an example in Appendix B.1.

In interpreting the sensitivity indices, we first note that keeping all other factors fixed, increasing disease prevalence will lead to a decrease in the equilibrium human population size. This is because of disease-induced death in infectious humans. Similarly, reducing the disease prevalence will lead to an increase in the equilibrium human population size.

In areas of low transmission, the order of the relative sensitivity of the different parameters for the equilibrium value of i_h is largely similar to that for R_0. As the reproductive number is based on a linearization around the disease-free equilibrium, x_{dfe}, and the endemic equilibrium in areas of low transmission is close to x_{dfe} (because R_0 is close to 1), the sensitivity indices are similar to those for R_0. The most sensitive parameter is the mosquito biting rate, σ_v, followed by the mosquito to human disease transmission probability, β_{hv}, and the human recovery rate, γ_h. Other important parameters include the

Table 5 The sensitivity indices, $\Upsilon_{p_j}^{x_i} = (\partial x_i / \partial p_j) \times (p_j / x_i)$, of the state variables at the endemic equilibrium, x_i, to the parameters, p_j, for baseline parameter values for areas of low transmission given in Table 3, measure the relative change in the solution to changes in the parameters

	e_h	i_h	r_h	N_h	e_v	i_v	N_v
Λ_h	−0.80	−0.81	−0.83	+0.39	−0.69	−0.69	0
ψ_h	−0.62	−0.63	−0.64	+0.30	−0.54	−0.54	0
ψ_v	−3.4	−3.4	−3.4	+0.026	−4.1	−5.1	+1.3
σ_v	+5.7	+5.7	+5.7	−0.044	+6.2	+6.2	0
σ_h	+1.8	+1.8	+1.8	−0.014	+2.0	+2.0	0
β_{hv}	+3.9	+3.9	+3.9	−0.030	+3.7	+3.7	0
β_{vh}	+3.3	+3.3	+3.3	−0.026	+4.0	+4.0	0
$\tilde{\beta}_{vh}$	+0.41	+0.41	+0.41	−0.0032	+0.50	+0.50	0
ν_h	−0.98	+0.019	+0.019	−0.00014	+0.018	+0.018	0
ν_v	+2.4	+2.4	+2.4	−0.018	+1.9	+2.9	0
γ_h	−2.8	−3.8	−2.8	+0.029	−3.5	−3.5	0
δ_h	+0.0022	−0.0025	−0.0022	−0.0077	−0.0042	−0.0042	0
ρ_h	+0.059	+0.059	−0.90	−0.00046	−0.045	−0.045	0
μ_{1h}	+0.092	+0.091	+0.090	−0.048	+0.076	+0.076	0
μ_{2h}	+1.2	+1.2	+1.2	−0.63	+1.0	+1.0	0
μ_{1v}	−0.69	−0.69	−0.69	+0.0053	−0.58	−0.58	−0.34
μ_{2v}	−2.0	−2.0	−2.0	+0.016	−1.7	−1.7	−1
ζ	+7.6	+7.6	+7.6	−0.059	+8.2	+8.2	0

Table 6 The sensitivity indices, $\Upsilon_{p_j}^{x_i} = (\partial x_i/\partial p_j) \times (p_j/x_i)$, of the state variables at the endemic equilibrium, x_i, to the parameters, p_j, for baseline parameter values for areas of high transmission given in Table 3, measure the relative change in the solution to changes in the parameters

