USING MATHEMATICAL MODELS IN CONTROLLING THE SPREAD OF MALARIA

by

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SIGNED: _____

Nakul Rashmin Chitnis

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DEDICATION

I dedicate this dissertation to my mother, Shama Chitnis, without whom this dissertation would not exist.

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ABSTRACT

Malaria is an infectious disease, transmitted between humans through mosquito bites, that kills about two million people a year. We derive and analyze a mathematical model to better understand the transmission and spread of this disease. Our main goal is to use this model to compare intervention strategies for malaria control for two representative areas of high and low transmission.

We model malaria using ordinary differential equations. We analyze the existence and stability of disease-free and endemic (malaria persisting in the population) equilibria. Key to our analysis is the definition of a reproductive number, R_0 (the number of new infections caused by one individual in an otherwise fully susceptible population through the duration of the infectious period). We prove the loss of stability of the disease-free equilibrium as R_0 increases through $R_0 = 1$. Using global bifurcation theory developed by Rabinowitz, we show the bifurcation of endemic equilibria at $R_0 = 1$. This bifurcation can be either supercritical (leading to stable endemic equilibria for $R_0 > 1$) or subcritical (leading to stable endemic equilibria for $R_0 < 1$ in the presence of hysteresis).

We compile two reasonable sets of values for the parameters in the model: for areas of high and low transmission. We compute sensitivity indices of R_0 and the endemic equilibrium to the parameters around the baseline values. R_0 is most sensitive to the mosquito biting rate in both high and low transmission areas. The fraction of infectious humans at the endemic equilibrium is most sensitive to the mosquito biting rate in low transmission areas, and to the human recovery rate in high transmission areas. This sensitivity analysis allows us to compare the effectiveness of different control strategies. According to our model, the most effective methods for malaria control are the use of insecticide-treated bed nets and the prompt diagnosis and treatment of infected individuals.

CHAPTER 1

INTRODUCTION

Malaria is an infectious disease caused by the *Plasmodium* parasite and transmitted between humans through the bite of the female *Anopheles* mosquito. An estimated 40% of the world's population live in malaria endemic areas. It kills about 700, 000 to 2.7 million people a year, 75% of whom are African children. The incidence of malaria has been growing recently due to increasing parasite drug-resistance and mosquito insecticide-resistance. Therefore, it is important to understand the important parameters in the transmission of the disease and develop effective solution strategies for its prevention and control.

We develop a mathematical model to better understand the transmission and spread of malaria. We model the disease through ordinary differential equations (ODEs) where humans and mosquitoes interact and infect each other. This model is used to determine which factors are most responsible for the spread of malaria.

The model divides the human population into four classes: susceptible, exposed, infectious, and recovered (immune). Humans enter the susceptible population through birth or immigration. Susceptible humans get infected at a certain probability when they are bitten by infectious mosquitoes. They then progress through the exposed, infectious, and recovered classes, before reentering the susceptible class. Humans leave the population through death and emigration out of all classes, and through additional disease-induced death out of the infectious class. There are three classes for the mosquito population: susceptible, exposed, and infectious. Mosquitoes enter the susceptible class through birth. Susceptible mosquitoes get infected at a certain probability when they bite infectious or recovered humans (at a lower probability) and then move through the exposed and infectious classes. Both species follow a logistic model for their population growth, with humans having additional immigration and disease-induced death.

The model contains a system of seven coupled nonlinear ODEs with one dependent variable representing each population class. For ease of analysis, we convert the population variables to fractional quantities to create a new system of seven ODEs with three variables representing the fractions of the "diseased" human population (exposed, infectious and recovered), two variables representing the fractions of the "diseased" mosquito population (exposed and infectious) and two variables representing the total sizes of human and mosquito populations.

We first show that there exists a domain, $\mathcal{D}$, in the positive cone of $\mathbb{R}^7$ where the model is epidemiologically and mathematically well-posed. Disease-free equilibrium points are steady state solutions where there is no malaria in either the human or mosquito populations. There are two disease-free equilibrium points in $\mathcal{D}$ on the boundary of the positive cone: one with only humans and no mosquitoes, x_{mfe}, and one with humans and mosquitoes, x_{dfe}.

We also define a reproductive number, R_0 (the number of new infections caused by one individual in an otherwise fully susceptible population through the duration of the infectious period), for the model using the next generation operator approach, as described by Diekmann *et al.* in [17]. The definition of R_0 makes epidemiological sense and can be formulated in the manner described by Hyman and Li [35] as the product of the number of contacts per unit time, the probability of transmission per contact and the duration of the infectious period. When $R_0 < 1$, x_{dfe} is locally asymptotically stable and the introduction of a small number of infected individuals would not lead to an epidemic. When $R_0 > 1$, x_{dfe} is unstable and the introduction of any infected individual would lead to an epidemic and malaria persisting in the population.

Endemic equilibrium points are steady state solutions where the disease persists in the population. Using a corollary by Rabinowitz [60] (Corollary 1.12), we prove that a positive endemic equilibrium exists for all $R_0 > 1$. Numerical simulations suggest that the endemic equilibrium is stable for $R_0 > 1$ and there is a transcritical bifurcation at $R_0 = 1$ where two branches of equilibrium points intersect and exchange stability. For the special case with no disease-induced death we prove that

the bifurcation at $R_0 = 1$ is supercritical (forward) and stable endemic equilibrium points exist for $R_0 > 1$. For some large (though still realistically feasible) values of the disease-induced death rate, there exists a subcritical (backward) bifurcation at $R_0 = 1$ where stable positive endemic equilibrium points exist for $R_0 < 1$. Thus even when $R_0 < 1$, malaria can persist in the population in the presence of a locally asymptotically stable disease-free equilibrium point.

We compile two reasonable sets of baseline values for the parameters in the model: one for areas of high transmission ($R_0 = 7.0$) and one for areas of low transmission ($R_0 = 1.1$). We compute the sensitivity indices of the reproductive number and the endemic equilibrium to the parameters around the baseline values. In both high and low transmission areas, R_0 is most sensitive to the number of bites on humans per mosquito per day. In areas of low transmission, the fraction of infectious humans at the endemic equilibrium, i_h, is also most sensitive to the mosquito biting rate. In areas of high transmission, as most people are either infectious or recovered, the most sensitive parameters for i_h are the rates of movement out of the infectious and recovered classes.

The sensitivity indices allow us to compare the effectiveness of different control strategies, as each strategy affects different parameters to different degrees. Our results agree with field studies that suggest that methods that reduce human-mosquito contact, such as the use of insecticide-treated bed nets, are effective in controlling the spread of malaria [30]. They also suggest that quickly identifying and treating infected individuals would be effective in reducing disease prevalence.

We describe the biological and medical background of malaria in Appendix A. Section 1.1 surveys some of the literature in the mathematical modeling of malaria. Chapter 2 describes the formulation and analysis of the mathematical model for malaria transmission. Section 2.1 describes the model, the state variables, and the parameters. In section 2.2, we derive the reproductive number, R_0, and show the existence and stability of the equilibrium points without disease, x_{mfe} and x_{dfe}. In section 2.3, we prove the existence of endemic equilibrium points, x_{ee}, and describe analysis and numerical simulations showing the direction of bifurcation at $R_0 = 1$.

Section 2.4 provides some concluding remarks to the chapter.

In chapter 3, we compare different strategies for malaria control by evaluating the sensitivity indices of R_0 and x_{ee} to the parameters at baseline values representative of areas of high and low malaria transmission. Section 3.1 lists the baseline parameter values, including their references and the reasoning behind them. In section 3.2, we calculate R_0 and x_{ee} at the baseline parameter values and show some numerical simulations. In section 3.3, we describe the idea and methodology of sensitivity analysis, and calculate the sensitivity indices for R_0 and x_{ee}. Section 3.4 describes some of the possible control strategies and their effects on disease transmission and spread. Section 3.5 provides concluding remarks on the comparison of the control strategies. In chapter 4, we summarize our results and discuss possibilities for future work and improvements to the model.

1.1 Survey of mathematical modeling of malaria

Mathematical modeling of malaria began in 1911 with Ross' model [62] and major extensions are described in Macdonald's 1957 book [49]. This Ross-Macdonald model is defined as

$$\frac{dx}{dt} = (abM/N)y(1-x) - rx \tag{1.1a}$$

$$\frac{dy}{dt} = ax(1-y) - \mu y \tag{1.1b}$$

where x is the fraction of infectious humans; y is the fraction of infectious female mosquitoes; a is the number of bites on humans by a single female mosquito per unit time (usually day); b is the probability of transmission of infection from an infected mosquito to a susceptible human per bite; M is the size of the total female mosquito population; N is the size of the total human population; r is the rate of recovery for infectious humans ($1/r$ is the average duration of the infectious period); and μ is the death rate of the female mosquito population ($1/\mu$ is the average lifespan of an adult mosquito). In a survey, Aron and May [3] describe the properties of this

model, including the derivation of the reproductive number, R_0, as

$$R_0 = \frac{M}{N}\frac{a^2 b}{\mu r}. \tag{1.2}$$

The reproductive number, R_0, is defined as the number of secondary infections that one infectious person would produce in a fully susceptible population through the entire duration of the infectious period. The idea is derived from the idea of a reproductive number in population dynamics which is defined as the expected number of offspring that one organism will produce over its lifespan. Heesterbeek in [32] conducts a review on the history of R_0. Numerous other articles, [17], [18], [31], [33], [61], [64] and [68] are devoted to the calculation of R_0 for different models of various diseases, including malaria.

For simple homogeneous models, the reproductive number can be defined as the product of the number of contacts that one individual has per unit time, the probability of transmission per contact and the duration of the infectious period. For (1.1), R_0 is defined as the product of the number of mosquitoes that one infectious human infects and the number of humans that one infectious mosquito infects, through the duration of their infectious periods. (aM/N) is the number of contacts with mosquitoes that one human has per unit time; the probability of transmission from an infectious human to a susceptible mosquito is assumed to be 1; and $1/r$ is the average duration of the infectious period of the human. Thus, $(M/N)(a/r)$ is the number of mosquitoes that one human infects over the entire infectious period. Similarly, a is the number of contacts with humans that one mosquito has per unit time; b is the probability of transmission from an infectious mosquito to a susceptible human; and $1/\mu$ is the average duration of the infectious period of the mosquito (female mosquitoes are infectious till death). Thus, (ab/μ) is the number of humans that one mosquito infects through its infectious lifetime. The product of the two, $(M/N)(a^2 b/(r\mu))$, thus forms the reproductive number: the number of humans that one infectious human will infect, through a generation of infectious mosquitoes.

Aron and May [3] continue their review by adding various characteristics of

malaria to the model, such as an incubation period in the mosquito, a periodically fluctuating density of mosquitoes, superinfection and a period of immunity in humans. They also include a continuum model for immunity where the dynamical variables are the population of asexual blood stages of *Plasmodium* in humans, the population of gametocytes (sexual stages of *Plasmodium* in humans), and the level of human immunity. In this system of partial differential equations, the variables depend on both time and age. The mosquitoes are modeled through V, the vectorial capacity, which is proportional to the mosquito density. This model is a significant deviation from the Ross-Macdonald model (1.1) as it does not keep track of the number of infected humans and mosquitoes. Instead, this continuum model measures the number of parasites and level of immunity in the average human. This is useful for malaria because there can be a large difference in the parasitemia load in different humans, that the Ross-Macdonald model ignores.

In a later review, Anderson and May [1] revisit many of the ideas discussed by Aron and May. Additionally, Anderson and May compile numerous data sets for parameter values, including the latent period in mosquitoes and humans, the rate of recovery for humans, the expected adult lifespan of mosquitoes and malaria prevalence data across age distributions for humans. Anderson and May also study the effect of adding age structure to the basic Ross-Macdonald model (1.1). Finally, they look at different control strategies, discussing the effects of a vaccine and the reduction of transmission rates on the malaria age-prevalence profile of the human population.

Other reviews on mathematical modeling in malaria include Nedelman [54] and Koella [39]. Nedelman surveys various data sets to statistically approximate parameters such as inoculation rates, rates of recovery and loss of immunity in humans, human-biting rates of mosquitoes and infectivity and susceptibility of humans and mosquitoes. Koella also begins with the Ross-Macdonald model (1.1) with an additional latent stage for the mosquitoes. He then studies the effect of variability of the parameters and adds an infection-rate dependent period of immunity. Using this model with immunity, he studies the effects of vaccines, comparing those that act

on asexual blood stages and those that block transmission, to show that the asexual blood stage vaccines are more effective.

An important advance for the mathematical modeling of malaria was the inclusion of acquired immunity in the model proposed by Dietz, Molineaux and Thomas in 1974 [19]. Dietz *et al.* proposed a model with two different classes of humans: one without immunity to malaria and one class with some immunity. As the non-immune class falls sick, some people recover with immunity. The immune class can get infected, but does not fall clinically ill and cannot be infectious.

The model by Dietz *et al.* also included superinfection, a phenomenon usually associated with macroparasites. As also described by Aron and May [3] and Anderson and May [1], superinfection is a significant increase of the parasite load, when an infected person is reinfected from the outside. This is usually modeled by making the recovery rate (r in the above equation (1.1)) a (usually monotonically nonincreasing) function of the inoculation rate . Various models, with superinfection, for the recovery rate, r, include:

$$\text{Ross [62]: } r = \gamma \tag{1.3a}$$

$$\text{Dietz [19]: } r = \lambda/[\exp(\lambda/\gamma) - 1] \tag{1.3b}$$

$$\text{Macdonald [49]: } r = \begin{cases} \gamma - \lambda & \gamma > \lambda \\ 0 & \gamma \leq \lambda \end{cases} \tag{1.3c}$$

where λ is the inoculation rate (defined in (1.1) as $\lambda = (abM/N)y$) and γ is the reinfection-free rate of recovery, i.e. $1/\gamma$ is the average duration of the infectious period in the absence of further infection. The model for superinfection by Dietz is also described by Bailey [6].

Another important feature of malaria is the transient nature of acquired immunity. Aron [2] reviews the compartmental and continuous models for temporary immunity in humans. In compartmental models, an additional recovered class is added. In the usual Susceptible-Infectious-Recovered-Susceptible (SIRS) or Susceptible-Exposed-Infectious-Recovered-Susceptible (SEIRS) model[1], the rate

[1] A good review of standard epidemiological models can be found in Hethcote [34].

of loss of immunity, ρ, is a constant parameter. However, sustained immunity to malaria requires continuous reinfection; thus in the absence of reinfection, immunity is lost quickly, while in the presence of a high infection rate, immunity is long-lived. This nonconstant period of immunity can be modeled by making the rate of loss of immunity, ρ, a function of the inoculation rate as in (1.4)

$$\rho(\lambda) = \frac{\lambda e^{-\lambda\tau}}{1 - e^{-\lambda\tau}} \tag{1.4}$$

where λ is again the inoculation rate and τ is the average duration of the immune period in the absence of infection.

Some of the more recent papers on the mathematical modeling of malaria have included environmental effects [48], [70] and [71]. Yang [70] describes a compartmental model where humans follow an SEIRS-type (with more than one immune class for humans) pattern and mosquitoes follow a Susceptible-Exposed-Infectious (SEI) pattern. Additionally, some of the parameters related to mosquitoes are now a function of temperature. These include the time taken for mosquito eggs to develop into adults and the time taken for *Plasmodium* gametocytes ingested by the mosquito to develop into sporozoites and migrate to the salivary glands (the incubation time in the mosquito). Yang defines a reproductive number, R_0 for this model and shows, through linear stability analysis, that the disease-free equilibrium is stable for $R_0 < 1$. He also derives an expression for an endemic equilibrium that is biologically relevant only when $R_0 > 1$. He uses numerical simulations to support his proposition that for $R_0 > 1$, the disease-free equilibrium is unstable and the endemic equilibrium is stable.

Yang and Ferreira [71] use the model by Yang [70] to study the effects of global warming. Using the estimated increase in temperature of 1.0°C – 3.5°C by the year 2100, they show that it is possible in some areas of the world for R_0 to increase above 1; for areas to change from a stable disease-free endemic state to one with low levels of endemicity and for other areas to change from low levels of endemicity to high levels. They do, however, conclude by saying that economic and social effects are still more important than temperature effects and a good health care system with

good malaria control techniques can overcome the negative effects of an increase in temperature.

Li *et al.* [48] derive a model where humans move through multiple Susceptible-Exposed-Infectious-Recovered (SEIR) stages, where a history is kept of previous infections. They include a submodel for the mosquito population with subdivisions for juveniles and adults. They use the steady state value for the adult mosquito population, from this submodel, as the input into their model for malaria transmission. They introduce dependence of the parameters for the mosquito population submodel on an environmental parameter (eg. temperature or rainfall) and calculate the dependence of the reproductive number, for the full malaria model, on this environmental parameter.

Other recent models have included the spread of drug-resistant *Plasmodium* [40] and of the evolution of immunity [41]. Koella and Antia [40] discuss a model where, starting with the Ross-Macdonald model (1.1) and moving to more complicated models, they include a strain of disease that is resistant to treatment. Their results show that in their simplest models, there is a threshold value of fraction of infectious humans treated, below which there is no resistance to drugs, and above which, resistance to treatment spreads. In the more complicated models, this kind of resistance is usually not fixed, but there is some level of sensitivity to drugs that is maintained in the population. Koella and Boëte [41] study a host-parasite evolution model of malaria where the host invests in its immune system over time and the parasite invests in its ability to evade the host's immune response.

The model for malaria transmission that we analyze, is an extension of the equations introduced by Ngwa and Shu [56]. In the Ngwa and Shu model, humans follow an SEIRS-like pattern and mosquitoes follow a SEI pattern, similar to that described by Yang [70] but with only one immune class for humans. Humans move from the susceptible to the exposed class at some probability when they come into contact with an infectious mosquito, and then to the infectious class, as in conventional SEIRS models. However, infectious people can then recover with, or without, a gain in immunity; and either return to the susceptible class, or move to the recovered

class. A new feature of this model is that although individuals in the recovered class are assumed to be "immune", in the sense that they do not suffer from serious illness and do not contract clinical malaria, they still have low levels of *Plasmodium* in their blood stream and can pass the infection to susceptible mosquitoes. After some period of time these recovered individuals return to the susceptible class.

Susceptible mosquitoes get infected and move to the exposed class, at some probability when they come into contact with either infectious humans or recovered humans (albeit at a much lower probability). They then pass on to the infectious class.