	e_h	i_h	r_h	N_h	e_v	i_v	N_v
Λ_h	+0.049	+0.036	−0.028	+0.31	+0.059	+0.059	0
ψ_h	+0.080	+0.060	−0.045	+0.51	+0.097	+0.097	0
ψ_v	−0.032	−0.032	−0.033	+0.0021	−0.56	−1.6	+1.3
σ_v	+0.094	+0.094	+0.095	−0.0062	+0.66	+0.66	0
σ_h	+0.024	+0.024	+0.025	−0.0016	+0.17	+0.17	0
β_{hv}	+0.068	+0.068	+0.069	−0.0045	+0.050	+0.050	0
β_{vh}	+0.034	+0.034	+0.034	−0.0022	+0.52	+0.52	0
$\tilde{\beta}_{vh}$	+0.017	+0.017	+0.017	−0.0011	+0.26	+0.26	0
ν_h	−0.99	+0.0063	+0.0064	−0.00041	+0.0046	+0.0046	0
ν_v	+0.040	+0.040	+0.040	−0.0026	−0.38	+0.62	0
γ_h	+0.078	−0.86	+0.13	+0.057	−0.39	−0.39	0
δ_h	+0.012	−0.0094	+0.0040	−0.065	−0.014	−0.014	0
ρ_h	+0.61	+0.61	−0.16	−0.040	+0.26	+0.26	0
μ_{1h}	+0.010	+0.0087	+0.0018	−0.075	−0.0068	−0.0068	0
μ_{2h}	+0.092	+0.080	+0.016	−0.69	−0.062	−0.062	0
μ_{1v}	−0.015	−0.015	−0.015	+0.00098	+0.041	+0.041	−0.34
μ_{2v}	−0.043	−0.043	−0.044	+0.0029	+0.12	+0.12	−1
ζ	+0.12	+0.12	+0.12	−0.0078	+0.83	+0.83	0

mosquito birth rate, ψ_v, the human to mosquito disease transmission probability, β_{vh}, and the mosquito rate of progression from the latent state, ν_v.

Similar to the case for R_0, the magnitude of the sensitivity index of x_{ee} to ζ, $\Upsilon_{\zeta}^{x_{ee}}$, is larger than that for all other parameters. Thus, reducing the mosquito-human contacts would have a large effect on disease prevalence at low transmission. Reducing ζ by 1% would approximately reduce i_h by 7.6%.

The sign of the sensitivity indices of the endemic equilibrium with respect to most of the parameters, for areas of low transmission, agrees with an intuitive expectation. The results that perhaps require some explanation are those for the mosquito birth rate, ψ_v, and the rate of loss of immunity, ρ_h. As explained in the section on the reproductive number, increasing the mosquito birth rate, given a density-dependent mosquito death rate, shortens the lifespan of the mosquito and results in a net decrease in the equilibrium proportion of infectious humans, i_h. Increasing ψ_v also affects the total number of mosquito bites on humans, which could further reduce i_h. As ρ_h increases, r_h decreases, which would tend to reduce disease prevalence. However, as a substantial fraction of people are in the recovered class, reducing the number of recovered people results in a redistribution of the population that increases the proportion of people in the exposed and infectious classes.

In areas of high transmission, the sensitivity of the endemic equilibrium to the parameters is different from the sensitivity of R_0 to the parameters. Since R_0 is large, the endemic equilibrium is far from the disease-free equilibrium. The magnitude of the sensitivity indices for the endemic equilibrium in high transmission is also much lower than in low transmission, because as R_0 increases, disease prevalence moves closer to 100% and even for large changes in the parameter values, there are only small changes in the endemic equilibrium.

The most sensitive parameter for i_h is γ_h followed by ρ_h. As the infectious and recovered periods are long and about 94% of the people are in the diseased classes, any changes in the recovery rate or rate of loss of immunity will have a relatively large effect on the fraction of infectious humans. The rate of loss of immunity has a large effect on i_h because as 77% of the people are in the recovered class, any increase will remove a large number of people from the recovered class. Since infection rates are high, most of these people will be absorbed into the other classes, especially the infectious class. (This effect is similar to and more pronounced than that seen in areas of low transmission. In areas of high transmission, the increase in i_h is also strong enough to increase disease prevalence in mosquitoes.)

Increases in the human demographic parameters, ψ_h, Λ_h, μ_{1h}, and μ_{2h}, change the equilibrium human population size which in turn changes the total number of mosquito bites on humans, resulting in substantial changes in i_h. Increasing the death rates, μ_{1h} and μ_{2h}, decreases the human population, which leads to an increase in the number of mosquito bites per human, which increases i_h. Similarly, increasing Λ_h and ψ_h increases the equilibrium human population which would tend to decrease i_h. However, as the incoming population is in the susceptible class and the inoculation rate is high, most of these people will get infected and move through the exposed and infectious classes to the recovered class. The net result of increasing the number of humans entering the population is the reduction of the fraction of recovered humans and an increase in the proportion of humans in the other classes. Increasing i_h also increases disease prevalence in mosquitoes. This effect is stronger than the decrease in mosquito disease prevalence due to a reduction in r_h and an increase in N_h.

Other important parameters for i_h in high transmission, are the mosquito biting rate, σ_v, followed by the mosquito to human disease transmission probability, β_{hv}, the rate of progression from the exposed state for mosquitoes, ν_v, and the density-dependent mosquito death rate, μ_{2v}. These are also most important parameters for R_0 and for the endemic equilibrium in areas of low transmission. Again, when ζ is considered as a parameter, it has a large effect on the equilibrium value of i_h.

For both sets of parameter values, we find that $\Upsilon_\zeta^{x_{ee}} = \Upsilon_{\sigma_v}^{x_{ee}} + \Upsilon_{\sigma_h}^{x_{ee}}$, although we cannot prove this relationship in general.

5. Discussion and conclusion

We analyzed a malaria model (Chitnis et al., 2006) by evaluating the sensitivity indices of the reproductive number, R_0, and the endemic equilibrium, x_{ee}, to model parameters. We did this for two sets of baseline values: one representing areas of high transmission and one representing areas of low transmission. Since R_0 is a measure of initial disease transmission, and x_{ee} represents disease prevalence, these sensitivity indices allow us to determine the relative importance of different parameters in malaria transmission and prevalence.

In areas of low transmission, the most important parameter for initial disease transmission is the mosquito biting rate, σ_v. Other important parameters are the mosquito-to-human disease transmission probability, β_{hv}, the mosquito birth rate, ψ_v, the human-to-mosquito disease transmission probability, β_{vh}, and the human rate of recovery, γ_h. These five parameters are also the most important parameters for equilibrium disease prevalence,

although γ_h is in this case more important than ψ_v and β_{vh}. If we consider ζ as a parameter (with θ fixed), it would be the most important parameter for both initial disease transmission and equilibrium disease prevalence.

In areas of high transmission, the most important parameter for initial disease transmission is the mosquito biting rate, σ_v. Other important parameters are the mosquito-to-human disease transmission probability, β_{hv}, the mosquito birth rate, ψ_v, the human-to-mosquito disease transmission probability, β_{vh}, the density-dependent mosquito death rate, μ_{2v}, and the human rate of recovery, γ_h. The most important parameter for equilibrium disease prevalence is the human rate of recovery, γ_h. Other important parameters are the human rate of loss of immunity, ρ_h, the mosquito biting rate, σ_v, the human density-dependent death and emigration rate, μ_{2h}, and the mosquito-to-human disease transmission probability, β_{hv}. If we consider ζ as a parameter, it is the most important parameter in initial disease transmission and the third most important parameter in equilibrium disease prevalence.

Although intervention strategies cannot target σ_v directly, they can target ζ through lowering mosquito-human contacts. According to our model, for the set of parameters representing areas of low transmission, strategies that affect ζ would be the most effective at reducing initial malaria transmission and equilibrium disease prevalence. Strategies that reduce mosquito-human contacts, such as the use of insecticide-treated bed nets (ITN's) and indoor residual spraying (IRS) have been shown to be effective in field studies (Hawley et al., 2003; Sharma et al., 2005). These strategies would also be the most effective in reducing initial transmission in areas of high transmission.

Our analysis also shows that intervention strategies that affect the human recovery rate, γ_h, would be the most effective in reducing equilibrium disease prevalence for the set of parameters representing areas of high transmission. The parameter γ_h can be reduced through prompt and effective case management (PECM) which emphasizes quick and accurate diagnosis and consequent treatment of malaria. Our model shows these strategies to also be effective in reducing equilibrium disease prevalence in areas of low transmission and initial disease transmission in both low and high transmission areas.

The second most important parameter for initial disease transmission and equilibrium disease prevalence in areas of low transmission and initial disease transmission in areas of high transmission is the probability of disease transmission from infectious mosquitoes to susceptible humans, β_{hv}. This parameter can be reduced through strategies such as intermittent preventive treatment (IPT) which has been shown to be effective in Tanzania (Massaga et al., 2003; Schellenberg et al., 2001).