Both humans and mosquitoes leave the population through a density dependent natural death rate. This allows the model to account for changing human and mosquito populations. Variations in mosquito populations are crucial to the dynamics of malaria, and constant population models do not account for this. The model also includes human disease-induced death as mortality for malaria in areas of high transmission can be high, especially in infants.

Ngwa and Shu analyze this model assuming a linear per capita death rate. They convert the system to dimensionless quantities and in these new variables, define a reproductive number, R_0.

They show that when $R_0 > 1$, there exists an endemic equilibrium (non-negative solution distinct from the disease-free equilibrium), and furthermore, with no disease-induced death, this endemic equilibrium is unique. Using linear analysis, they also show that the disease-free equilibrium is locally asymptotically stable when $R_0 \leq 1$ and the unique endemic equilibrium (for no disease-induced death) is locally asymptotically stable when $R_0 > 1$. They conclude by using numerical simulations to support their proposition that the endemic equilibrium is stable for $R_0 > 1$.

In a second paper [55], Ngwa rewrites the reproductive number in terms of the original (with dimension) parameters. He also includes a small disease induced death rate, using perturbation analysis to evaluate a first order approximation to the endemic equilibrium with disease induced death. Finally, he conducts some

numerical simulations on a stochastic expansion of the model.

This profusion of models has been driven by the need to understand different aspects of the complex malaria epidemiology. In the model we analyze, we aim to capture some of the more important aspects of this epidemiology while still keeping it mathematically tractable. Some of the important factors that we include are the presence of an exposed state in mosquitoes and dynamically changing human and mosquito populations, including human immigration and disease-induced death.

CHAPTER 2

DESCRIPTION AND ANALYSIS OF MATHEMATICAL MODEL

2.1 Malaria model

We analyze a model, similar to that by Ngwa and Shu [56], describing the transmission of malaria. The new model (Figure 2.1) divides the human population into 4 classes: susceptible, S_h, exposed, E_h, infectious, I_h, and recovered (immune), R_h. People enter the susceptible class, either through birth (at a constant per capita rate) or through immigration (at a constant rate). When an infectious mosquito bites a susceptible human, there is some finite probability that the parasite (in the form of sporozoites) will be passed on to the human and the person will move to the exposed class. The parasite then travels to the liver where it develops into its next life stage. After a certain period of time, the parasite (in the form of merozoites) enters the blood stream, usually signaling the clinical onset of malaria. In our model, people from the exposed class enter the infectious class at a rate that is the reciprocal of the duration of the latent period. After some time, the infectious humans recover and move to the recovered class. The recovered humans have some immunity to the disease and do not get clinically ill, but they still harbour low levels of parasite in their blood stream and can pass the infection to mosquitoes. After some period of time, they lose their immunity and return to the susceptible class. Humans leave the population through a density-dependent per capita emigration and natural death rate, and through a per capita disease-induced death rate.

We divide the mosquito population into 3 classes: susceptible, S_v, exposed, E_v, and infectious, I_v. Female mosquitoes (we do not include male mosquitoes in our model because only female mosquitoes bite animals for blood meals) enter the susceptible class through birth. The parasite (in the form of gametocytes) enters the mosquito, with some probability, when the mosquito bites an infectious human

or a recovered human (the probability of transmission of infection from a recovered human is much lower than that from an infectious human); and the mosquito moves from the susceptible to the exposed class. After some period of time, dependent on the ambient temperature and humidity, the parasite develops into sporozoites and enters the mosquito's salivary glands; and the mosquito moves from the exposed class to the infectious class. The mosquito remains infectious for life. Mosquitoes leave the population through a per capita density-dependent natural death rate.

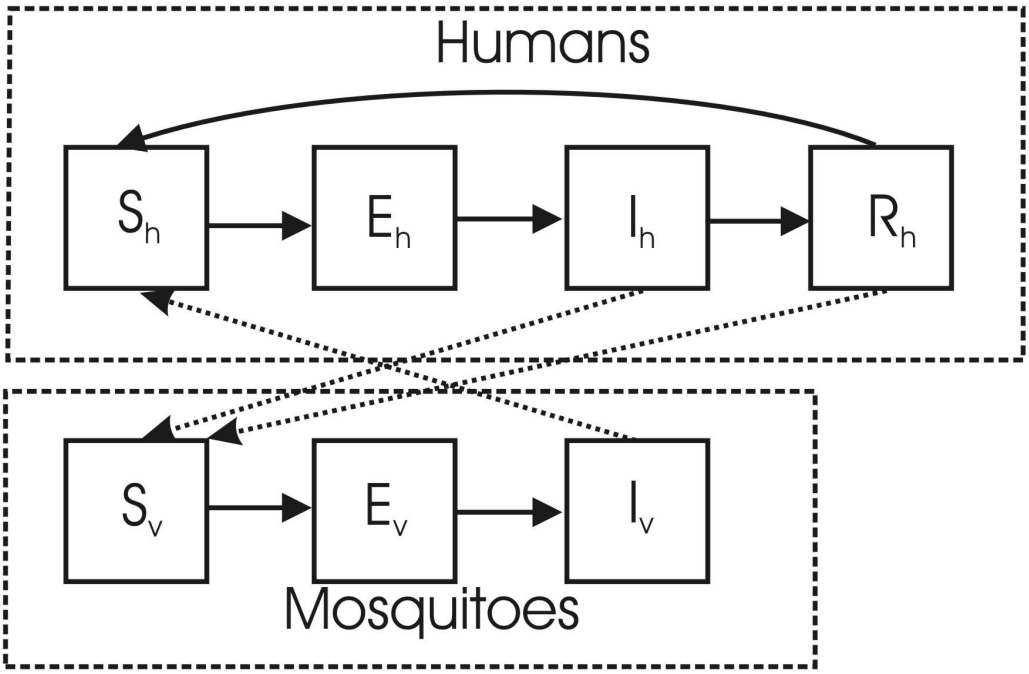


Figure 2.1: A schematic of the mathematical model for malaria transmission. Susceptible humans, S_h, get infected at a certain probability when they contact infectious mosquitoes. They then progress through the exposed, E_h, infectious, I_h, and recovered, R_h, classes, before reentering the susceptible class. Susceptible mosquitoes, S_v, get infected at a certain probability when they contact infectious or recovered humans and then move through the exposed, E_v, and infectious, I_v, classes. Both species follow a logistic model for their population growth, 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.

The main differences of our model, from that of Ngwa and Shu [56], is that we

have included human immigration and have excluded direct human recovery from the infectious to the susceptible class. Human migration is present throughout the world and plays a large role in the epidemiology of diseases, including malaria. In many parts of the developing world, there is rapid urbanization as many people leave rural areas and migrate to cities in search of employment. We include this movement as a constant immigration rate into the susceptible class. We do not include immigration of infectious humans as we assume that most people who are sick will not travel. We also exclude the movement of exposed humans because, given the short time of the exposed stage, the number of exposed people is small. We do make a simplifying assumption in excluding the immigration of recovered humans. We also exclude the direct infectious-to-susceptible recovery that the model of Ngwa and Shu [56] contains. This is a realistic simplifying assumption because most people show some period of immunity before becoming susceptible again. As our model includes an exponential distribution of movement from the recovered to the susceptible class, it will include the quick return to susceptibility of some individuals. Our model is not a generalization of that of Ngwa and Shu [56]; nor is it a special case of that model.

The equations for the malaria model (Figure 2.1) are shown in (2.1). The state variables of the model are shown in Table 2.1 and the parameters used in the model are shown in Table 2.2. All parameters are assumed to be strictly positive with the exception of the disease-induced death rate, δ_h, which we assume to be nonnegative.

$$\frac{dS_h}{dt} = \Lambda_h + \psi_h N_h + \rho_h R_h - \lambda_h(t) S_h - f_h(N_h) S_h \tag{2.1a}$$
$$\frac{dE_h}{dt} = \lambda_h(t) S_h - \nu_h E_h - f_h(N_h) E_h \tag{2.1b}$$
$$\frac{dI_h}{dt} = \nu_h E_h - \gamma_h I_h - f_h(N_h) I_h - \delta_h I_h \tag{2.1c}$$
$$\frac{dR_h}{dt} = \gamma_h I_h - \rho_h R_h - f_h(N_h) R_h \tag{2.1d}$$
$$\frac{dS_v}{dt} = \psi_v N_v - \lambda_v(t) S_v - f_v(N_v) S_v \tag{2.1e}$$
$$\frac{dE_v}{dt} = \lambda_v(t) S_v - \nu_v E_v - f_v(N_v) E_v \tag{2.1f}$$
$$\frac{dI_v}{dt} = \nu_v E_v - f_v(N_v) I_v \tag{2.1g}$$

The total population sizes are $N_h = S_h + E_h + I_h + R_h$ and $N_v = S_v + E_v + I_v$ with

$$\frac{dN_h}{dt} = \Lambda_h + \psi_h N_h - f_h(N_h) N_h - \delta_h I_h \tag{2.2a}$$
$$\frac{dN_v}{dt} = \psi_v N_v - f_v(N_v) N_v \tag{2.2b}$$

and the inoculation rates are

$$\lambda_h = \frac{\beta_{hv} \sigma_{vh} I_v}{N_h} \tag{2.3a}$$
$$\lambda_v = \frac{\beta_{vh} \sigma_{vh} I_h}{N_h} + \frac{\tilde{\beta}_{vh} \sigma_{vh} R_h}{N_h}. \tag{2.3b}$$

Table 2.1: The state variables for the malaria model (2.1).

S_h: The number of susceptible humans.
E_h: The number of exposed humans.
I_h: The number of infectious humans.
R_h: The number of recovered (immune and asymptomatic, but slightly infectious) humans.
S_v: The number of susceptible mosquitoes.

E_v: The number of exposed mosquitoes.
I_v: The number of infectious mosquitoes.
N_h: The total human population.
N_v: The total mosquito population.

Table 2.2: The parameters for the malaria model (2.1).

Λ_h:	The immigration rate of humans. Dimensions: Humans $\times$ Time^{-1}.
ψ_h:	The per capita birth rate of humans. Dimensions: Time^{-1}.
ψ_v:	The per capita birth rate of mosquitoes. Dimensions: Time^{-1}.
σ_{vh}:	The number of bites on humans per mosquito per unit time. Dimensions: Time^{-1}.
β_{hv}:	The probability of transmission of infection from an infectious mosquito to a susceptible human given that a contact between the two occurs. Dimensionless.
β_{vh}:	The probability of transmission of infection from an infectious human to a susceptible mosquito given that a contact between the two occurs. Dimensionless.
$\tilde{\beta}_{vh}$:	The 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:	The 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. Dimensions: Time^{-1}.
ν_v:	The 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. Dimensions: Time^{-1}.
γ_h:	The 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. Dimensions: Time^{-1}.
δ_h:	The per capita disease-induced death rate for humans. Dimensions: Time^{-1}.
ρ_h:	The per capita rate of loss of immunity for humans. $1/\rho_h$ is the average duration of the immune period. Dimensions: Time^{-1}.
$f_h(N_h)$:	$= \mu_{1h} + \mu_{2h}N_h$. The per capita density-dependent death and emigration rate for humans. Dimensions: Time^{-1}.
$f_v(N_v)$:	$= \mu_{1v} + \mu_{2v}N_v$. The per capita density-dependent death rate for mosquitoes. Dimensions: Time^{-1}.
μ_{1h}:	The density independent part of the death (and emigration) rate for humans. Dimensions: Time^{-1}.

μ_{2h}: The density dependent part of the death (and emigration) rate for humans. Dimensions: Humans^{-1} $\times$ Time^{-1}.

μ_{1v}: The density independent part of the death rate for mosquitoes. Dimensions: Time^{-1}.

μ_{2v}: The density dependent part of the death rate for mosquitoes. Dimensions: Mosquitoes^{-1} $\times$ Time^{-1}.

To analyze the malaria model (2.1) more easily, we work with fractional quantities instead of actual populations by scaling the population of each class by the total species population. We let:

$$e_h = \frac{E_h}{N_h} \text{ and } i_h = \frac{I_h}{N_h} \text{ and } r_h = \frac{R_h}{N_h} \tag{2.4}$$

with

$$S_h = s_h N_h = (1 - e_h - i_h - r_h)N_h \tag{2.5}$$

and

$$e_v = \frac{E_v}{N_v} \text{ and } i_v = \frac{I_v}{N_v} \tag{2.6}$$

with

$$S_v = s_v N_v = (1 - e_v - i_v)N_v. \tag{2.7}$$

Differentiation of the scaling equations (2.4) and (2.6) gives us

$$\frac{dE_h}{dt} = \frac{de_h}{dt}N_h + e_h\frac{dN_h}{dt} \tag{2.8}$$

and

$$\frac{dE_v}{dt} = \frac{de_v}{dt}N_v + e_v\frac{dN_v}{dt} \tag{2.9}$$

and so on for the rest of the variables.

Solving for the derivatives of the scaled variables we obtain

$$\frac{de_h}{dt} = \frac{1}{N_h}\left[\frac{dE_h}{dt} - e_h\frac{dN_h}{dt}\right] \tag{2.10}$$

and

$$\frac{de_v}{dt} = \frac{1}{N_v}\left[\frac{dE_v}{dt} - e_v\frac{dN_v}{dt}\right] \tag{2.11}$$

and so on for the other variables.

This creates a new 7-dimensional system of equations with two dimensions for the two total population variables, N_h and N_v, and five dimensions for the fractional population variables with disease, e_h, i_h, r_h, e_v and i_v:

$$\begin{aligned}
\frac{de_h}{dt} &= \sigma_{vh}\beta_{hv}\frac{N_v}{N_h}i_v\left(1-e_h-i_h-r_h\right) - \left(\nu_h+\psi_h+\frac{\Lambda_h}{N_h}\right)e_h + \\
&\quad \delta_h i_h e_h && \text{(2.12a)}\\
\frac{di_h}{dt} &= \nu_h e_h - \left(\gamma_h+\delta_h+\psi_h+\frac{\Lambda_h}{N_h}\right)i_h + \delta_h i_h^2 && \text{(2.12b)}\\
\frac{dr_h}{dt} &= \gamma_h i_h - \left(\rho_h+\psi_h+\frac{\Lambda_h}{N_h}\right)r_h + \delta_h i_h r_h && \text{(2.12c)}\\
\frac{dN_h}{dt} &= \Lambda_h + \psi_h N_h - (\mu_{1h}+\mu_{2h}N_h)N_h - \delta_h i_h N_h && \text{(2.12d)}\\
\frac{de_v}{dt} &= \sigma_{vh}\left(\beta_{vh}i_h+\tilde{\beta}_{vh}r_h\right)(1-e_v-i_v) - (\nu_v+\psi_v)e_v && \text{(2.12e)}\\
\frac{di_v}{dt} &= \nu_v e_v - \psi_v i_v && \text{(2.12f)}\\
\frac{dN_v}{dt} &= \psi_v N_v - (\mu_{1v}+\mu_{2v}N_v)N_v && \text{(2.12g)}
\end{aligned}$$

Note that e_v and i_v do not have any meaning when $N_v = 0$, and e_h, i_h and r_h do not have any meaning when $N_h = 0$.

For this model (2.12), there exists a domain where the system of equations is epidemiologically and mathematically well-posed. We define this domain, $\mathcal{D}$, as:

$$\mathcal{D} = \left\{ \left(\begin{array}{c} e_h \\ i_h \\ r_h \\ N_h \\ e_v \\ i_v \\ N_v \end{array} \right) \in \mathbb{R}^7 \left| \begin{array}{c} e_h \geq 0, \\ i_h \geq 0, \\ r_h \geq 0, \\ e_h + i_h + r_h \leq 1, \\ N_h \geq M_{N_h} > 0, \\ e_v \geq 0, \\ i_v \geq 0, \\ e_v + i_v \leq 1, \\ N_v > 0 \end{array} \right. \right\} \cup \left\{ \left(\begin{array}{c} 0 \\ 0 \\ 0 \\ N_h \\ 0 \\ 0 \\ 0 \end{array} \right) \in \mathbb{R}^7 \left| \begin{array}{c} \\ \\ \\ N_h \geq M_{N_h} > 0 \\ \\ \\ \\ \\ \end{array} \right. \right\} \tag{2.13}$$

for some positive M_{N_h} that depends on the parameter values. This domain, $\mathcal{D}$, is valid epidemiologically as the fractionally 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 population, N_h, is positive, while the mosquito population, N_v, is nonnegative. However, if the mosquito population is zero, there is no disease. We require an artificial positive lower bound, M_{N_h}, on the human population because e_h', i_h' and r_h' are not defined at $N_h = 0$. We use the notation f' to denote df/dt.

Theorem 2.1.1 *Assuming that the initial conditions lie in $\mathcal{D}$, the system of equations for the malaria model* (2.12) *has a unique solution that exists and remains in $\mathcal{D}$ for all time $t \geq 0$.*

Proof The right hand side of the system of equations (2.12) is continuous with continuous partial derivatives in $\mathcal{D}$. It remains to show that $\mathcal{D}$ is forward-invariant. We can see from (2.12) that if $e_h = 0$, then $e_h' \geq 0$; if $i_h = 0$, then $i_h' \geq 0$; if $r_h = 0$, then $r_h' \geq 0$; if $e_v = 0$, then $e_v' \geq 0$; and if $i_v = 0$, then $i_v' \geq 0$. It is also true that if $e_h + i_h + r_h = 1$ then $e_h' + i_h' + r_h' < 0$; and if $e_v + i_v = 1$ then $e_v' + i_v' < 0$. Finally, we note that if $N_v = 0$, then $N_v' = 0$; and if $N_h = M_{N_h}$, then

$$\begin{aligned} N_h' &= \Lambda_h + \psi_h M_{N_h} - \mu_{1h} M_{N_h} - \mu_{2h} M_{N_h}^2 - \delta_h i_h M_{N_h} \\ &> \Lambda_h + \psi_h M_{N_h} - \mu_{1h} M_{N_h} - \mu_{2h} M_{N_h}^2 - \delta_h M_{N_h}. \end{aligned}$$

Thus, $N_h' > 0$ for some M_{N_h} small enough[1]. Therefore, none of the orbits can leave $\mathcal{D}$ and a unique solution exists for all time. □

We denote points in $\mathcal{D}$ by x, where

$$x = (e_h, i_h, r_h, N_h, e_v, i_v, N_v).$$

2.2 Equilibrium points without disease and reproductive number

2.2.1 Existence of equilibrium points without disease

We first look at equilibrium points 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. We denote the positive cone in $\mathbb{R}^7$ by $\mathbb{R}^7_+$ and the boundary of $\mathbb{R}^7_+$ by $\partial\mathbb{R}^7_+$.