The second most important parameter for equilibrium disease prevalence in areas of high transmission is the human rate of loss of immunity, ρ_h. This parameter cannot easily be targeted by current intervention strategies and represents a simplification of our model. The rate of loss of immunity is not well understood (Anderson and May, 1991) and is generally thought of as dependent on the prevailing incidence rate. However, where the incidence rate is constant over time (as it is in our model at equilibrium), the rate of loss of immunity may be assumed to be constant and we use reasonable estimates of this constant rate in high and low transmission. However, ρ_h, representing a nonlinear process, remains difficult to directly control through an intervention strategy.

The mosquito birth rate, ψ_v, has a substantial effect on initial disease transmission in both high and low transmission areas and on equilibrium disease prevalence in low transmission areas. However, for the parameter values used in the model, this effect is

detrimental and contrary to common practice, such as the destruction of breeding sites. This detrimental effect depends on the assumption that the mosquito death rate is density-dependent, as decreasing the birth rate then leads to a longer life span for each mosquito.

Another important parameter in initial disease transmission in high and low transmission areas and equilibrium disease prevalence in low transmission areas is the probability of disease transmission from infectious humans to susceptible mosquitoes, β_{vh}. This parameter can be reduced through current intervention strategies such as the use of gametocytocidal drugs, or possible future strategies, such as the use of a transmission-blocking vaccine or the release of transgenetically modified mosquitoes.

The particular values of the sensitivity indices of the endemic equilibrium point, x_{ee}, and the reproductive number, R_0, to the different parameters depend on the parameter values that we have chosen, and on the assumptions upon which this model is based. To effectively guide public policy and public health decision making, the model and parameter values would need to be tested against data from malaria-endemic field sites. The current analysis, however, remains an important first step toward comparing the effectiveness of different control strategies.

To compare control strategies with more certainty, there are numerous additions that we would like to make to our model. We want to include the effects of the incidence rate on the period of immunity, and age and spatial structure, both of which are important in the spread of malaria. We would also like to improve our entomological submodel by the addition of juvenile mosquito stages. We could then include the effects of seasonality and the environment on the number and life span of mosquitoes, and on the development of the parasite in the mosquito. An increase in ambient temperature, with high relative humidity and rainfall, increases the emergence rate of mosquitoes, lengthens the life span of adult mosquitoes, and reduces the latency period in mosquitoes; resulting in a multifaceted increase in malaria transmission levels. Environmental effects and changes play an important role in malaria transmission (Zhou et al., 2004) and need to be taken into account.

Finally, we would like to quantify the relationship between the parameters in our model and the intervention strategies used to control malaria. A quantitative relationship would then allow us to directly relate the cost of each strategy to the reduction in disease burden and allow for the definite comparison of the efficiency and cost-effectiveness of different intervention strategies on reducing malaria morbidity and mortality.

Acknowledgements

Appendix A: Data for baseline parameter value

This Appendix shows the tables of data and explanations for the baseline parameter values of the model (2) including references.

Table A.1 Demographic data for countries with areas of high levels of malaria transmission. The unit for life expectancy is years and the unit for the birth rate is total births per 1,000 people per year. This table is current as of December 7, 2007

Country	Life expectancy	Birth rate	
Botswana	50.58	23.17	Central Intelligence Agency (2007)
Congo, DR	57.20	42.96	Central Intelligence Agency (2007)
Kenya	55.31	38.94	Central Intelligence Agency (2007)
Malawi	42.98	42.09	Central Intelligence Agency (2007)
Zambia	38.44	40.78	Central Intelligence Agency (2007)

Table A.2 Demographic data for countries with areas of low levels of malaria transmission. The unit for life expectancy is years and the unit for the birth rate is total births per 1,000 people per year. This table is current as of December 7, 2007

Country	Life expectancy	Birth rate	
Brazil	72.24	16.30	Central Intelligence Agency (2007)
India	68.59	22.69	Central Intelligence Agency (2007)
Indonesia	70.16	19.65	Central Intelligence Agency (2007)
Mexico	75.63	20.36	Central Intelligence Agency (2007)
Saudi Arabia	75.88	29.10	Central Intelligence Agency (2007)

Population data for humans: Table A.1 shows the life expectancy and birth rate estimates for the year 2007 for some African countries with areas of high malaria transmission. Using this data, we assume a birth rate of 40 births per year per 1,000 people so $\psi_h = 40/365.25/1,000$. We also assume an immigration rate of 12 people per year. We set values of $\mu_{1h} = 1.6 \times 10^{-5}$ and $\mu_{2h} = 3.0 \times 10^{-7}$. These correspond to, in the absence of malaria, a life expectancy of 48 years and 4.2% of the population emigrating every year. The stable population size for these parameter values, in the absence of malaria is 523.