Lemma 2.2.1 *For all equilibrium points on $\mathcal{D} \cap \partial\mathbb{R}^7_+$, $e_h = i_h = r_h = e_v = i_v = 0$.*

Proof We need to show that for an equilibrium point in $\mathcal{D}$, if any one of diseased classes is zero, all the rest are also equal to zero. We first define the conditions:

(H1): $e_h = 0$
(H2): $i_h = 0$
(H3): $r_h = 0$
(H4): $e_v = 0$
(H5): $i_v = 0$
(H6): (H1) and (H2) and (H3)
(H7): (H4) and (H5).

We show by setting the right hand side of (2.12) equal to 0, that if any one of the above statements is true, all the others are true. For $i_h' = 0$, (H1) is true if and

[1]If we were to allow the case $\Lambda_h = 0$, then we would require $\psi_h > (\mu_{1h} + \delta_h)$ for a different appropriate M_{N_h} small enough.

only if (H2) is true[2]. Similarly, for $r_h' = 0$, (H2) is true if and only if (H3) is true. Thus, if any one of (H1), (H2) or (H3) is true, (H6) is true. From $e_h' = 0$, we see that if (H6) is true, then (H5) is true. Also, for $i_v' = 0$, (H4) is true if and only if (H5) is true. Thus, if either one of (H4) or (H5) is true, then (H7) is true. Finally, for $e_v' = 0$, if (H7) is true, then both (H2) and (H3) are true. □

Theorem 2.2.2 *The malaria model* (2.12) *has exactly two equilibrium points with no disease in the population (on* $\mathcal{D} \cap \partial\mathbb{R}^7_+$*). One equilibrium point contains only humans without disease (and no mosquitoes) and we label that as the mosquito-free equilibrium,* x_{mfe}*:*

$$x_{mfe} = \left(0, 0, 0, \frac{(\psi_h - \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}}{2\mu_{2h}}, 0, 0, 0\right). \tag{2.14}$$

The second point contains humans and mosquitoes but no disease, which we label as the disease-free equilibrium, x_{dfe}*:*

$$x_{dfe} = \left(0, 0, 0, \frac{(\psi_h - \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}}{2\mu_{2h}}, 0, 0, \frac{\psi_v - \mu_{1v}}{\mu_{2v}}\right). \tag{2.15}$$

Proof We need to show that x_{mfe} and x_{dfe} are equilibrium points of (2.12); and that there are no other equilibrium points on $\mathcal{D} \cap \partial\mathbb{R}^7_+$. The first can be seen by substituting the equilibrium points, (2.14) and (2.15), into the system of equations (2.12).

We know from Lemma 2.2.1 that on $\mathcal{D} \cap \partial\mathbb{R}^7_+$, $e_h = i_h = r_h = e_v = i_v = 0$. For $i_h = 0$, the only equilibrium point for N_h from (2.12d) is
$N_h = ((\psi_h - \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h})/(2\mu_{2h})$; and the only two equilibrium points for N_v from (2.12g) are $N_v = 0$ and $N_v = (\psi_v - \mu_{1v})/\mu_{2v}$. Thus, the only two equilibrium points on $\mathcal{D} \cap \partial\mathbb{R}^7_+$ are x_{mfe} and x_{dfe}. □

[2]As the right-hand side of (2.12b) is a quadratic function of i_h, there are 2 possible solutions of i_h when $i_h' = 0$ and $e_h = 0$. However, the nonzero solution of i_h is greater than 1 and is thus outside of $\mathcal{D}$.

For ease of notation, we label the positive equilibrium human and mosquito population values (in the absence of disease) by N_h^* and N_v^*, respectively.

$$N_h^* = \frac{(\psi_h - \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}}{2\mu_{2h}} \tag{2.16a}$$

$$N_v^* = \frac{\psi_v - \mu_{1v}}{\mu_{2v}} \tag{2.16b}$$

2.2.2 Reproductive number

We use the next generation operator approach, as described by Diekmann *et al.* in [17] to define the reproductive number, R_0, as the number of secondary infections that one infectious individual would create over the duration of the infectious period provided that everyone else is susceptible. We define the next generation operator, K, which provides the number of secondary infections in humans and mosquitoes caused by one generation of infectious humans and mosquitoes, as

$$K = \begin{pmatrix} 0 & K_{hv} \\ K_{vh} & 0 \end{pmatrix} \tag{2.17}$$

where

K_{hv}: The number of humans that one mosquito infects through its infectious lifetime, assuming all humans are susceptible.

K_{vh}: The number of mosquitoes that one human infects through the duration of the infectious period, assuming all mosquitoes are susceptible.

Using the ideas of Hyman and Li [35], we define K_{hv} and K_{vh} as a product of the probability of surviving till the infectious state, the number of contacts per unit time, the probability of transmission per contact and the duration of the infectious period:

$$K_{hv} = \frac{\nu_v}{\nu_v + \mu_{1v} + \mu_{2v}N_v^*} \cdot \sigma_{vh} \cdot \beta_{hv} \cdot \frac{1}{\mu_{1v} + \mu_{2v}N_v^*} \tag{2.18a}$$

$$\begin{aligned} K_{vh} = & \frac{\nu_h}{\nu_h + \mu_{1h} + \mu_{2h}N_h^*} \cdot \frac{\sigma_{vh}N_v^*}{N_h^*} \cdot \beta_{vh} \cdot \frac{1}{\gamma_h + \delta_h + \mu_{1h} + \mu_{2h}N_h^*} \\ & + \frac{\nu_h}{\nu_h + \mu_{1h} + \mu_{2h}N_h^*} \cdot \frac{\gamma_h}{\gamma_h + \delta_h + \mu_{1h} + \mu_{2h}N_h^*} \\ & \cdot \frac{\sigma_{vh}N_v^*}{N_h^*} \cdot \tilde{\beta}_{vh} \cdot \frac{1}{\rho_h + \mu_{1h} + \mu_{2h}N_h^*}. \end{aligned} \tag{2.18b}$$

In (2.18a), $\nu_v/(\nu_v + \mu_{1v} + \mu_{2v}N_v^*)$ is the probability that a mosquito will survive the exposed state to become infectious[3]; σ_{vh} is the number of contacts that one mosquito has with humans per unit time; β_{hv} is the probability of transmission of infection from an infectious mosquito to a susceptible human; and $1/(\mu_{1v} + \mu_{2v}N_v^*)$ is the average duration of the infectious lifetime of the mosquito. In (2.18b), the total number of mosquitoes infected by one human is the sum of the new infections from the infectious and from the recovered states of the human. In the first term of K_{vh}, $\nu_h/(\nu_h + \mu_{1h} + \mu_{2h}N_h^*)$ is the probability that a human will survive the exposed state to become infectious; $\sigma_{vh}(N_v^*/N_h^*)$ is the number of contacts that one human has with mosquitoes per unit time; β_{vh} is the probability of transmission of infection from an infectious human to a susceptible mosquito; and $1/(\gamma_h + \delta_h + \mu_{1h} + \mu_{2h}N_h^*)$ is the average duration of the infectious period of a human. In the second term, $\nu_h/(\nu_h + \mu_{1h} + \mu_{2h}N_h^*)$ is the probability that a human will survive the exposed state to become infectious; $\gamma_h/(\gamma_h + \delta_h + \mu_{1h} + \mu_{2h}N_h^*)$ is the probability that the human will then survive the infectious state to move to the recovered state; $\sigma_{vh}(N_v^*/N_h^*)$ is the number of contacts that one human has with mosquitoes per unit time; $\tilde{\beta}_{vh}$ is the probability of transmission of infection from a recovered human to a susceptible mosquito; and $1/(\rho_h + \mu_{1h} + \mu_{2h}N_h^*)$ is the average duration of the recovered period of a human.

[3]In defining periods of time and probabilities for R_0, we use the original system of equations (2.1) and not the scaled equations (2.12). As the two models are equivalent, the reproductive number is the same with either definition: $\mu_{1h} + \mu_{2h}N_h^*$ is equal to $\psi_h + \Lambda_h/N_h^*$ and $\mu_{1v} + \mu_{2v}N_v^*$ is equal to ψ_v.

R_0 is defined as the spectral radius of the next generation operator, i.e.,

$$R_0^2 = K_{vh}K_{hv} \tag{2.19}$$

Then, R_0^2 is the number of humans that one infectious human will infect, through a generation of infections in mosquitoes, assuming that previously all other humans and mosquitoes were susceptible.

Definition We define the reproductive number, R_0, as

$$R_0 = \sqrt{K_{vh}K_{hv}} \tag{2.20}$$

where K_{vh} and K_{hv} are defined in (2.18).

The original definition of R_0 (1.2) of the Ross-Macdonald model (1.1), as described by Aron and May [3] and Anderson and May [1], like the definition of R_0 given by Ngwa and Shu [56], is equivalent to our definition for R_0^2 (2.19), not R_0 (2.20). They ([1], [3] and [56]) use the traditional definition of R_0 which approximates the number of secondary infections in humans caused by one infected human, while we stay consistent with the definition given by the next generation operator approach [17] which approximates the number of secondary infections due to one infected individual (be it human or mosquito). Our definition of R_0 (2.20) includes the generation of infections in mosquitoes, so is the square root of the original definition (1.2). However, the threshold condition for both definitions is the same. Since R_0 is positive, $R_0 < 1$ is equivalent to $R_0^2 < 1$; $R_0 = 1$ is equivalent to $R_0^2 = 1$; and $R_0 > 1$ is equivalent to $R_0^2 > 1$.

2.2.3 Stability of equilibrium points without disease

We conduct linear stability on the two equilibrium points without disease, x_{mfe} (2.14) and x_{dfe} (2.15). The Jacobian of the malaria model (2.12) is:

$$J = \begin{pmatrix} J_{11} & J_{12} & J_{13} & J_{14} & 0 & J_{16} & J_{17} \\ J_{21} & J_{22} & 0 & J_{24} & 0 & 0 & 0 \\ 0 & J_{32} & J_{33} & J_{34} & 0 & 0 & 0 \\ 0 & J_{42} & 0 & J_{44} & 0 & 0 & 0 \\ 0 & J_{52} & J_{53} & 0 & J_{55} & J_{56} & 0 \\ 0 & 0 & 0 & 0 & J_{65} & J_{66} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & J_{77} \end{pmatrix} \tag{2.21}$$

with

$$\begin{aligned}
J_{11} &= -\sigma_{vh}\beta_{hv}N_v i_v/N_h - (\nu_h + \psi_h + \Lambda_h/N_h) + \delta_h i_h \\
J_{12} &= -\sigma_{vh}\beta_{hv}N_v i_v/N_h + \delta_h e_h \\
J_{13} &= -\sigma_{vh}\beta_{hv}N_v i_v/N_h \\
J_{14} &= -(\sigma_{vh}\beta_{hv}N_v i_v/N_h^2)(1 - e_h - i_h - r_h) + \Lambda_h e_h/N_h^2 \\
J_{16} &= (\sigma_{vh}\beta_{hv}N_v/N_h)(1 - e_h - i_h - r_h) \\
J_{17} &= (\sigma_{vh}\beta_{hv}i_v/N_h)(1 - e_h - i_h - r_h) \\
J_{21} &= \nu_h \\
J_{22} &= -(\gamma_h + \delta_h + \psi_h + \Lambda_h/N_h) + 2\delta_h i_h \\
J_{24} &= \Lambda_h i_h/N_h^2 \\
J_{32} &= \gamma_h + \delta_h r_h \\
J_{33} &= -(\rho_h + \psi_h + \Lambda_h/N_h) + \delta_h i_h \\
J_{34} &= \Lambda_h r_h/N_h^2 \\
J_{42} &= -\delta_h N_h \\
J_{44} &= \psi_h - \mu_{1h} - 2\mu_{2h}N_h - \delta_h i_h \\
J_{52} &= \sigma_{vh}\beta_{vh}(1 - e_v - i_v) \\
J_{53} &= \sigma_{vh}\tilde{\beta}_{vh}(1 - e_v - i_v) \\
J_{55} &= -\sigma_{vh}(\beta_{vh}i_h + \tilde{\beta}_{vh}r_h) - (\nu_v + \psi_v) \\
J_{56} &= -\sigma_{vh}(\beta_{vh}i_h + \tilde{\beta}_{vh}r_h) \\
J_{65} &= \nu_v \\
J_{66} &= -\psi_v \\
J_{77} &= \psi_v - \mu_{1v} - 2\mu_{2v}N_v
\end{aligned}$$

Theorem 2.2.3 *The mosquito-free equilibrium point, x_{mfe}, is locally asymptotically stable if the mosquito birth rate is less than the mosquito death rate ($\psi_v < \mu_{1v}$) and unstable if the mosquito birth rate is greater than the mosquito death rate ($\psi_v > \mu_{1v}$).*

Proof The Jacobian evaluated at x_{mfe} (2.14) is a lower triangular matrix of the form:

$$J = \begin{pmatrix} J_{11} & 0 & 0 & 0 & 0 & 0 & 0 \\ J_{21} & J_{22} & 0 & 0 & 0 & 0 & 0 \\ 0 & J_{32} & J_{33} & 0 & 0 & 0 & 0 \\ 0 & J_{42} & 0 & J_{44} & 0 & 0 & 0 \\ 0 & J_{52} & J_{53} & 0 & J_{55} & 0 & 0 \\ 0 & 0 & 0 & 0 & J_{65} & J_{66} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & J_{77} \end{pmatrix}. \tag{2.22}$$

The eigenvalues are the diagonal entries of the Jacobian:

$$\begin{aligned} \eta_1 &= -(\nu_h + \psi_h + \Lambda_h/N_h^*) \\ \eta_2 &= -(\gamma_h + \delta_h + \psi_h + \Lambda_h/N_h^*) \\ \eta_3 &= -(\rho_h + \psi_h + \Lambda_h/N_h^*) \\ \eta_4 &= \psi_h - \mu_{1h} - 2\mu_{2h}N_h^* \\ &= -\sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h} \\ \eta_5 &= -(\nu_v + \psi_v) \\ \eta_6 &= -\psi_v \\ \eta_7 &= \psi_v - \mu_{1v} \end{aligned}$$

We see that all eigenvalues are negative for $\psi_v < \mu_{1v}$ and one eigenvalue, η_7, is positive for $\psi_v > \mu_{1v}$. □

It makes perfect sense that the mosquito free equilibrium point is locally asymptotically stable if the mosquito death rate is greater than the mosquito birth rate, and unstable if the mosquito birth rate is greater than the mosquito death rate.

Theorem 2.2.4 *The disease-free equilibrium point, x_{dfe}, is locally asymptotically stable if $R_0 < 1$ and the mosquito birth rate is greater than the mosquito death rate ($\psi_v > \mu_{1v}$); and is unstable if either $R_0 > 1$ or the mosquito birth rate is less than the mosquito death rate ($\psi_v < \mu_{1v}$).*

Proof The Jacobian evaluated at x_{dfe} (2.15) is of the form:

$$J = \begin{pmatrix} J_{11} & 0 & 0 & 0 & 0 & J_{16} & 0 \\ J_{21} & J_{22} & 0 & 0 & 0 & 0 & 0 \\ 0 & J_{32} & J_{33} & 0 & 0 & 0 & 0 \\ 0 & J_{42} & 0 & J_{44} & 0 & 0 & 0 \\ 0 & J_{52} & J_{53} & 0 & J_{55} & 0 & 0 \\ 0 & 0 & 0 & 0 & J_{65} & J_{66} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & J_{77} \end{pmatrix}. \tag{2.23}$$

As the fourth and seventh columns (corresponding to the total human and mosquito populations) contain only the diagonal terms, these diagonal terms form two eigenvalues of the Jacobian:

$$\begin{aligned} \eta_6 &= \psi_h - \mu_{1h} - 2\mu_{2h}N_h^* && \text{(2.24a)} \\ &= -\sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h} \\ \eta_7 &= \psi_v - \mu_{1v} - 2\mu_{2v}N_v^* && \text{(2.24b)} \\ &= -(\psi_v - \mu_{1v}). \end{aligned}$$

The other 5 eigenvalues are the roots of the characteristic equation of the matrix formed by excluding the 4^{th} and 7^{th} rows and columns of the Jacobian (2.23):

$$A_5\eta^5 + A_4\eta^4 + A_3\eta^3 + A_2\eta^2 + A_1\eta + A_0 = 0 \tag{2.25}$$

with

$$\begin{aligned} A_5 &= 1 \\ A_4 &= B_1 + B_2 + B_3 + B_4 + B_5 \\ A_3 &= B_1B_2 + B_1B_3 + B_1B_4 + B_1B_5 + B_2B_3 + B_2B_4 + B_2B_5 \\ &\quad + B_3B_4 + B_3B_5 + B_4B_5 \\ A_2 &= B_1B_2B_3 + B_1B_2B_4 + B_1B_2B_5 + B_1B_3B_4 + B_1B_3B_5 + \\ &\quad B_1B_4B_5 + B_2B_3B_4 + B_2B_3B_5 + B_2B_4B_5 + B_3B_4B_5 \\ A_1 &= B_1B_2B_3B_4 + B_1B_2B_3B_5 + B_1B_2B_4B_5 + B_1B_3B_4B_5 + \\ &\quad B_2B_3B_4B_5 - B_6B_7B_8B_9 \\ A_0 &= B_1B_2B_3B_4B_5 - (B_3B_6B_7B_8B_9 + B_6B_7B_9B_{10}B_{11}) \end{aligned}$$

and

$$
\begin{aligned}
B_1 &= \nu_h + \psi_h + \Lambda_h/N_h^* \\
&= \nu_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right) \\
B_2 &= \gamma_h + \delta_h + \psi_h + \Lambda_h/N_h^* \\
&= \gamma_h + \delta_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right) \\
B_3 &= \rho_h + \psi_h + \Lambda_h/N_h^* \\
&= \rho_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right) \\
B_4 &= \nu_v + \psi_v \\
B_5 &= \psi_v \\
B_6 &= \sigma_{vh}\beta_{hv}N_v^*/N_h^* \\
B_7 &= \nu_h \\
B_8 &= \sigma_{vh}\beta_{vh} \\
B_9 &= \nu_v \\
B_{10} &= \gamma_h \\
B_{11} &= \sigma_{vh}\tilde{\beta}_{vh}.
\end{aligned}
$$

From (2.24b) we can see that if $\psi_v < \mu_{1v}$, x_{dfe} is unstable; and ψ_v must be greater than μ_{1v} for x_{dfe} to be locally asymptotically stable. To evaluate the signs of the roots of (2.25), we use the Routh-Hurwitz criterion and Descartes' Rule of Sign. Using the Routh-Hurwitz criterion, we prove that when $R_0 < 1$, all roots of (2.25) have negative real part; and using Descartes' Rule of Sign, we prove that when $R_0 > 1$, there is one positive real root.