Table A.2 shows the life expectancy and birth rate estimates for the year 2007 for some Asian and American countries with areas of low malaria transmission. Using this data, we assume a birth rate of 20 births per year per 1,000 people so $\psi_h = 20/365.25/1,000$. We also assume an immigration rate of 15 people per year. We set values of $\mu_{1h} = 8.8 \times 10^{-6}$ and $\mu_{2h} = 2.0 \times 10^{-7}$. These correspond to, in the absence of malaria, a life expectancy of 70 years and 3.2% of the population emigrating every year. The stable population size for these parameter values, in the absence of malaria is 583.

To determine the range of these parameters, we allow the immigration rate, Λ_h, to vary from 1 migrant per year to 100 migrants per year. This is a location specific parameter so it has a large range of values. We allow the birth rate to vary from 10 births per 1,000 people per year to 50 births per 1,000 people per year. We allow μ_{1h} and μ_{2h} to vary so that the minimum removal rate corresponds to a life expectancy of 80 years and no emigration, and the maximum removal rate corresponds to a life expectancy of 30 years and 33% annual emigration. The exact values of μ_{1h} and μ_{2h}, for a given life expectancy and emigration rate, would depend on the values of the immigration rate and the birth rate.

Population data for mosquitoes: We use the results for the mosquito birth rate calculated by Briët (2002, Fig. 2) for *An. gambiae* to give us a rate of 130 new adult female

Table A.3 Mosquito life expectancy data

Lifespan (days)	Mosquito	
20	*An. balabacensis*	Slooff and Verdrager (1972)
8.5	*An. coustani*	Garrett-Jones and Grab (1964)
5.6	*An. funestus*	Krafsur and Garrett-Jones (1977)
5.89	*An. funestus*	Gillies and Wilkes (1963)
10.2	*An. funestus*	Garrett-Jones and Grab (1964)
11.26	*An. gambiae*	Gillies and Wilkes (1965)
15.4	*An. gambiae*	Garrett-Jones and Shidrawi (1969)
8.0	*An. gambiae*	Garrett-Jones and Grab (1964)
9	*An. gambiae*	Molineaux et al. (1979)
3.6	*An. gambiae*	Zahar (1974)
9	*An. minimus*	Khan and Talibi (1972)
5.8	*An. nili*	Garrett-Jones and Grab (1964)
7.1	*An. punctulatus*	Peters and Standfast (1960)

mosquitoes per day per 1,000 female mosquitoes. The stable equilibrium value of the mosquito population, N_v, varies depending on the location. For areas of high transmission, we use estimates derived from quarterly data for the average number of *An. gambiae* and *An. funestus* mosquitoes in a region of Western Kenya (Asembo) from Gimnig et al. (2003b). From this data, we use an estimate of 2 *An. gambiae* and 0.8 *An. funestus* mosquitoes per house. We also assume that there are 1.5 people per house (Gimnig et al. (2003a) state that in Asembo there are 17,000 people living in approximately 2,500 family compounds with about 3–5 houses per compound) and there are a total of about 5 times as many mosquitoes as are found in the houses. Given the size of the human population in the model and the mosquito birth rate, we set $\mu_{1v} = 0.033$ and $\mu_{2v} = 2.0 \times 10^{-5}$ so that there is a stable equilibrium value of 4,850 mosquitoes.

For areas with low transmission, we use the same mosquito birth rate and mosquito (density independent) death rate, as that for areas of high transmission, but a higher density dependent death rate, $\mu_{2v} = 4.0 \times 10^{-5}$, to provide a stable equilibrium value of about 2,425 mosquitoes (half as many as in areas of high transmission).

Table A.3 shows different estimates for mosquito life expectancy.