Korn and Korn [42] in §1.6-6(b) state the Routh-Hurwitz criterion as: the number of roots with positive real parts of a real algebraic equation

$$a_n x^n + a_{n-1}x^{n-1} + \ldots + a_1 x + a_0 = 0 \tag{2.26}$$

is equal to the number of sign changes (disregard vanishing terms) in either of the sequences

$$T_0, T_1, \frac{T_2}{T_1}, \frac{T_3}{T_2}, \ldots, \frac{T_n}{T_{n-1}}$$

or

$$T_0, T_1, T_1T_2, T_2T_3, \ldots, T_{n-2}T_{n-1}, a_0$$

where

$$\begin{aligned}
T_0 &= a_n \\
T_1 &= a_{n-1} \\
T_2 &= \begin{vmatrix} a_{n-1} & a_n \\ a_{n-3} & a_{n-2} \end{vmatrix} \\
T_3 &= \begin{vmatrix} a_{n-1} & a_n & 0 \\ a_{n-3} & a_{n-2} & a_{n-1} \\ a_{n-5} & a_{n-4} & a_{n-3} \end{vmatrix} \\
T_4 &= \begin{vmatrix} a_{n-1} & a_n & 0 & 0 \\ a_{n-3} & a_{n-2} & a_{n-1} & a_n \\ a_{n-5} & a_{n-4} & a_{n-3} & a_{n-2} \\ a_{n-7} & a_{n-6} & a_{n-5} & a_{n-4} \end{vmatrix} \\
\ldots &= \ldots
\end{aligned}$$

and $a_i = 0$ for $i < 0$. Given $a_n > 0$, all roots have negative real parts if and only if $T_0, T_1, T_2, \ldots, T_n$ are all positive. This is true if and only if all a_i and either all even-numbered T_k or all odd-numbered T_k are positive (Liénard-Chipart Test).

Korn and Korn [42] in §1.6-6(c) state Descartes' Rule of Sign as: the number of positive real roots of a real algebraic equation (2.26) is equal to the number, N_a, of sign changes in the sequence, $a_n, a_{n-1}, \ldots, a_0$, of coefficients, where the vanishing terms are disregarded, or it is less than N_a by a positive even integer.

We show that when $R_0 < 1$, all the coefficients, A_i, of the characteristic equation (2.25), and T_0, T_2, and T_4, are positive, so by the Routh-Hurwitz criterion, all the eigenvalues of the Jacobian (2.23) have negative real part. We then show that when $R_0 > 1$, there is one and only one sign change in the sequence $A_5, A_4, \ldots, A_0$, so by Descartes' Rule of Sign, there is one eigenvalue with positive real part and the disease-free equilibrium point is unstable.

When R_0 is less (greater) than 1, R_0^2 is also less (greater) than 1 since R_0 is strictly positive. The expression for R_0^2 (2.20) can be written, in terms of B_i, as

$$R_0^2 = \frac{B_3B_6B_7B_8B_9 + B_6B_7B_9B_{10}B_{11}}{B_1B_2B_3B_4B_5}. \tag{2.27}$$

For $R_0 < 1$, by (2.27),

$$B_3B_6B_7B_8B_9 + B_6B_7B_9B_{10}B_{11} < B_1B_2B_3B_4B_5 \tag{2.28}$$

and

$$\begin{aligned} B_3B_6B_7B_8B_9 &< B_1B_2B_3B_4B_5 & (2.29)\\ B_6B_7B_8B_9 &< B_1B_2B_4B_5. & (2.30) \end{aligned}$$

As all the B_i are positive, A_5, A_4, A_3 and A_2 are always positive. From (2.30), we see that $A_1 > 0$ and from (2.28), we see that $A_0 > 0$. Thus, for $R_0 < 1$, all A_i are positive. We now show that the even-numbered T_k are positive for $R_0 < 1$.

For the fifth-degree polynomial (2.25),

$$T_0 = A_5 \tag{2.31}$$

which is always positive.

$$T_2 = A_3A_4 - A_2A_5 \tag{2.32}$$

which we can show[4] to be a positive sum of products of B_i's so $T_2 > 0$. Lastly,

$$T_4 = A_1[A_2A_3A_4 - (A_1A_4^2 + A_2^2A_5)] - A_0[A_3(A_3A_4 - A_2A_5) - (2A_1A_4A_5 - A_2A_5^2)] \tag{2.33}$$

For ease of notation, we introduce

$$\begin{aligned} C_1 &= A_2A_3A_4 - (A_1A_4^2 + A_2^2A_5)\\ C_2 &= A_3(A_3A_4 - A_2A_5) - (2A_1A_4A_5 - A_2A_5^2), \end{aligned}$$

where can show that $C_1 > 0$ and $C_2 > 0$, so that

[4]To evaluate the T_k's, we expand the expressions in Mathematica.

$$T_4 = A_1C_1 - A_0C_2.$$

We define

$$C_2^{(1)} = C_2 + B_6B_7B_9B_{10}B_{11}.$$

As $C_2^{(1)} > C_2$ and $A_0 > 0$, for

$$T_4^{(1)} = A_1C_1 - A_0C_2^{(1)},$$

$T_4 > T_4^{(1)}$. Similarly, we define

$$A_0^{(1)} = A_0 + (B_3B_6B_7B_8B_9 + B_6B_7B_9B_{10}B_{11}).$$

As $A_0^{(1)} > A_0$ and $C_2^{(1)} > 0$, for

$$T_4^{(2)} = A_1C_1 - A_0^{(1)}C_2^{(1)},$$

$T_4^{(1)} > T_4^{(2)}$. Finally, we define

$$A_1^{(1)} = A_1 - (B_1B_2B_4B_5 - B_6B_7B_8B_9).$$

As $A_1^{(1)} < A_1$ (for $R_0 < 1$) and $C_1 > 0$, for

$$T_4^{(3)} = A_1^{(1)}C_1 - A_0^{(1)}C_2^{(1)},$$

$T_4^{(2)} > T_4^{(3)}$. We can show, using Mathematica, that $T_4^{(3)}$ is a sum of positive terms, so $T_4^{(3)} > 0$. As $T_4 > T_4^{(1)} > T_4^{(2)} > T_4^{(3)}$, $T_4 > 0$. Thus, for $R_0 < 1$, all roots of (2.25) have negative real parts.

When $R_0 > 1$

$$B_3B_6B_7B_8B_9 + B_6B_7B_9B_{10}B_{11} > B_1B_2B_3B_4B_5$$

so $A_0 < 0$. As A_5, A_4, A_3, and A_2 are positive, the sequence, $A_5, A_4, A_3, A_2, A_1, A_0$ has exactly one sign change. Thus, by Descartes' Rule of Sign, (2.25) has one positive real root when $R_0 > 1$.

Thus, the disease-free equilibrium point, x_{dfe}, is locally asymptotically stable if

$R_0 < 1$ (the disease will not spread) and $\psi_v > \mu_{1v}$ (the mosquitoes will not become extinct); and unstable if $R_0 > 1$, or if $\psi_v < \mu_{1v}$. Note that the Jacobian of the disease-free equilibrium (2.15) has one eigenvalue equal to 0 at $R_0 = 1$. This result makes sense intuitively because if $R_0 < 1$, on average each infected individual infects less than other individual so we would expect the disease to die out. If $R_0 > 1$, on average each infected individual infects more than other individual so we would expect the disease to spread.

□

2.3 Endemic equilibrium points

Endemic equilibrium points are steady state solutions where the disease persists in the population (all state variables are positive). The complexity of the system of equations (2.12) has prevented us from finding an explicit representation of the endemic equilibrium point(s). We use general bifurcation theory to prove the existence of at least one endemic equilibrium point for all $R_0 > 1$. We prove that the transcritical bifurcation at $R_0 = 1$ is supercritical when $\delta_h = 0$ (there is no disease-induced death). However, numerical results show that the bifurcation can be subcritical for some positive values of δ_h, giving rise to endemic equilibria for $R_0 < 1$.

We first rewrite the equilibrium equations for (2.12) in the form of a nonlinear eigenvalue problem:

$$\begin{aligned} u &= G(\zeta, u) \\ &= \zeta L u + h(\zeta, u) \end{aligned} \tag{2.34}$$

where $u \in Y \subset \mathbb{R}^2$, with Euclidean norm, $\|\cdot\|$; $\zeta \in Z \subset \mathbb{R}$ is the bifurcation parameter; L is a compact linear map on Y; and $h(\zeta, u)$ is $\mathcal{O}(\|u\|^2)$ uniformly on bounded ζ intervals. We require that both Y and Z be open and bounded sets, and that Y contains the point, 0. Z is the open and bounded set, $Z = \{\zeta \in \mathbb{R} | -M_Z < \zeta < M_Z\}$. Z must include the characteristic values of L so there is

minimum value that M_Z can have, but M_Z may be arbitrarily large. We take the equilibrium equations (the right hand side of (2.12)), reduce the dimension through some algebraic manipulations, and rewrite them in the form of (2.34) with

$$u = \begin{pmatrix} e_h \\ e_v \end{pmatrix}$$

where e_h and e_v are equilibrium values. We use $\zeta = \sigma_{vh}$ for the bifurcation parameter. We also define $\Omega = Z \times Y$ so that the pair $(\zeta, u) \in \Omega$. We denote the boundary of Ω by $\partial\Omega$.

A corollary by Rabinowitz [60] (Corollary 1.12) states that if $\zeta_0 \in Z$ is a characteristic value (reciprocal of an eigenvalue) of L of odd multiplicity, then there exists a continuum of nontrivial solution-pairs, (ζ, u) of (2.34) that intersects the trivial solution (that is, $(\zeta, 0)$ for any ζ) at $(\zeta_0, 0)$ and either meets $\partial\Omega$ or meets $(\hat{\zeta}_0, 0)$ where $\hat{\zeta}_0$ is also a characteristic value of L of odd multiplicity.

We use this corollary to show that there exists a continuum of solution-pairs $(\zeta, u) \in \Omega$ for the eigenvalue equation (2.34). To each of these solution-pairs, there corresponds an equilibrium-pair (ζ, x^*) of the malaria model (2.12), where ζ is a parameter value and $x^* \in \mathbb{R}^7$ is an equilibrium point of the malaria model (2.12). We define the equilibrium-pair, $(\zeta, x^*) \in Z \times \mathbb{R}^7$, as the collection of a parameter value, ζ, and the corresponding equilibrium point, x^*, for that parameter value.

Theorem 2.3.1 *Assuming that the mosquito birth rate is greater than the mosquito death rate ($\psi_v > \mu_{1v}$), the malaria model* (2.12) *has a continuum of equilibrium-pairs, $(\zeta, x^*) \in Z \times \mathbb{R}^7$, that connects the point (ξ_1, x_{dfe}) to the hyperplane $\zeta = M_Z$ in $\mathbb{R} \times \mathbb{R}^7$ on the boundary of $Z \times \mathbb{R}^7$ for any $M_Z > \xi_1$, where x^* is in the positive cone of $\mathbb{R}^7$. The number $\xi_1 = 1/\sqrt{AB}$ where A and B are defined in* (2.55).

Proof The equilibrium equations for (2.12) are shown below in (2.35). For the remainder of this proof and §2.3, we will use the terms, e_h, i_h, r_h, N_h, e_v, i_v and N_v to represent their respective equilibrium values and not their actual values at a given time, t.

$$\begin{aligned}
\sigma_{vh}\beta_{hv}\frac{N_v}{N_h}i_v(1-e_h-i_h-r_h)-(\nu_h+\psi_h+\Lambda_h/N_h)e_h+\delta_h i_h e_h &= 0 \quad (2.35a)\\
\nu_h e_h-(\gamma_h+\delta_h+\psi_h+\Lambda_h/N_h)i_h+\delta_h i_h^2 &= 0 \quad (2.35b)\\
\gamma_h i_h-(\rho_h+\psi_h+\Lambda_h/N_h)r_h+\delta_h i_h r_h &= 0 \quad (2.35c)\\
\Lambda_h+\psi_h N_h-(\mu_{1h}+\mu_{2h}N_h)N_h-\delta_h i_h N_h &= 0 \quad (2.35d)\\
\sigma_{vh}\left(\beta_{vh}i_h+\tilde{\beta}_{vh}r_h\right)(1-e_v-i_v)-(\nu_v+\psi_v)e_v &= 0 \quad (2.35e)\\
\nu_v e_v-\psi_v i_v &= 0 \quad (2.35f)\\
\psi_v N_v-(\mu_{1v}+\mu_{2v}N_v)N_v &= 0 \quad (2.35g)
\end{aligned}$$

We do not attempt to rewrite the entire system (2.35) in the form of (2.34), but reduce the equilibrium equations to a two-dimensional system for e_h and e_v. We do so by solving for the other variables, either explicitly as functions of the parameters, or in terms of e_h and e_v.

We solve (2.35g) for N_v, explicitly expressing the positive equilibrium for the total mosquito population in terms of parameters (exactly as in the disease-free case (2.16b)).

$$N_v=\frac{\psi_v-\mu_{1v}}{\mu_{2v}} \tag{2.36}$$

Solving for i_v in (2.35f) in terms of e_v we find:

$$i_v=\frac{\nu_v}{\psi_v}e_v. \tag{2.37}$$

Similarly, we write the positive equilibrium for the total human population, N_h, in terms of i_h from (2.35d) as

$$N_h=\frac{(\psi_h-\mu_{1h}-\delta_h i_h)+\sqrt{(\psi_h-\mu_{1h}-\delta_h i_h)^2+4\mu_{2h}\Lambda_h}}{2\mu_{2h}}. \tag{2.38}$$

Using (2.38) in (2.35c), we solve for r_h in terms of i_h.

$$r_h=\frac{2\gamma_h i_h}{2\rho_h+(\psi_h+\mu_{1h}-\delta_h i_h)+\sqrt{(\psi_h-\mu_{1h}-\delta_h i_h)^2+4\mu_{2h}\Lambda_h}} \tag{2.39}$$

Given the nonlinear nature of (2.35b), it is not feasible (or useful) to solve for i_h in terms of e_h explicitly. We therefore use (2.38) to rewrite (2.35b) as

$$\begin{aligned} e_h &= \frac{\gamma_h + \delta_h + \frac{1}{2}\left((\psi_h + \mu_{1h} - \delta_h i_h) + \sqrt{(\psi_h - \mu_{1h} - \delta_h i_h)^2 + 4\mu_{2h}\Lambda_h}\right)}{\nu_h} i_h \\ &= g(i_h) \end{aligned} \tag{2.40}$$

We note that

$$g(0) = 0$$

and

$$e_h^{max} = g(1) = \frac{\gamma_h + \delta_h + \frac{1}{2}\left((\psi_h + \mu_{1h} - \delta_h) + \sqrt{(\psi_h - \mu_{1h} - \delta_h)^2 + 4\mu_{2h}\Lambda_h}\right)}{\nu_h}. \tag{2.41}$$

The right-hand side of (2.40) is a smooth function of i_h with range $[0, \infty)$. We can show (using Mathematica) that $g'(i_h) > 0$ for $i_h \in [0, 1]$ so $g(i_h)$ is monotonically increasing for i_h between 0 and 1. Thus for $e_h \in [0, e_h^{max}]$, there exists a smooth function,

$$i_h = y(e_h) \tag{2.42}$$

with domain, $[0, e_h^{max}]$, and range, $[0, 1]$. As $g'(0) > 0$, the smooth function, $y(e_h)$ would extend to some small $e_h < 0$. Using (2.38) and (2.39), we can also express N_h and r_h as functions of e_h. We now introduce the bounded open subset of $\mathbb{R}^2$,

$$Y = \left\{ \begin{pmatrix} e_h \\ e_v \end{pmatrix} \in \mathbb{R}^2 \;\middle|\; \begin{array}{l} -\epsilon_h < e_h < e_h^{max} \\ -\epsilon_v < e_v < 1 \end{array} \right\} \tag{2.43}$$

for some $\epsilon_v > 0$ and some $\epsilon_h > 0$. By substituting (2.36), (2.37), (2.38), (2.39), and (2.42) into (2.35a) and (2.35e), we reformulate the seven equilibrium equations (2.35) equivalently as two equations for the components $(e_h, e_v) \in Y$. In order to place these two equations into the Rabinowitz form (2.34), we need to determine

lower order terms. Towards this end, we rewrite (2.35b) as

$$f(e_h, i_h) = 0 \tag{2.44}$$

where

$$\begin{aligned} f(e_h, i_h) &= \nu_h e_h - \\ &\left[\gamma_h + \delta_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h} - \delta_h i_h) + \sqrt{(\psi_h - \mu_{1h} - \delta_h i_h)^2 + 4\mu_{2h}\Lambda_h}\right)\right] i_h. \end{aligned} \tag{2.45}$$

and use implicit differentiation to write $i_h = y(e_h)$ as a Taylor polynomial of the form

$$i_h = y_1 e_h + y_2 e_h^2 + \ldots \tag{2.46}$$

where

$$y_1 = -\left.\frac{\frac{\partial f}{\partial e_h}}{\frac{\partial f}{\partial i_h}}\right|_{i_h = e_h = 0}.$$

The partial derivatives of $f(e_h, i_h)$ are

$$\frac{\partial f}{\partial e_h}(e_h, i_h) = \nu_h \tag{2.47}$$

$$\begin{aligned} \frac{\partial f}{\partial i_h}(e_h, i_h) &= \frac{1}{2}\delta_h \left[i_h + \frac{\psi_h - \mu_{1h} - \delta_h i_h}{\sqrt{(\psi_h - \mu_{1h} - \delta_h i_h)^2 + 4\Lambda_h \mu_{2h}}}\right] i_h \\ &- \left[\gamma_h + \delta_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h} - \delta_h i_h) + \sqrt{(\psi_h - \mu_{1h} - \delta_h i_h)^2 + 4\mu_{2h}\Lambda_h}\right)\right] \end{aligned} \tag{2.48}$$

and

$$y_1 = \frac{\nu_h}{\gamma_h + \delta_h + \frac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)}. \tag{2.49}$$

Finally, we substitute the Taylor approximation for i_h (2.46) into r_h (2.39) and N_h (2.38), and then all three, along with i_v (2.37) and N_v (2.36) into the equilibrium equations for e_h (2.35a) and e_v (2.35e), to provide first order approximations to the

equilibrium equations

$$0 = f_{1\_10}e_h + f_{1\_01}e_v + \mathcal{O}(u^2) \tag{2.50a}$$
$$0 = f_{2\_10}e_h + f_{2\_01}e_v + \mathcal{O}(u^2) \tag{2.50b}$$

where

$$u = \begin{pmatrix} e_h \\ e_v \end{pmatrix} \tag{2.51}$$

and

$$f_{1\_10} = -\left[\nu_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)\right] \tag{2.52a}$$
$$f_{1\_01} = \sigma_{vh}\frac{2\mu_{2h}\nu_v\beta_{hv}(\psi_v - \mu_{1v})}{\psi_v\mu_{2v}\left((\psi_h - \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)} \tag{2.52b}$$
$$f_{2\_10} = \sigma_{vh}\frac{\nu_h}{\gamma_h + \delta_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)} \tag{2.52c}$$
$$\times\left[\beta_{vh} + \frac{\gamma_h\tilde{\beta}_{vh}}{\rho_h + \tfrac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)}\right]$$
$$f_{2\_01} = -(\psi_v + \nu_v)\,. \tag{2.52d}$$

Although we have calculated y_2 in (2.46) and have expressions for the coefficients of the second order terms in (2.50), we do not explicitly show them here as they are lengthy and not needed for our purposes.

To apply Corollary 1.12 of Rabinowitz [60], we factor out $\zeta = \sigma_{vh}$, after some algebraic manipulations on (2.50), to produce

$$\begin{pmatrix} e_h \\ e_v \end{pmatrix} = \zeta\begin{pmatrix} 0 & A \\ B & 0 \end{pmatrix}\begin{pmatrix} e_h \\ e_v \end{pmatrix} + \mathcal{O}\left(\begin{pmatrix} e_h \\ e_v \end{pmatrix}^2\right) \tag{2.53}$$

or

$$u = \zeta Lu + h(\zeta, u) \tag{2.54}$$

where

$$L = \begin{pmatrix} 0 & A \\ B & 0 \end{pmatrix}$$

with

$$A = \frac{1}{\nu_h + \frac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)} \times \frac{2\mu_{2h}\nu_v\beta_{hv}(\psi_v - \mu_{1v})}{\psi_v\mu_{2v}\left((\psi_h - \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)} \tag{2.55a}$$

$$B = \left(\beta_{vh} + \frac{\gamma_h\tilde{\beta}_{vh}}{\rho_h + \frac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)}\right) \times \frac{\nu_h}{(\psi_v + \nu_v)\left(\gamma_h + \delta_h + \frac{1}{2}\left((\psi_h + \mu_{1h}) + \sqrt{(\psi_h - \mu_{1h})^2 + 4\mu_{2h}\Lambda_h}\right)\right)}. \tag{2.55b}$$

The matrix, L, has 2 distinct eigenvalues: $\pm\sqrt{AB}$. Characteristic values of a matrix are the reciprocals of its eigenvalues. For the matrix, L, we denote the two characteristic values by $\xi_1 = 1/\sqrt{AB}$ and $\xi_2 = -1/\sqrt{AB}$. The right eigenvector corresponding to the characteristic value, ξ_1 is

$$v = \begin{pmatrix} \sqrt{A} \\ \sqrt{B} \end{pmatrix}. \tag{2.56}$$

We note here that B is always positive and A is positive if and only if $\psi_v > \mu_{1v}$. Thus ξ_1 is real and corresponds to the dominant eigenvalue of L if and only if $\psi_v > \mu_{1v}$. We require this condition for the existence of the endemic equilibrium because if the mosquito death rate were greater than the mosquito birth rate, the positive equilibrium for the total mosquito population would be unstable; and the mosquito population would die out.

As $M_Z > \xi_1$ and $0 \in Y$, $(\xi_1, 0) \in \Omega$. By Corollary 1.12 of Rabinowitz [60], we know that there is a continuum of solution-pairs $(\zeta, u) \in \Omega$, whose closure contains the point $(\xi_1, 0)$, that either meets the boundary of Ω, $\partial\Omega$, or the point $(\xi_2, 0)$. We

denote the continuum of solution pairs emanating from $(\xi_1, 0)$ by $\mathscr{C}_1$ where $\mathscr{C}_1 \subset \Omega$; and from $(\xi_2, 0)$ by $\mathscr{C}_2$ where $\mathscr{C}_2 \subset \Omega$. We introduce the sets

$$\begin{aligned} Z_1 &= \{\zeta \in Z |\ \exists u \text{ such that } (\zeta, u) \in \mathscr{C}_1\} && (2.57a)\\ U_1 &= \{u \in Y |\ \exists \zeta \text{ such that } (\zeta, u) \in \mathscr{C}_1\} && (2.57b)\\ Z_2 &= \{\zeta \in Z |\ \exists u \text{ such that } (\zeta, u) \in \mathscr{C}_2\} && (2.57c)\\ U_2 &= \{u \in Y |\ \exists \zeta \text{ such that } (\zeta, u) \in \mathscr{C}_2\}\,. && (2.57d) \end{aligned}$$

We denote part of Y in the positive cone of, $\mathbb{R}^2$, by

$$Y^+ = \{(e_h, e_v) \in Y | 0 < e_h \text{ and } 0 < e_v\}$$

and the boundary of Y^+ by,

$$\partial Y^+ = \left\{ \begin{pmatrix} e_h \\ e_v \end{pmatrix} \in Y \,\middle|\, \begin{pmatrix} e_h > 0 \\ \text{and} \\ e_v = 0 \end{pmatrix} \text{ or } \begin{pmatrix} e_h = 0 \\ \text{and} \\ e_v > 0 \end{pmatrix} \text{ or } \begin{pmatrix} e_h = 0 \\ \text{and} \\ e_v = 0 \end{pmatrix} \right\}$$

From Lemma 2.2.1, we know that there are no equilibrium points on ∂Y^+ other than $e_h = e_v = 0$, so $U_1 \cap \partial Y^+ = 0$ and $U_2 \cap \partial Y^+ = 0$. Additionally, as shown in Lemma 2.3.5 below, the initial direction of U_i, the projection of the continuum of solution pairs $\mathscr{C}_i$ in Y, near the bifurcation point $(\xi_i, 0)$, is given by the eigenvector corresponding to the characteristic value, ξ_i — where i is either 1 or 2. The eigenvector, v (2.56), corresponding to ξ_1 contains only positive terms, while the eigenvector corresponding to ξ_2 is $(-\sqrt{A} \quad \sqrt{B})^{\mathrm{T}}$. Thus U_1 is entirely contained in Y^+ and U_2 is entirely outside of Y^+. Therefore, $\mathscr{C}_1$ and $\mathscr{C}_2$ do not intersect and by Corollary 1.12 of Rabinowitz [60], $\mathscr{C}_1$ meets $\partial\Omega$. By Lemma 2.3.3 below, the set U_1 does not meet the boundary of Y, so $\mathscr{C}_1$ only meets $\partial\Omega$ at $\zeta = M_Z$.

By Lemma 2.3.2 below, for every $u \in U_1$, there corresponds an x^* in the positive cone of $\mathbb{R}^7$, except for $u = 0$ which corresponds to x_{dfe} (on the boundary of the

positive cone of $\mathbb{R}^7$). Thus, there exists a continuum of equilibrium-pairs $(\zeta, x^*) \in Z \times \mathbb{R}^7$ that connects the point (ξ_1, x_{dfe}) to the hyperplane $\zeta = M_Z$ in $\mathbb{R} \times \mathbb{R}^7$. □

Lemma 2.3.2 *The point, $u = 0 \in Y$ corresponds to $x_{dfe} \in \mathbb{R}^7$ (on the boundary of the positive cone of $\mathbb{R}^7$). For every other solution-pair $(\zeta, u) \in \mathscr{C}_1$, there corresponds one equilibrium-pair $(\zeta, x^*) \in Z \times \mathbb{R}^7$ where x^* is in the positive cone of $\mathbb{R}^7$.*

Proof We first show that $u = (0, 0)$ corresponds to x_{dfe}. As $e_h = e_v = 0$, by Theorem 2.2.2 we know that the only 2 possible equilibrium points are x_{mfe} and x_{dfe}. As we picked the positive mosquito equilibrium population in solving for N_v (2.36), the equilibrium point that we bifurcate from is x_{dfe}.

We now show that for every $\zeta \in Z_1$ there exists at least one x^* in the positive cone of $\mathbb{R}^7$ for the corresponding $u \in U_1$. For this, we need to show that for every positive and bounded e_h and e_v, there exist positive and bounded i_h, r_h, i_v, N_h and N_v. By looking at the equilibrium equation for i_v (2.37), we see that for every positive and bounded e_v there exists a positive and bounded i_v. The equilibrium equation for N_v has a positive and bounded solution depending only on parameter values (2.36). From (2.42), we see that for every positive and bounded e_h, there exists a positive and bounded i_h. The equilibrium equations for r_h (2.39) and N_h (2.38) show that for every positive and bounded i_h there exists a positive and bounded r_h and N_h, respectively. □

Lemma 2.3.3 *The set, U_1, does not meet the boundary of Y.*

Proof We have already shown that for $u \in U_1$, $e_h > 0$ and $e_v > 0$. We need to show that $e_h < e_h^{max}$ and $e_v < 1$. By Lemma 2.3.2, we know that all state variables are positive. Therefore, for (2.35e) to have a solution, $e_v + i_v < 1$ so $e_v < 1$. From (2.40) we know that as i_h increases, e_h increases monotonically, reaching e_h^{max} at $i_h = 1$. However, we have already shown that when $e_h + i_h + r_h = 1$, $e_h' + i_h' + r_h' < 0$, thus there can be no equilibrium point at $e_h + i_h + r_h = 1$. Therefore, i_h is always less than 1 and e_h is always less than e_h^{max}. □

Theorem 2.3.4 *Assume $\psi_v > \mu_{1v}$. The transcritical bifurcation point at $\zeta = \xi_1$ corresponds to $R_0 = 1$. For the set of ζ for which there exists an equilibrium-pair (ζ, x^*), the corresponding set of values for R_0 includes, but is not necessarily identical to the interval, $1 < R_0 < \infty$. Thus, there exists at least one endemic equilibrium point of the malaria model (2.12) for all $R_0 > 1$.*

Proof As $\zeta = \sigma_{vh}$, some algebraic manipulations of R_0 (2.20) produces

$$R_0 = \zeta\sqrt{AB}. \tag{2.58}$$

Thus, R_0 is linearly related to ζ; and when $\zeta = \xi_1$, $R_0 = 1$. For any $R_0 > 1$, (2.58) gives us a corresponding ζ. We pick an M_Z larger than this ζ. Then, Theorem 2.3.1 guarantees the existence of an endemic equilibrium point for ζ, and thereby for the corresponding value of R_0. Note that it is possible, though not necessary, for the continuum of equilibrium-pairs to include values of $\zeta < \xi_1$ ($R_0 < 1$). □

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). In the absence of disease-induced death ($\delta_h = 0$), the bifurcation is supercritical (forward) in this model (2.12). However for the general case, a subcritical (backward) bifurcation can occur for some parameter values.

For the case with no disease-induced death, we analytically determine the direction of the bifurcation using the Lyapunov-Schmidt expansion as described by Cushing (1998) [14]. We begin by expanding the terms of the nonlinear eigenvalue equation (2.34) about the bifurcation point, $(\xi_1, 0)$. The expanded variables are

$$\begin{aligned}
u &= 0 + \varepsilon u^{(1)} + \varepsilon^2 u^{(2)} + \dots && (2.59a)\\
\zeta &= \xi_1 + \varepsilon\zeta_1 + \varepsilon^2\zeta_2 + \dots && (2.59b)\\
L &= L && (2.59c)\\
h(\zeta, u) &= h(\xi_1 + \varepsilon\zeta_1 + \varepsilon^2\zeta_2 + \dots, \varepsilon u^{(1)} + \varepsilon^2 u^{(2)} + \dots) && (2.59d)\\
&= \varepsilon^2 h_2(\xi_1, u^{(1)}) + \dots
\end{aligned}$$

We substitute the expansions (2.59) into the eigenvalue equation (2.34) and evaluate at different orders of ε.

Evaluating the substitution of the expansions (2.59) into the eigenvalue equation (2.54) at $\mathcal{O}(\varepsilon^0)$ produces $0 = 0$ which gives us no information. We need to calculate the $\mathcal{O}(\varepsilon^1)$ terms.

Lemma 2.3.5 *The initial direction of the branch of equilibrium points, $u^{(1)}$ near the bifurcation point $(\xi_1, 0)$, is equal to the right eigenvector of L corresponding to the characteristic value, ξ_1.*

Proof Evaluating the substitution of the expansions (2.59) into the eigenvalue equation (2.54) at $\mathcal{O}(\varepsilon^1)$ we obtain:

$$u^{(1)} = \xi_1 L u^{(1)}.$$

This implies that $u^{(1)}$ is the right eigenvector of L corresponding to the eigenvalue $1/\xi_1$, v (2.56). Thus, close to the bifurcation point, the equilibrium point can be approximated by $e_h = \varepsilon\sqrt{A}$ and $e_v = \varepsilon\sqrt{B}$. □

Lemma 2.3.6 *The bifurcation at $\zeta = \xi_1$ of the nonlinear eigenvalue equation* (2.54) *is supercritical if $\zeta_1 > 0$ and subcritical if $\zeta_1 < 0$ where*

$$\zeta_1 = -\frac{w \cdot h_2}{w \cdot Lv} \tag{2.60}$$

where v is the right eigenvector of L and w is the left eigenvector of L corresponding to the eigenvalue $1/\xi_1$.

Proof Evaluating the substitution of the expansions (2.59) into the eigenvalue equation (2.54) at $\mathcal{O}(\varepsilon^2)$ we obtain:

$$u^{(2)} = \xi_1 L u^{(2)} + \zeta_1 L u^{(1)} + h_2$$

which we can rewrite as

$$(\mathbb{I} - \xi_1 L)u^{(2)} = \zeta_1 Lv + h_2 \tag{2.61}$$

where $\mathbb{I}$ is the 2×2 identity matrix. As ξ_1 is a characteristic value of L, $(\mathbb{I}-\xi_1 L)$ is a singular matrix. Thus, for (2.61) to have a solution, $\zeta_1 Lv + h_2$ must be in the range of $(\mathbb{I} - \xi_1 L)$, i.e., it must be orthogonal to the null space of the adjoint of $(\mathbb{I} - \xi_1 L)$. The null space of the adjoint of $(\mathbb{I} - \xi_1 L)$ is spanned by the left eigenvector of L (corresponding to the eigenvalue $1/\xi_1$), which we denote by $w := \begin{pmatrix} \sqrt{B} & \sqrt{A} \end{pmatrix}$. The Fredholm condition for the solvability of (2.61) gives us

$$w \cdot (\zeta_1 Lv + h_2) = 0.$$

This requires

$$\zeta_1 = -\frac{w \cdot h_2}{w \cdot Lv}.$$

If ζ_1 is positive, then for small positive ε, $u > 0$ and $\zeta > \xi_1$ and we have a supercritical (forward) bifurcation. Similarly, if ζ_1 is negative, then for small positive ε, $u > 0$ and $\zeta < \xi_1$ and we have a subcritical (backward) bifurcation. □

Theorem 2.3.7 *Assuming $\psi_v > \mu_{1v}$, in the absence of disease-induced death ($\delta_h = 0$), the bifurcation at $R_0 = 1$ is supercritical (forward).*

Proof When $\delta_h = 0$, we can explicitly evaluate $h(\zeta, u)$ in the nonlinear eigenvalue equation (2.54) from the equilibrium equations (2.50) as

$$h = \zeta \begin{pmatrix} C_{(\delta_h=0)} e_h e_v \\ D_{(\delta_h=0)} e_h e_v \end{pmatrix} \tag{2.62}$$

since the coefficients of all the other higher order terms are zero. We have explicit representations for $C_{(\delta_h=0)}$ and $D_{(\delta_h=0)}$, but we do show them here. It suffices to say that both $C_{(\delta_h=0)}$ and $D_{(\delta_h=0)}$ are negative. From (2.62) and (2.59) we can evaluate the second order expansion, h_2.

$$\begin{aligned} h_2 &= \xi_1 \begin{pmatrix} C_{(\delta_h=0)} \sqrt{A}\sqrt{B} \\ D_{(\delta_h=0)} \sqrt{A}\sqrt{B} \end{pmatrix} \\ &= \begin{pmatrix} C_{(\delta_h=0)} \\ D_{(\delta_h=0)} \end{pmatrix} \end{aligned} \tag{2.63}$$

As h_2 contains only negative terms and w, v and L contain only nonnegative terms, (2.60) implies that ζ_1 is positive. Thus, by Lemma 2.3.6, with no disease-induced death, for any positive values of the other parameters there is a supercritical (forward) bifurcation at $R_0 = 1$. □

For positive values of δ_h, it is possible for this model to exhibit a subcritical bifurcation where, near the bifurcation point, positive endemic equilibria exist for $R_0 < 1$. Other examples of epidemiological models with subcritical (backward) bifurcations at $R_0 = 1$ include those described by Castillo-Chavez and Song [11], Gómez-Acevedo and Yi [28] and van den Driessche and Watmough [67].

Although we cannot prove the existence of a subcritical (backward) bifurcation, we show through numerical examples that it is possible for some positive values of δ_h. This is important because it implies that there can be a stable endemic equilibrium even if R_0 is less than 1.

We first use the bifurcation software program AUTO [20] to create bifurcation diagrams around $R_0 = 1$. We show two examples of these bifurcation diagrams in Figure 2.2. One has all parameter values as described in Table 2.3 except for the bifurcation parameter, σ_{vh}, which is varied as shown in the figure. The other curve has parameter values described in Table 2.3, except for $\delta_h = 3.41938 \times 10^{-5}$ and the bifurcation parameter, σ_{vh}, which is also varied as shown in the figure.