Data for mosquito-human biting rates: The number of times a mosquito bites a human per day depends on the relative sizes of the mosquito and human populations, the mosquito's gonotrophic cycle (the number of days a mosquito requires to produce eggs before it searches for a blood meal again), the mosquito's anthropophilic rate (the mosquito's innate preference for human blood), and the number of bites that a human will tolerate per day (depending on the human's exposed surface area and any preventive measures the human takes to avoid being bitten).

The parameter, σ_v, models the mosquito's gonotrophic cycle and its anthropophilic rate. As we do not have data to differentiate between the effects of the anthropophilic rate and the relative sizes of the human and mosquito populations, we assign values to σ_v based on only the gonotrophic cycle. From Bloland *et al.* (2002), we use estimates of a gonotrophic cycle length of 3 days in areas of low transmission and 2 days in areas of high transmission (with the assumption that areas of high transmission have higher temperatures and humidity).

From Table A.4, which shows estimates from field studies for the average number of bites on humans per mosquito per day, we use an estimate of 0.40 bites on humans per

Table A.4 Mosquito daily biting rate data.

Human bites per mosquito	Mosquito	Year(s)	Location	
0.25	*An. balabacensis*	1964	Khmer	Slooff and Verdrager (1972)
0.25	*An. gambiae*	1967	Kankiya, Nigeria	Garrett-Jones and Shidrawi (1969)
0.13	*An. gambiae*	1967	Khashm El Girba, Sudan	Zahar (1974)
0.44	*An. gambiae*	1972	Garki, Nigeria	Molineaux et al. (1979)
0.47	*An. minimus*	1966–1967	Bangladesh	Khan and Talibi (1972)
0.40	*An. punctulatus*	1957–1958	Maprik, New Guinea	Peters and Standfast (1960)

Table A.5 Data for probability of transmission of infection from mosquitoes to humans

Probability of transmission	Comments	
0.0223±0.0028	Calculations from data from (Pull and Grab, 1974)	Nedelman (1985)
0.01	–	Davidson and Draper (1953)
0.015–0.026	–	Pull and Grab (1974)
0.06–0.27	Children	Krafsur and Armstrong (1978)
0.05–0.13	Adults	Krafsur and Armstrong (1978)
0.012	Village with relative highest mosquito density	Nedelman (1984)
0.086	Village with relative lowest mosquito density	Nedelman (1984)

mosquito per day in areas of high transmission and 0.25 bites on humans per mosquito per day in areas of low transmission, at the disease-free equilibrium population sizes. Based on these estimates and the values of σ_v, N_v^*, and N_h^*, we calculate σ_h to be 19 in areas of high transmission and 4.3 in areas of low transmission. These values are reasonable given the assumption that in areas of low transmission people suffer from fewer mosquito bites.

Data for β_{hv}: Table A.5 shows the probability of transmission of infection from an infectious mosquito to a susceptible human given that a contact between the two occurs. We use an estimate of $\beta_{hv} = 0.022$ for both, areas of high and low transmission.

Data for β_{vh} and $\tilde{\beta}_{vh}$: Table A.6 shows the probability of transmission of infection from infectious humans to susceptible mosquitoes given that a contact between the two occurs. We use an estimate of $\beta_{vh} = 0.48$ for areas of high transmission and $\beta_{vh} = 0.24$ for areas of low transmission. We assume that the probability of transmission from recovered humans to susceptible mosquitoes is one tenth the probability of transmission from infectious humans (Ngwa and Shu, 2000), so $\tilde{\beta}_{vh} = 0.048$ for areas of high transmission and $\tilde{\beta}_{vh} = 0.024$ for areas of low transmission.

Data for ν_h: We assume a latent period in humans of 10 days, for both baseline cases, from the data shown in Table A.7.

Data for ν_v: We assume the latent period in mosquitoes to be 11 days in areas of high transmission and 12 days in areas of low transmission. Table A.8 shows some estimates for the latent period in mosquitoes.

Table A.6 Data for probability of transmission of infection from humans to mosquitoes

Probability of transmission	Comments	
0.24	*P. falciparum* to *An. gambiae*	Muirhead-Thomson (1957)
0.48	*P. falciparum*	Boyd (1949)
0.51	*P. falciparum*	Draper (1953)
0.47	*P. falciparum*	Draper (1953)
0.09	*P. falciparum*	Draper (1953)
0.64	*P. falciparum* after 1–4 days of gametocytemia	Smalley and Sinden (1977)
0.072	*P. falciparum* after 11–12 days of gametocytemia	Smalley and Sinden (1977)
0.48	From a differential equation model	Nedelman (1984)
0.38	From a vectorial capacity approximation	Nedelman (1984)

Table A.7 Data for the latent period in humans measured in days

Latent period	*Plasmodium*	
10–14	*P. ovale*	Molineaux and Gramiccia (1980)
15–16	*P. malariae*	Molineaux and Gramiccia (1980)
9–10	*P. falciparum*	Molineaux and Gramiccia (1980)
5–15	–	Oaks et al. (1991)

Table A.8 Data for the latent period in mosquitoes measured in days

Latent period	*Plasmodium*	Mosquito	Temperature (°C)	
9	*P. vivax*	–	25–27	Anderson and May (1991)
12	*P. falciparum*	–	25–27	Anderson and May (1991)
11	*P. falciparum*	*An. gambiae*	24	Baker (1966)
3–35	*P. vivax*	–	17–31	Macdonald (1957)
5–35	*P. falciparum*	–	20–33	Macdonald (1957)

Table A.9 Data for the duration of the infectious period for humans in months

Infectious period	*Plasmodium*	Comments	
2	*P. ovale*	–	Molineaux and Gramiccia (1980)
4	*P. malariae*	–	Molineaux and Gramiccia (1980)
9.5	*P. falciparum*	–	Molineaux and Gramiccia (1980)
12–24	*P. falciparum*	No treatment	Bloland and Williams (2002)
18–60	*P.vivax*	No treatment	Bloland and Williams (2002)
18–60	*P. ovale*	No treatment	Bloland and Williams (2002)
36–600	*P. malariae*	No treatment	Bloland and Williams (2002)

Data for γ_h: We use an estimated recovery period of 9.5 months in both areas of high and low transmission. Table A.9 shows some estimates of the duration of the infectious period in humans.

Data for δ_h: The value of the disease-induced death rate varies across different regions, depending on the availability and quality of treatment facilities. Arudo et al. (2003) give the malaria mortality rate for all children under 5 years old in Asembo (a region in western

Kenya) as 32.9 deaths per year per 1,000 children. Although the data in Arudo et al. (2003) is sampled only from children under the age of five (as opposed to the general population) and includes all children (as opposed to only those that are infectious), we use it as an estimate for the per capita disease-induced death rate of infectious humans in the entire population. This assumption is reasonable because in areas of high malaria transmission like Asembo, almost all children are infectious (I_h) and most adults are immune (R_h). For areas of low transmission, we assume improved availability and quality of treatment facilities, so that the per capita disease-induced death rate is a fifth that of Asembo. We assume that the range of δ_h can vary from no disease-induced deaths to 150 deaths per year per 1,000 infectious humans.

Data for ρ_h: Immunity to malaria in humans is a complicated mechanism that is not completely understood. While it is generally believed that immunity is short-lived and re-quires repeated reinfection to sustain itself (Aron, 1988; Dietz et al., 1974), in an epidemic in Madagascar, after two malaria-free decades, older adults still had some protection to malaria when compared to younger adults with no previous malaria exposure (Deloron and Chougnet, 1992). The model (1) is based on the assumption that infected humans eventually lose their immunity to malaria and return to the susceptible class. This rate of loss of immunity is a nonlinear process that depends on the transmission rate. However, for ease of analysis, we make the simplifying assumption that immunity is lost at a con-stant rate. We allow the rate to be higher in areas of low transmission so that humans with less exposure are immune for shorter periods of time. The assumption of a constant rate of loss of immunity is reasonable if the level of malaria does not change significantly over time in the modeled area.

For areas of high transmission, we assume that the period of immunity lasts for 5 years, while in areas of low transmission, we assume that the period lasts for 1 year. We also assume that the range can vary from 3 months to 50 years.