For the curve with $\delta_h = 3.45392 \times 10^{-4}$, we can see both unstable and stable endemic equilibrium points. There is a subcritical (backward) bifurcation at $\sigma_{vh} = 0.5779$ ($R_0 = 1$); and a saddle-node bifurcation at $\sigma_{vh} = 0.5515$ ($R_0 = 0.9543$). Thus a locally asymptotically stable endemic equilibrium is possible for values of R_0 below 1. For comparison we show the bifurcation diagram with $\delta_h = 3.41938 \times 10^{-5}$. Here, we only see a stable branch of endemic equilibrium points. There is a supercritical (forward) bifurcation at $\sigma_{vh} = 0.5559$ ($R_0 = 1$). There are no endemic equilibrium points for R_0 less than 1.

As Figure 2.3 shows, numerical simulations suggest that even as σ_{vh} increases to large levels, the size of the projection of the endemic equilibrium on the fraction of exposed humans, e_h, increases monotonically, and the equilibrium point remains

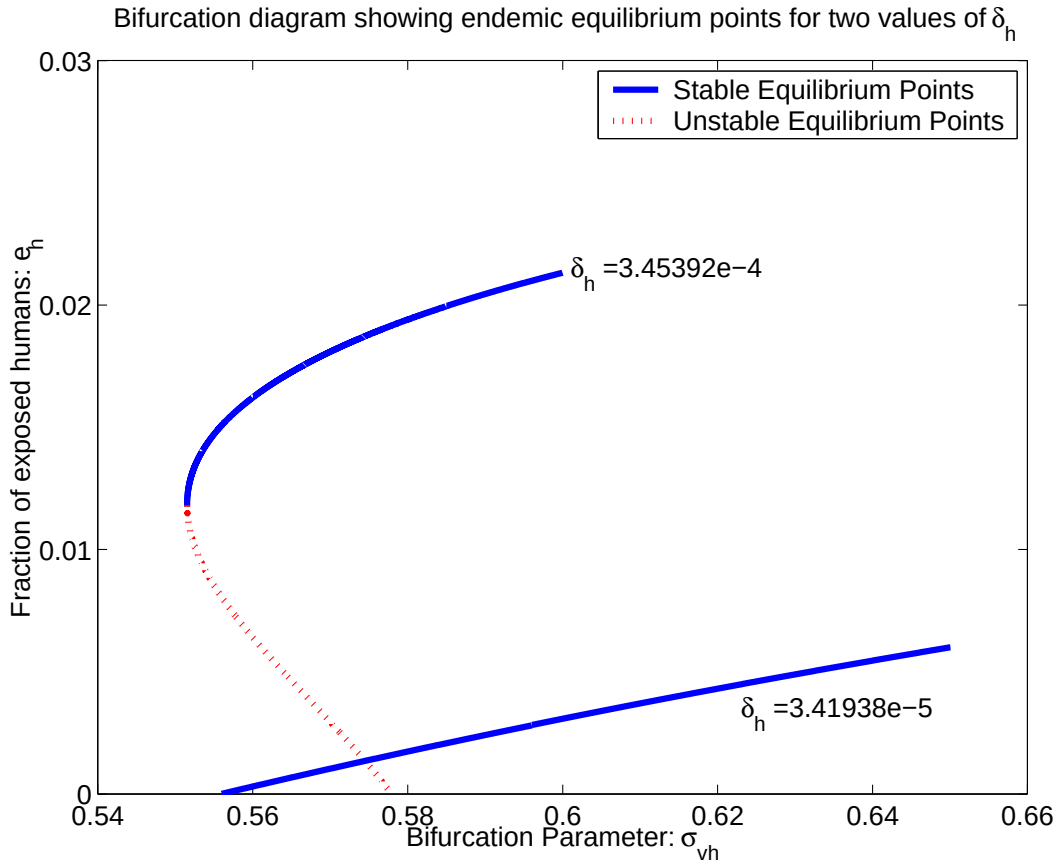
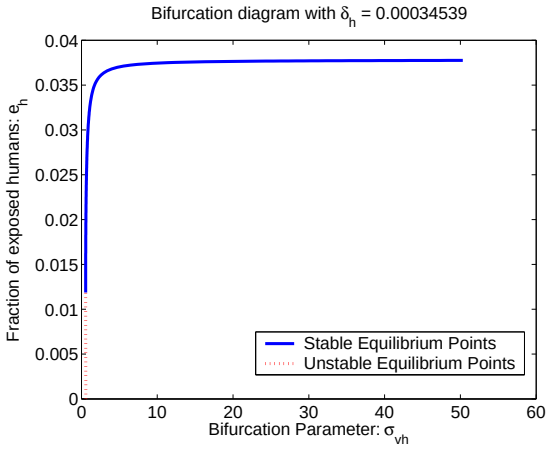


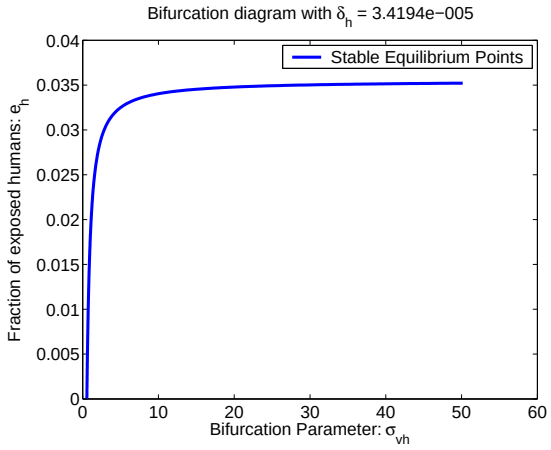
Figure 2.2: Two bifurcation diagrams for (2.12) showing only the endemic equilibrium points. The top curve (labeled $\delta_h = 3.45392 \times 10^{-4}$) is for parameter values described in Table 2.3. The bottom curve (labeled $\delta_h = 3.41938 \times 10^{-5}$) has the same parameters as the first curve, except for δ_h. Only the equilibrium value of the fraction of exposed humans, e_h, is shown on the y-axis.

stable. Although we only show the bifurcation diagram for e_h, the same is true for the other fractional variables, i_h, r_h, e_v, and i_v.

We now focus on an example with parameter values described in Table 2.3. The reproductive number corresponding to these parameter values is $R_0 = 0.9690$. Most of these parameter values are within the bounds of a realistically feasible range, with the exception of the mosquito birth rate which has been significantly increased to lower the value of the reproductive number below 1. The value of δ_h corresponds



(a) Bifurcation diagram with parameters as described in Table 2.3 (except for σ_{vh} which is varied as shown).



(b) Bifurcation diagram with parameters as described in Table 2.3 (except for $\delta_h = 3.41938 \times 10^{-5}$ and σ_{vh} which is varied as shown).

Figure 2.3: Two bifurcation diagrams for (2.12) showing only the fraction of exposed humans of the endemic equilibrium points, for a larger interval of σ_{vh} values than is shown in Figure 2.2. As the bifurcation parameter increases, the equilibrium value of the fraction of the exposed human population increases monotonically and the endemic equilibrium remains stable.

to a death rate of 12.62% of infectious humans per year. We numerically[5] find four equilibrium points: two on the boundary of, and two in, the positive cone of $\mathbb{R}^7$. The two equilibrium points on the boundary are the mosquito-free equilibrium point,

$$x_{mfe}^{(\mathrm{PT2.3})} = (0, 0, 0, 771.3, 0, 0, 0), \tag{2.64}$$

and the disease-free equilibrium point,

$$x_{dfe}^{(\mathrm{PT2.3})} = (0, 0, 0, 771.3, 0, 0, 1129). \tag{2.65}$$

The two equilibrium points inside the positive cone are two endemic equilibria:

$$x_{ee1}^{(\mathrm{PT2.3})} = (0.006400, 0.1287, 0.03244, 525.8, 0.1067, 0.02668, 1129) \tag{2.66}$$

[5]The numerical solutions to the equilibrium equations were found using the `NSolve` command in Mathematica.

Table 2.3: The parameter values for which there exist positive endemic equilibrium points when $R_0 < 1$: $R_0 = 0.9690$. The unit of time is days.

$\Lambda_h = 3.285 \times 10^{-2}$	
$\psi_h = 7.666 \times 10^{-5}$	$\psi_v = 0.4000$
$\beta_{vh} = 0.8333$	$\beta_{hv} = 2.000 \times 10^{-2}$
$\tilde{\beta}_{vh} = 8.333 \times 10^{-3}$	
$\sigma_{vh} = 0.5600$	
$\nu_h = 8.333 \times 10^{-2}$	$\nu_v = 0.1000$
$\gamma_h = 3.704 \times 10^{-3}$	
$\delta_h = 3.45392 \times 10^{-4}$	
$\rho_h = 1.460 \times 10^{-2}$	
$\mu_{1h} = 4.212 \times 10^{-5}$	$\mu_{1v} = 0.1429$
$\mu_{2h} = 1.000 \times 10^{-7}$	$\mu_{2v} = 2.279 \times 10^{-4}$

and

$$x_{ee2}^{(\mathrm{PT2.3})} = (0.01622, 0.3297, 0.08279, 301.7, 0.2254, 0.05635, 1129). \tag{2.67}$$

Linear stability analysis shows that the "larger" endemic equilibrium point, $x_{ee2}^{(\mathrm{PT2.3})}$, is locally asymptotically stable, while the "smaller" point, $x_{ee1}^{(\mathrm{PT2.3})}$, is unstable. Further linear analysis with an increased value of $\sigma_{vh} = 0.6$ and all other parameters as in Table 2.3 (with $R_0 = 1.038$) shows that there is one stable endemic equilibrium point.

Figure 2.4 shows simulations of the original unscaled equations (2.1) for parameter values in Table 2.3. These plots illustrate the stability of the "larger" endemic equilibrium, $x_{ee2}^{(\mathrm{PT2.3})}$, in the presence of a stable disease-free equilibrium point. Figure 2.5, for the same parameter values, shows only the infectious human population for two different initial conditions. One solution approaches the locally asymptotically stable endemic equilibrium point, while the other approaches the locally asymptotically stable disease-free equilibrium point.

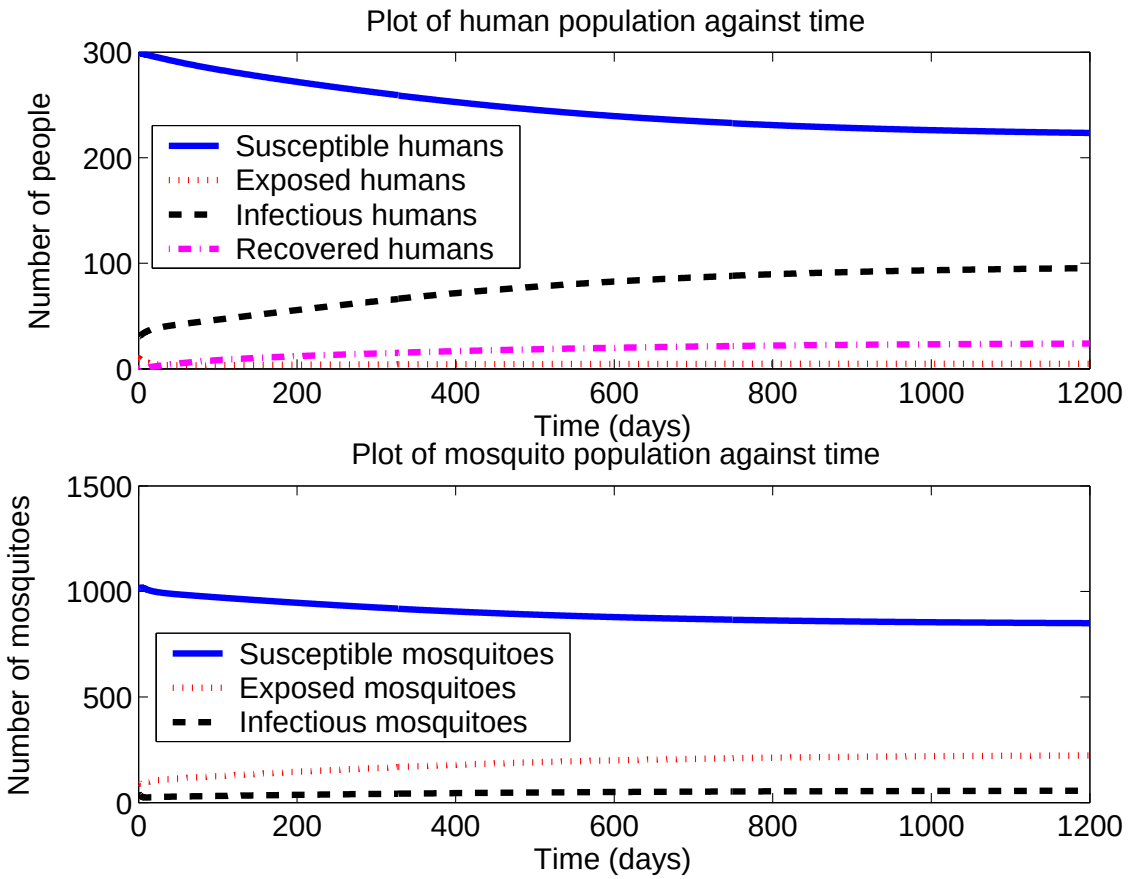


Figure 2.4: A numerical simulation of the malaria model (2.1) (using the original system variables before normalization) with parameter values defined in Table 2.3. These parameters correspond to $R_0 = 0.969$. The initial conditions used were $S_h = 300$, $E_h = 10$, $I_h = 30$, $R_h = 0$, $S_v = 1000$, $E_v = 100$ and $I_v = 50$; which correspond to $e_h = 0.0294$, $i_h = 0.0882$, $r_h = 0$, $N_h = 340$, $e_v = 0.0870$, $i_v = 0.0435$ and $N_v = 1150$. The system approaches an endemic equilibrium point, showing the existence of a stable endemic equilibrium for $R_0 < 1$. The simulations were conducted using MATLAB's `ode45` — a variable order Runge-Kutta method — with a relative tolerance of 10^{-5} and an absolute tolerance of 10^{-7}.

2.4 Summary and conclusions

We analyzed a 7-dimensional ODE model for the transmission of malaria, with 4 variables for humans and 3 variables for mosquitoes. We showed that there exists a domain where the model is epidemiologically and mathematically well-posed.

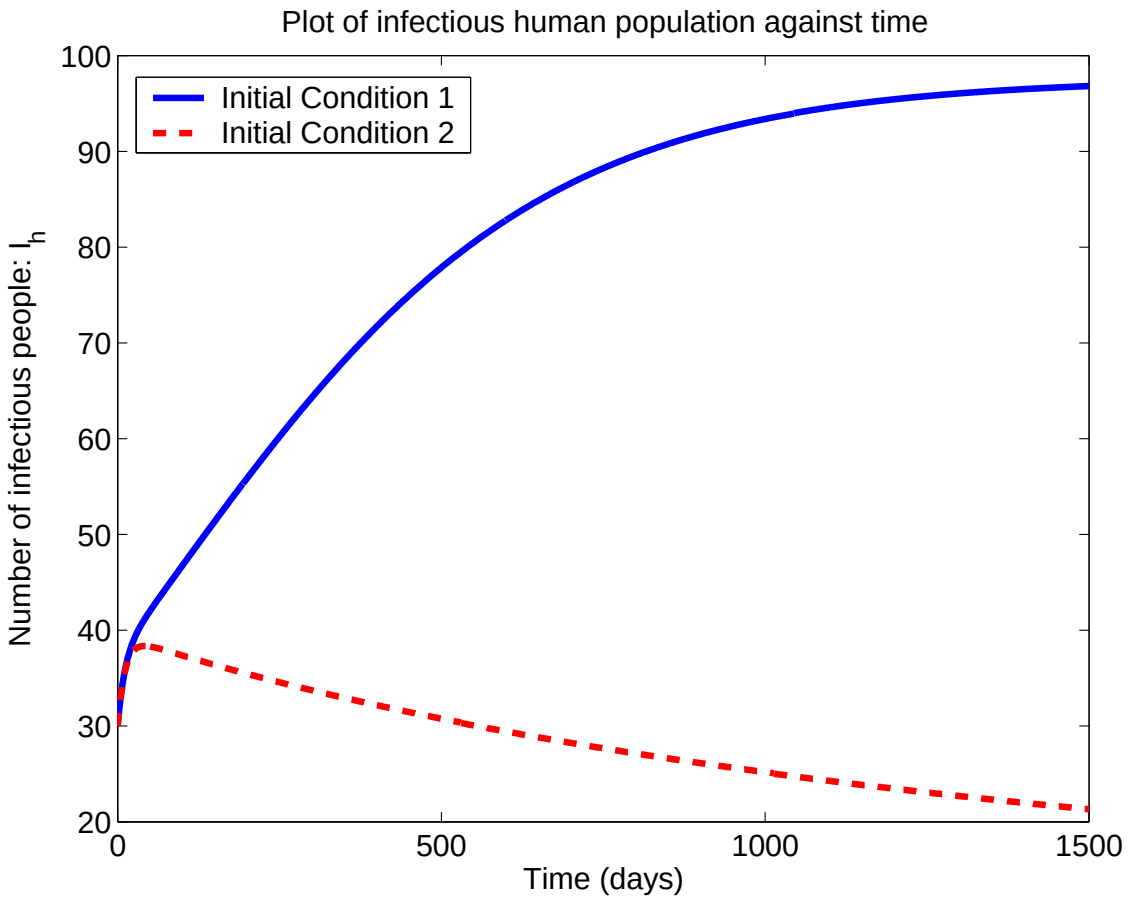


Figure 2.5: A numerical simulation of the malaria model (2.1) with parameter values defined in Table 2.3. These parameters correspond to $R_0 = 0.969$. Only the number of infectious humans, I_h, is shown for two different initial conditions. Initial condition 1 is: $S_h = 300$, $E_h = 10$, $I_h = 30$, $R_h = 0$, $S_v = 1000$, $E_v = 100$ and $I_v = 50$; which corresponds to $e_h = 0.0294$, $i_h = 0.0882$, $r_h = 0$, $N_h = 340$, $e_v = 0.0870$, $i_v = 0.0435$ and $N_v = 1150$. Initial condition 2 is: $S_h = 700$, $E_h = 10$, $I_h = 30$, $R_h = 0$, $S_v = 1000$, $E_v = 100$ and $I_v = 50$; which corresponds to $e_h = 0.0135$, $i_h = 0.0405$, $r_h = 0$, $N_h = 740$, $e_v = 0.0870$, $i_v = 0.0435$ and $N_v = 1150$. The solution for Initial Condition 1 approaches the locally asymptotically stable endemic equilibrium point, while the solution for Initial Condition 2 approaches the locally asymptotically stable disease-free equilibrium point. The simulations were conducted using MATLAB's `ode45` — a variable order Runge-Kutta method — with a relative tolerance of 10^{-5} and an absolute tolerance of 10^{-7}.