Appendix B: Calculation of sensitivity indices

In this Appendix, we describe the methods used to determine the sensitivity indices of the endemic equilibrium to the parameters. To calculate the indices, we first need to evaluate the partial derivatives of the state variables at the endemic equilibrium with respect to the parameters.

For ease of notation, we label the seven state variables at the endemic equilibrium point $(e_h, i_h, \ldots, N_v)$ by $x_1, x_2, \ldots, x_7$; the seventeen parameters $(\Lambda_h, \psi_h, \ldots, \mu_{2v})$ by $p_1, p_2, \ldots, p_{17}$; and the seven equilibrium equations of (2) by

$$g_1(x_1, \ldots, x_7; p_1, \ldots, p_{17}) = 0,$$

$$\vdots \qquad\qquad\qquad\qquad\qquad\qquad (B.1)$$

$$g_7(x_1, \ldots, x_7; p_1, \ldots, p_{17}) = 0.$$

We want to evaluate $\partial x_i / \partial p_j$ for $1 \le i \le 7$ and $1 \le j \le 17$ for both sets of parameter val-ues in Table 3 (with the corresponding endemic equilibrium points given by (7) and (8)).

Taking full derivatives of the seven equilibrium equations (B.1) with respect to the seventeen parameters, p_j, gives us 119 equations of the form,

$$\frac{dg_k}{dp_j} = \sum_{i=1}^{7} \left(\frac{\partial g_k}{\partial x_i} \frac{\partial x_i}{\partial p_j} \right) + \sum_{l=1}^{17} \left(\frac{\partial g_k}{\partial p_l} \frac{\partial p_l}{\partial p_j} \right) = 0, \tag{B.2}$$

for $1 \leq k \leq 7$ and $1 \leq j \leq 17$. However, $\partial p_l / \partial p_j = 0$ if $l \neq j$ so each equation in (B.2) reduces to

$$\sum_{i=1}^{7} \frac{\partial g_k}{\partial x_i} \frac{\partial x_i}{\partial p_j} = -\frac{\partial g_k}{\partial p_j}. \tag{B.3}$$

These equations are decoupled in terms of the parameters, p_j, but are coupled in terms of the function, g_k. Equations (B.3) are thus seventeen linear systems of seven coupled equations. They may be written as

$$Az^{(j)} = b^{(j)}, \tag{B.4}$$

where A is the (7×7) Jacobian of the malaria model (2) with $A_{ki} = \partial g_k / \partial x_i$; $z^{(j)}$ is the unknown (7×1) vector with the ith term of $z^{(j)}$ given by $\partial x_i / \partial p_j$; and $b^{(j)}$ is a (7×1) vector with the kth term given by $-\partial g_k / \partial p_j$. The matrix A is known because we can evaluate the Jacobian of (2) for the given parameter values and the corresponding endemic equilibrium point. Similarly, we can directly evaluate $b^{(j)}$ by calculating the derivative, $-\partial g_k / \partial p_j$, at the given parameter values.

Solving these seventeen linear systems of (B.4) for $z^{(j)}$ gives us what we want: $\partial x_i / \partial p_j$ for $1 \leq i \leq 7$ and $1 \leq j \leq 17$. Finally, we multiply $\partial x_i / \partial p_j$ by p_j / x_i, as in the definition of the sensitivity index (9), to find the sensitivity of each state variable in the endemic equilibrium point, x_i, to the parameter, p_j.

B.1 Sensitivity analysis of the equilibrium mosquito population

As we have an explicit expression for the equilibrium value of N_v, we can analytically evaluate the sensitivity of N_v to the parameters. At equilibrium,

$$N_v = \frac{\psi_v - \mu_{1v}}{\mu_{2v}}. \tag{B.5}$$

As N_v depends on only three parameters, the sensitivity indices of N_v to all other parameters is 0. For example, the sensitivity index for N_v to ψ_v is

$$\Upsilon_{\psi_v}^{N_v} = \frac{\partial N_v}{\partial \psi_v} \cdot \frac{\psi_v}{N_v} = \frac{\psi_v}{\psi_v - \mu_{1v}}.$$

For the baseline parameter values given in Table 3, for areas of high and low transmission, $\Upsilon_{\psi_v}^{N_v} = +1.3$.

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