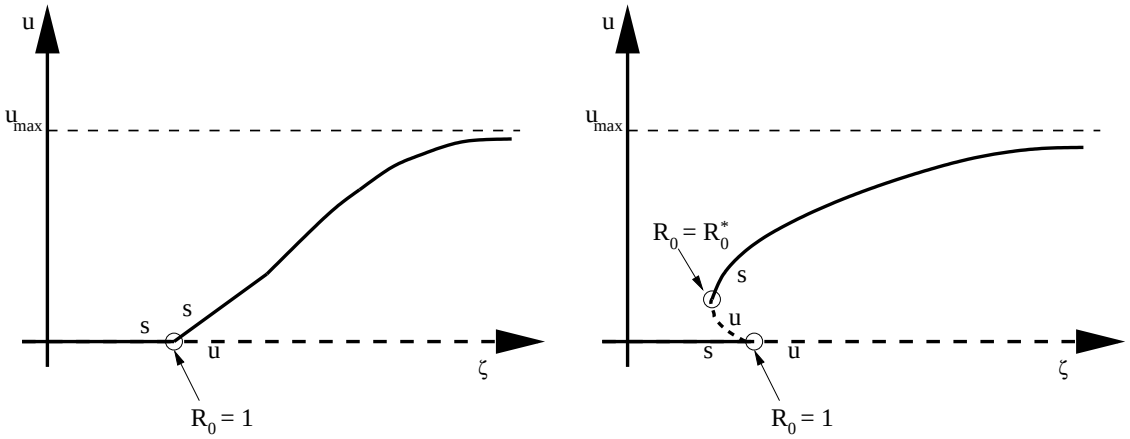
For this model, we were able to show the existence of two equilibrium points

with no disease: one with only humans and no mosquitoes, x_{mfe}, and one with both humans and mosquitoes, x_{dfe}. The equilibrium point with no mosquitoes, x_{mfe}, is locally asymptotically stable if the mosquito birth rate, ψ_v, is less than the mosquito death rate, μ_{1v}.

We defined a reproductive number, R_0, that is epidemiologically accurate in that it provides the expected number of new infections (in mosquitoes or humans) from one infectious individual (human or mosquito) over the duration of the infectious period given that all other members of the population are susceptible. We showed that, provided the mosquito birth rate is greater than the mosquito death rate, if $R_0 < 1$, then the disease-free equilibrium point, x_{dfe}, is locally asymptotically stable and if $R_0 > 1$, then x_{dfe} is unstable.

We also proved that an endemic equilibrium point exists for all $R_0 > 1$ with a transcritical bifurcation at $R_0 = 1$. The analysis and the numerical simulations showed that for $\delta_h = 0$, (no disease-induced death) and for some small positive values of δ_h, there is a supercritical (forward) transcritical bifurcation at $R_0 = 1$ with an exchange of stability between the disease-free equilibrium and the endemic equilibrium as shown in Figure 2.6(a). For larger values of δ_h, there is a subcritical (backward) transcritical bifurcation at $R_0 = 1$, with an exchange of stability between the endemic equilibrium and the disease free equilibrium; and there is a saddle-node bifurcation at $R_0 = R_0^*$ for some $R_0^* < 1$. A schematic of this bifurcation diagram is shown in Figure 2.6(b).

While we do not have any analytical results on the stability of the endemic equilibrium for large values of R_0, numerical results suggest that the equilibrium is stable. However, it follows from Theorem 2.1.1 that all orbits of the system of equations (2.12) are bounded. Thus, if there were no stable endemic equilibria in $\mathcal{D}$, then there would exist a nonequilibrium attractor (such as a limit cycle or strange attractor), though for this model we have no evidence for nonequilibrium attractors. Also, although we cannot prove in general that the endemic equilibrium point is unique for $R_0 > 1$, numerical results for particular parameter sets seem to suggest that there is a unique endemic equilibrium point for $R_0 > 1$.



(a) A supercritical bifurcation for small values of δ_h. We have proved the stability of the disease-free equilibrium point (locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$) and the existence of the endemic equilibrium point for all $R_0 > 1$. We have also proved that the bifurcation is supercritical when $\delta_h = 0$. Numerical simulations suggest that the endemic equilibrium is stable for $R_0 > 1$. Numerical results also suggest that for some small positive values of δ_h, the bifurcation is supercritical. We have no analytical results for the stability of the endemic equilibrium as R_0 approaches ∞.

(b) A subcritical bifurcation for large values of δ_h. We have proved the stability of the disease-free equilibrium point (locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$) and the existence of the endemic equilibrium point for all $R_0 > 1$. Numerical simulations show that for some values of δ_h, there is a saddle-node bifurcation at some $R_0^* < 1$ (dependent on the parameter values) and a subcritical transcritical bifurcation at $R_0 = 1$. Thus, for some values of $R_0 < 1$, there exist two endemic equilibrium points, the smaller of which is unstable while the larger is locally asymptotically stable. We have no analytical results for the stability of the endemic equilibrium as R_0 approaches ∞.

Figure 2.6: Schematics of the two possible bifurcation scenarios for different values of δ_h for the malaria model (2.12). It is important to note that this figure is a cartoon, which summarizes the results for the bifurcation, and not an actual numerical study of the bifurcation.

The possible existence of a subcritical (backward) bifurcation at $R_0 = 1$ and a saddle-node bifurcation at some $R_0^* < 1$, as shown in Figure 2.6(b), can have strong implications for public health. Simply reducing R_0 to a value below 1 is not always sufficient to eradicate the disease; it is now necessary to reduce R_0 to a value less than R_0^* to ensure that there is no endemic equilibrium. The existence of a saddle-node bifurcation also implies that in some areas with endemic malaria, it may be possible to significantly reduce prevalence or eradicate the disease with small increases in control programs (a small reduction in R_0 so that it is less than R_0^*).

Note that it may also be possible in some areas where malaria has been eradicated, for a slight disruption, like a change in environmental or control variables or an influx of infectious humans or mosquitoes, for the disease to reestablish itself in the population with a significant increase in disease prevalence (increasing R_0 above R_0^* or moving the system into the basin of attraction of the stable endemic equilibrium).

The possibility of a subcritical (backward) bifurcation in our model is also a significant difference from the model of Ngwa and Shu [56], as that model only exhibited a supercritical (forward) bifurcation at $R_0 = 1$.

CHAPTER 3

PARAMETER VALUES AND SENSITIVITY ANALYSIS

We compile two reasonable sets of baseline values for the parameters in the model: one for areas of high transmission ($R_0 = 7.0$) and one for areas of low transmission ($R_0 = 1.1$). We compute the sensitivity indices of the reproductive number and the endemic equilibrium to the parameters around these baseline values. The sensitivity indices allow us to compare the effectiveness of different control strategies, as each strategy affects different parameters to different degrees.

3.1 Baseline parameter values

We show baseline values and ranges in Table 3.1 for the parameters described in Table 2.2. We include two baseline values: for areas of high transmission and low transmission. We also describe our reasons for using these values and the references, where available. We estimate parameter values from published studies and country-wide data. For location specific parameters, such as migration rates, we pick realistically feasible values. For the human population in our model, we consider 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 2 significant figure accuracy for all the parameters.

3.1.1 Population data for humans

Table 3.2 shows the life expectancy and birth rate estimates for the year 2005 for some African countries with areas of high malaria transmission. Using this data, we assume a birth rate of 40 births per year per 1000 people so $\psi_h = 40/365.25/1000$. 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

Table 3.1: Baseline values and ranges for parameters for the malaria model (2.12). Descriptions of the parameters are in Table 2.2.

	Dimension	Baseline high	Baseline low	Range	Details
Λ_h	Humans $\times$ Days^{-1}	0.033	0.041	0.0027 – 0.27	§3.1.1
ψ_h	Days^{-1}	1.1×10^{-4}	5.5×10^{-5}	2.7×10^{-5} – 1.4×10^{-4}	§3.1.1
ψ_v	Days^{-1}	0.13	0.13	0.020 – 0.27	§3.1.2
σ_{vh}	Days^{-1}	0.40	0.25	0.13 – 0.47	§3.1.3
β_{hv}	1	0.022	0.022	0.010 – 0.27	§3.1.4
β_{vh}	1	0.48	0.24	0.072 – 0.64	§3.1.5
$\widetilde{\beta}_{vh}$	1	0.048	0.024	0.0072 – 0.64	§3.1.5
ν_h	Days^{-1}	0.10	0.10	0.067 – 0.20	§3.1.6
ν_v	Days^{-1}	0.091	0.083	0.029 – 0.33	§3.1.7
γ_h	Days^{-1}	0.0035	0.0035	0.0014 – 0.017	§3.1.8
δ_h	Days^{-1}	9.0×10^{-5}	1.8×10^{-5}	0 – 4.1×10^{-4}	§3.1.9
ρ_h	Days^{-1}	5.5×10^{-4}	2.7×10^{-3}	1.1×10^{-2} – 5.5×10^{-5}	§3.1.10
μ_{1h}	Days^{-1}	1.6×10^{-5}	8.8×10^{-6}	1.0×10^{-6} – 1.0×10^{-3}	§3.1.1
μ_{2h}	Humans^{-1} $\times$ Days^{-1}	3.0×10^{-7}	2.0×10^{-7}	1.0×10^{-8} – 1.0×10^{-6}	§3.1.1
μ_{1v}	Days^{-1}	0.033	0.033	0.0010 – 0.10	§3.1.2
μ_{2v}	Mosquitoes^{-1} $\times$ Days^{-1}	8.0×10^{-6}	4.0×10^{-5}	1.0×10^{-6} – 1.0×10^{-3}	§3.1.2

life expectancy of 40 years and 3.8% of the population emigrating every year. The stable population size for these parameter values, in the absence of malaria, is 523.

Table 3.3 shows the life expectancy and birth rate estimates for the year 2005 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 1000 people so $\psi_h = 20/365.25/1000$. 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,

Table 3.2: 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 1000 people per year.

Country	**Life Expectancy**	**Birth Rate**	**References**
Botswana	33.87	23.33	CIA (2005) [13]
Congo, DR	49.35	44.38	CIA (2005) [13]
Kenya	47.99	40.13	CIA (2005) [13]
Malawi	36.97	43.95	CIA (2005) [13]
Zambia	39.7	41.38	CIA (2005) [13]

Table 3.3: 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 1000 people per year.

Country	**Life Expectancy**	**Birth Rate**	**References**
Brazil	71.69	16.83	CIA (2005) [13]
India	64.35	22.32	CIA (2005) [13]
Indonesia	69.57	20.71	CIA (2005) [13]
Mexico	75.19	21.01	CIA (2005) [13]
Saudi Arabia	75.46	29.56	CIA (2005) [13]

to vary from 1 migrant per year to 100 migrants per year. This is a location specific parameter so it can vary greatly. We allow the birth rate to vary from 10 births per 1000 people per year to 50 births per 1000 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.

3.1.2 Population data for mosquitoes

We use the results for the mosquito birth rate calculated by Briët (2002) (Fig. 2 in [10]) for *An. gambiae* to give us a rate of 130 new adult female mosquitoes per day per 1000 female mosquitoes. The stable equilibrium value of the mosquito population, N_v, varies greatly depending on the location. For areas of high transmission, we use estimates derived from the data from Gimnig *et al.* (2003) [27]. Gimnig *et al.* (2003) [27] provide quarterly data for the average number of *An. gambiae* and *An. funestus* mosquitoes in a region of Western Kenya (Asembo). 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.* (2003) [26] state that in Asembo there are 17000 people living in approximately 2500 family compounds with about 3–5 houses per compound) and there are a total of about 12 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 $\mu_{2v} = 8.0 \times 10^{-6}$ so that there is a stable equilibrium value of about 12000 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 2400 mosquitoes.

Table 3.4 shows different estimates for mosquito life expectancy.

Table 3.4: Mosquito life expectancy data.

Lifespan (days)	**Mosquito species**	**References**
5.6	*An. funestus*	Krafsur and Garrett-Jones (1977) [44]
5.89	*An. funestus*	Gillies and Wilkes (1963) [24]
10.2	*An. funestus*	Garrett-Jones and Grab (1964) [22]
11.26	*An. gambiae*	Gillies and Wilkes (1965) [25]
15.4	*An. gambiae*	Garrett-Jones and Shidrawi (1969) [23]
8.0	*An. gambiae*	Garrett-Jones and Grab (1964) [22]
5.8	*An. nili*	Garrett-Jones and Grab (1964) [22]
8.5	*An. coustani*	Garrett-Jones and Grab (1964) [22]
7.1	*An. punctulatus*	Peters and Standfast (1960) [58]
20	*An. balabacensis*	Slooff and Verdgrager (1972) [65]
9	*An. minimus*	Khan and Talibi (1972) [36]
9	*An. gambiae*	Molineaux *et al.* (1979) [51]
3.6	*An. gambiae*	Zahar (1974) [72]

3.1.3 Data for σ_{vh}

We use an estimate of 0.40 bites on humans per mosquito per day in areas of high transmission and 0.25 bites on humans per mosquito per day in areas of low transmission. Table 3.5 shows different estimates for the average number of bites on humans per mosquito per day. These estimates include both, the dependence on the mosquito's gonotrophic cycle (the number of days a mosquito requires to produce eggs before it searches for a blood meal again), and the dependence on the mosquito's anthropophilic rate (the mosquito's preference for human blood as opposed to other mammalian blood).

Table 3.5: Mosquito biting rate data.

Human bites per mosquito per day	**Mosquito species**	**Year**	**Location**	**References**
0.25	*An. gambiae*	1967	Kankiya, Nigeria	Garrett-Jones and Shidrawi (1969) [23]
0.40	*An. punctulatus*	1957–58	Maprik, New Guinea	Peters and Standfast (1960) [58]
0.25	*An. balabacensis*	1964	Khmer	Slooff and Verdgrager (1972) [65]
0.47	*An. minimus*	1966–67	Bangladesh	Khan and Talibi (1972) [36]
0.44	*An. gambiae*	1972	Garki, Nigeria	Molineaux *et al.* (1979) [51]
0.13	*An. gambiae*	1967	Khashm El Girba, Sudan	Zahar (1974) [72]

3.1.4 Data for β_{hv}

Table 3.6 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.

Table 3.6: Data for probability of transmission of infection from mosquitoes to humans.

Probability of Transmission	**Human characteristic**	**References**
0.0223±0.0028	-	Nedelman (1985) [54][1]
0.01	-	Davidson and Draper (1953) [15]
0.015–0.026	-	Pull and Grab (1974) [59]
0.06–0.27	Children	Krafsur and Armstrong (1978) [43]
0.05–0.13	Adults	Krafsur and Armstrong (1978) [43]
0.012	Village 1[2]	Nedelman (1984) [53]
0.086	Village 2[3]	Nedelman (1984) [53]

3.1.5 Data for β_{vh} and $\tilde{\beta}_{vh}$

Table 3.7 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 [56], so $\tilde{\beta}_{vh} = 0.048$ for areas of high transmission and $\tilde{\beta}_{vh} = 0.024$ for areas of low transmission.

[1] Calculations from data from Pull and Grab (1974) [59].
[2] With relative highest mosquito density.
[3] With relative lowest mosquito density.

Table 3.7: Data for probability of transmission of infection from humans to mosquitoes.

Probability of Transmission	**Plasmodium species**	**Time (days) of gametocytemia**	**References**
0.24[4]	*P. falciparum*	-	Muirhead-Thomson (1957) [52]
0.48	*P. falciparum*	-	Boyd (1941) [9]
0.51	*P. falciparum*	-	Draper (1953) [21]
0.47	*P. falciparum*	-	Draper (1953) [21]
0.09	*P. falciparum*	-	Draper (1953) [21]
0.64	*P. falciparum*	1–4	Smalley and Sinden (1977) [66]
0.072	*P. falciparum*	11–12	Smalley and Sinden (1977) [66]
0.48[5]	-	-	Nedelman (1984) [53]
0.38[6]	-	-	Nedelman (1984) [53]

[4]Mosquito species is *An. gambiae*.
[5]From a differential equation model.
[6]From a vectorial capacity approximation.

Table 3.8: Data for the latent period in humans.

Latent Period (days)	**Plasmodium species**	**References**
10–14	*P. ovale*	Molineaux and Gramiccia (1980) [50]
15–16	*P. malariae*	Molineaux and Gramiccia (1980) [50]
9–10	*P. falciparum*	Molineaux and Gramiccia (1980) [50]
5–15	-	Oaks *et al.* (1991) [57]

3.1.6 Data for ν_h

We assume a latent period in humans of 10 days, for both baseline cases, from the data shown in Table 3.8.

3.1.7 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 3.9 shows some estimates for the latent period in mosquitoes.

Table 3.9: Data for the latent period in mosquitoes.

Latent Period (days)	**Plasmodium species**	**Temperature (°C)**	**References**
9	*P. vivax*	25–27	Anderson and May (1991) [1]
12	*P. falciparum*	25–27	Anderson and May (1991) [1]
11[7]	*P. falciparum*	24	Baker (1966) [7]
3–35	*P. vivax*	17–31	Macdonald (1957) [49]
5–35	*P. falciparum*	20–33	Macdonald (1957) [49]

3.1.8 Data for γ_h

We use an estimated recovery period of 9.5 months in, both, areas of high and low transmission. Table 3.10 shows some estimates of the duration of the infectious period in humans.

[7]Mosquito species is *An. gambiae*.

Table 3.10: Data for the duration of the infectious period for humans.

Infectious period (months)	**Plasmodium species**	**Comments**	**References**
2	*P. ovale*		Molineaux and Gramiccia (1980) [50]
4	*P. malariae*		Molineaux and Gramiccia (1980) [50]
9.5	*P. falciparum*		Molineaux and Gramiccia (1980) [50]
12–24	*P. falciparum*	No treatment	Bloland *et al.* (2002) [8]
18–60	*P.vivax*	No treatment	Bloland *et al.* (2002) [8]
18–60	*P. ovale*	No treatment	Bloland *et al.* (2002) [8]
36–600	*P. malariae*	No treatment	Bloland *et al.* (2002) [8]

3.1.9 Data for δ_h

The value of the disease-induced death rate varies considerably across different regions, depending on the diagnosis and treatment facilities available. Arudo *et al.* (2003) [5] give the mortality rate for malaria for children under 5 years old in Asembo (a region in western Kenya) as 32.9 deaths per year per 1000 children. Although this data is only for children and for all children (not only those that are infectious), we use it as an estimate for the per capita disease-induced death rate. This assumption is reasonable because in areas of high malaria transmission like Asembo, almost all children suffer from clinical malaria and most adults (with the exception of pregnant women and immigrants from areas of low malaria transmission) do not contract clinical malaria. For areas of low transmission, we assume that diagnostic and treatment facilities are more advanced and the 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 1000 infected people.

3.1.10 Data for ρ_h

Immunity to malaria in humans is a complicated mechanism that is not completely understood. It has been shown that immunity is short-lived and requires repeated reinfection to sustain itself ([2] and [19]). Thus, people in areas of high transmission are generally immune for long periods of time, while people in areas of low transmission lose their immunity relatively quickly after contracting malaria. The 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 constant rate. This assumption is ok if the level of malaria does not change significantly over time in the area where we model malaria. For areas of high transmission, we assume that the period of immunity lasts 5 years, while in areas of low transmission, we assume that the period lasts for one year. We also assume that the range can vary from 3 months to 50 years.

Table 3.11: The endemic equilibrium for the malaria model (2.1) for the baseline parameter values described in Table 3.1 for areas of high transmission.

$$\begin{aligned} S_h &= 12.6454 \quad & S_v &= 8911 \\ E_h &= 3.0060 \quad & E_v &= 1891 \\ I_h &= 80.1010 \quad & I_v &= 1323 \\ R_h &= 393.3509 & & \end{aligned}$$

Table 3.12: The endemic equilibrium for the malaria model (2.12) for the baseline parameter values described in Table 3.1 for areas of high transmission.

$$\begin{aligned} e_h &= 0.0061 \quad & e_v &= 0.1559 \\ i_h &= 0.1638 \quad & i_v &= 0.1091 \\ r_h &= 0.8042 & & \\ N_h &= 489.10 \quad & N_v &= 12125 \end{aligned}$$

3.2 Derived quantities and numerical simulations

In this section, we calculate the reproductive number, R_0 (2.20) and the endemic equilibrium point(s), x_{ee}, for the malaria model (2.1) and (2.12) for the baseline parameter values given in Table 3.1.

3.2.1 High transmission

For the baseline parameters for high malaria transmission, $R_0 = 6.9859$. There is only one endemic equilibrium point, x_{ee}, shown in the original variables in Table 3.11, and in normalized variables in Table 3.12. We show a numerical simulation of the malaria model (2.1) in Figure 3.1.

3.2.2 Low transmission

For the baseline parameters for low malaria transmission, $R_0 = 1.1261$. There is only one endemic equilibrium point, x_{ee}, shown in the original variables in Table 3.13, and in normalized variables in Table 3.14. We show a numerical simulation of the malaria model (2.1) in Figure 3.2.

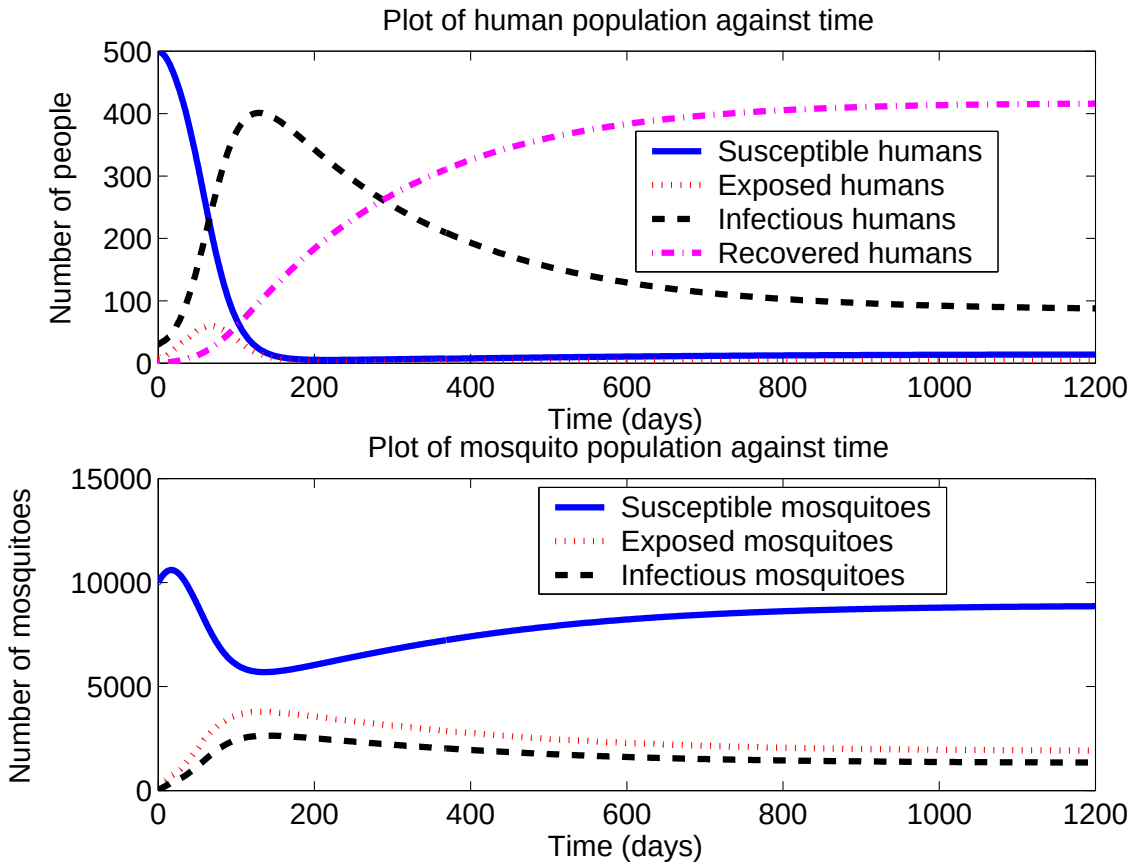


Figure 3.1: A numerical simulation of the malaria model (2.1) (using the original system variables before normalization) with baseline parameter values defined in Table 3.1 for areas of high transmission. These parameters correspond to $R_0 = 6.9859$. The initial conditions used were $S_h = 500$, $E_h = 10$, $I_h = 30$, $R_h = 0$, $S_v = 10000$, $E_v = 100$ and $I_v = 50$; which correspond to $e_h = 0.0185$, $i_h = 0.0556$, $r_h = 0$, $N_h = 540$, $e_v = 0.0099$, $i_v = 0.0049$ and $N_v = 10150$. The system approaches the endemic equilibrium point given in Table 3.11. The simulations were conducted using MATLAB's `ode45` — a variable order Runge-Kutta method — with a relative tolerance of 10^{-5} and an absolute tolerance of 10^{-7}.

3.3 Sensitivity analysis

In determining how best to tackle malaria, and reduce malaria mortality, 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,

Table 3.13: The endemic equilibrium for the malaria model (2.1) for the baseline parameter values described in Table 3.1 for areas of low transmission.

$$\begin{array}{ll} S_h = 471.3376 & S_v = 2326.95 \\ E_h = 1.1708 & E_v = 59.84 \\ I_h = 46.9698 & I_v = 38.21 \\ R_h = 58.2041 & \end{array}$$

Table 3.14: The endemic equilibrium for the malaria model (2.12) for the baseline parameter values described in Table 3.1 for areas of low transmission.

$$\begin{array}{ll} e_h = 0.0030 & e_v = 0.0247 \\ i_h = 0.0812 & i_v = 0.0158 \\ r_h = 0.1007 & \\ N_h = 578.22 & N_v = 2425 \end{array}$$

and disease prevalence is directly related to the endemic equilibrium point, specifically the sizes of e_h, i_h, r_h, e_v and i_v. These sizes represent the individuals (humans and mosquitoes) who have some life stage of *Plasmodium* in their bodies. The fraction of infectious humans, i_h, is especially important because it represents the people that suffer the most 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 to the different parameters in the model. These indices tell us how crucial each parameter is to disease transmission and prevalence.

In conducting the sensitivity analysis, we use methods described by Arriola and Hyman [4]. 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 continuously on a parameter, p, is defined as:

$$\Upsilon_p^u := \frac{\partial u}{\partial p} \cdot \frac{p}{u}. \tag{3.1}$$

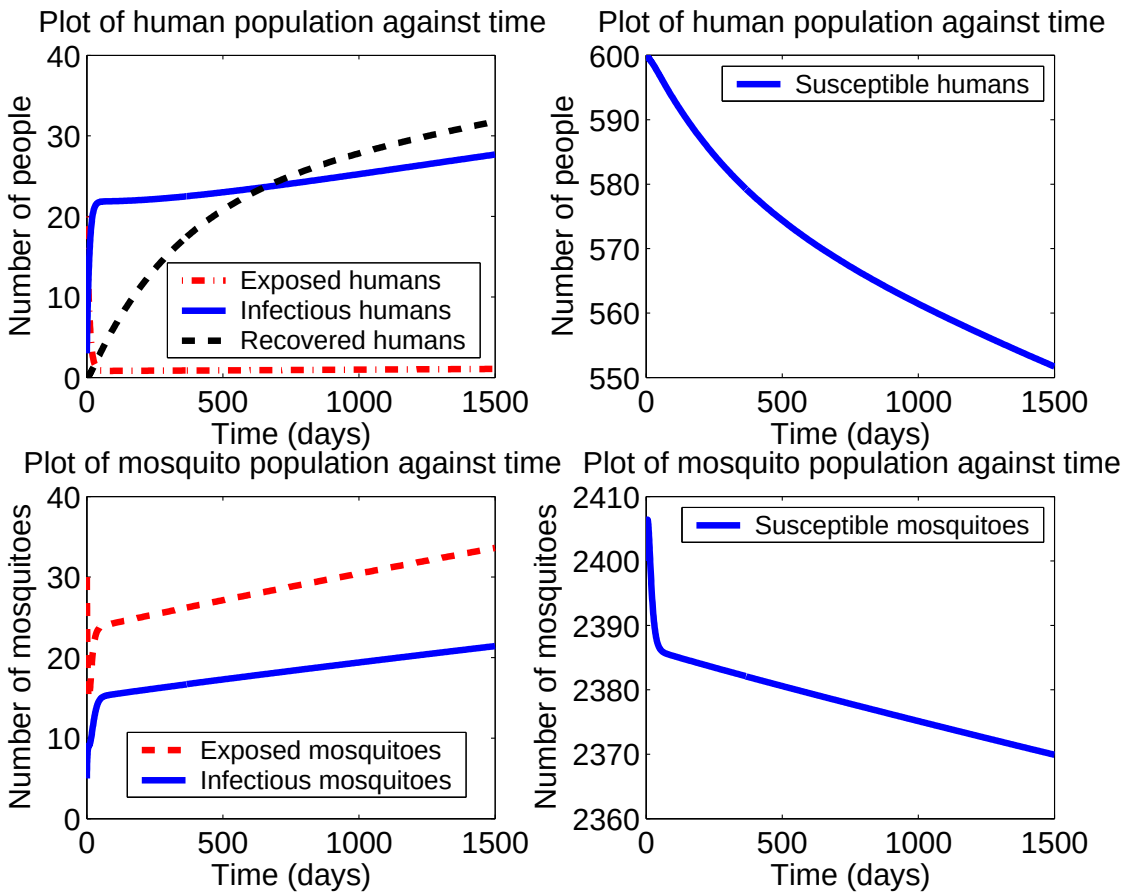


Figure 3.2: A numerical simulation of the malaria model (2.1) (using the original system variables before normalization) with baseline parameter values defined in Table 3.1 for areas of low transmission. These parameters correspond to $R_0 = 1.1261$. The initial conditions used were $S_h = 600$, $E_h = 20$, $I_h = 3$, $R_h = 0$, $S_v = 2400$, $E_v = 30$ and $I_v = 5$; which correspond to $e_h = 0.0321$, $i_h = 0.0048$, $r_h = 0$, $N_h = 623$, $e_v = 0.0123$, $i_v = 0.0021$ and $N_v = 2435$. The system approaches the endemic equilibrium point given in Table 3.13. The simulations were conducted using MATLAB's `ode45` — a variable order Runge-Kutta method — with a relative tolerance of 10^{-5} and an absolute tolerance of 10^{-7}.

We show detailed examples of evaluating these sensitivity indices in §3.3.2.1.

Sensitivity analysis is also commonly used to determine the robustness of model predictions to parameter values, as there are usually errors in data collection and presumed parameter values. However, as we do not use our model to make predic-

tions, we do not utilize this aspect of sensitivity analysis.

3.3.1 Reproductive number

As we have an explicit expression for R_0 (2.20), we can evaluate the sensitivity of R_0 to the sixteen different parameters described in Table 2.2 as,

$$\Upsilon_p^{R_0} := \frac{\partial R_0}{\partial p} \cdot \frac{p}{R_0}, \tag{3.2}$$

to provide an analytical expression for the sensitivity index. However, with the exception of $\Upsilon_{\sigma_{vh}}^{R_0}$, these 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 3.1. For example, the sensitivity index of R_0 (2.20) with respect to β_{vh} is $\Upsilon_{\beta_{vh}}^{R_0} = (\partial R_0/\partial \beta_{vh}) \times (\beta_{vh}/R_0)$ evaluated at the parameter values in Table 3.1. The sensitivity indices of R_0 to the sixteen different parameters in the model for areas of high and low transmission are shown in Table 3.15. We note here that the sensitivity index of R_0 with respect to σ_{vh}, $\Upsilon_{\sigma_{vh}}^{R_0}$, does not depend on the values of the parameters because $\Upsilon_{\sigma_{vh}}^{R_0} = (\partial R_0/\partial \sigma_{vh}) \times (\sigma_{vh}/R_0)$ is always exactly equal to 1.

In both cases, of high and low transmission, the most sensitive parameter is the mosquito biting rate, σ_{vh}. Other important parameters include the probability of disease transmission from infectious mosquitoes to susceptible humans, β_{hv}, the density-dependent mosquito death rate, μ_{2v}, and the human to mosquito disease transmission probability, β_{vh}. As $\Upsilon_{\sigma_{vh}}^{R_0} = +1.0$, decreasing (or increasing) σ_{vh} by 10% decreases (or increases) R_0 by 10%. Similarly, as $\Upsilon_{\mu_{2v}}^{R_0} = -0.5$, increasing (or decreasing) μ_{2v} by 10% decreases (or increases) R_0 by 5%.

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 as the mosquito birth rate increases. We would expect R_0 to increase because increasing ψ_v increases the

Table 3.15: Sensitivity indices of R_0 (2.20) to parameters for the malaria model, evaluated at the baseline parameter values given in Table 3.1. 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_{vh}, and the least sensitive parameter is the human rate of progression from the latent period, ν_h.

High Transmission				Low Transmission			
	Parameter	Sign	Value		Parameter	Sign	Value
1.	σ_{vh}	+	1.0	1.	σ_{vh}	+	1.0
2.	β_{hv}	+	0.50	2.	β_{hv}	+	0.50
2.	μ_{2v}	−	0.50	2.	μ_{2v}	−	0.50
4.	μ_{2h}	+	0.34	4.	β_{vh}	+	0.44
5.	β_{vh}	+	0.34	5.	γ_h	−	0.43
6.	γ_h	−	0.30	6.	ν_v	+	0.31
7.	ν_v	+	0.29	7.	μ_{2h}	+	0.30
8.	ψ_h	−	0.28	8.	Λ_h	−	0.20
9.	μ_{1v}	−	0.17	9.	μ_{1v}	−	0.17
10.	$\tilde{\beta}_{vh}$	+	0.16	10.	ψ_h	−	0.15
11.	Λ_h	−	0.16	11.	ψ_v	−	0.14
12.	ρ_h	−	0.12	12.	$\tilde{\beta}_{vh}$	+	0.055
13.	ψ_v	−	0.12	13.	ρ_h	−	0.053
14.	μ_{1h}	+	0.035	14.	μ_{1h}	+	0.023
15.	δ_h	−	0.012	15.	δ_h	−	0.0025
16.	ν_h	+	0.00086	16.	ν_h	+	0.00063

number of mosquitoes.

However, the mosquito death rate is 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 of the same order as the lifespan of the mosquitoes, shortening the lifespan of the mosquito reduces the reproductive number.

Thus any changes in ψ_v have two opposite effects. Increasing ψ_v increases the number of mosquitoes which tends to increase R_0, and 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.

We should expect however, that for other parameter values, it is possible for R_0 to increase when ψ_v increases. We evaluate the sensitivity indices for R_0 with parameter values exactly as in Table 3.1 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:

1. $\Upsilon_{\mu_{1v}}^{R_0} = -8.8$
2. $\Upsilon_{\psi_v}^{R_0} = +8.5$
3. $\Upsilon_{\sigma_{vh}}^{R_0} = +1.0$

Thus, when there are few mosquitoes, R_0 increases when ψ_v increases.

3.3.2 Endemic equilibrium

As we do not have an explicit expression for the endemic equilibrium, x_{ee}, we cannot find analytical expressions for the sensitivity indices. We therefore, evaluate the local sensitivity indices at the baseline parameter values in Table 3.1. To calculate these 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 sixteen parameters $(\Lambda_h, \psi_h, \ldots, \mu_{2v})$ by $p_1, p_2, \ldots, p_{16}$; and the seven equilibrium equations (2.35) by

$$\begin{aligned} g_1(x_1,\ldots,x_7;p_1,\ldots,p_{16}) &= 0 \\ \vdots &= \vdots \\ g_7(x_1,\ldots,x_7;p_1,\ldots,p_{16}) &= 0. \end{aligned} \tag{3.3}$$

We want to evaluate $\partial x_i/\partial p_j$ for $1 \le i \le 7$ and $1 \le j \le 16$ for the parameter values in Table 3.1 (with the corresponding endemic equilibrium point given in Table 3.12 or 3.14). To do so, we take full derivatives of the equilibrium equations (3.3) with respect to all the parameters, p_j. This gives us 7×16 equations of the form

$$\frac{dg_k}{dp_j} = \sum_{i=1}^{7} \left(\frac{\partial g_k}{\partial x_i} \frac{\partial x_i}{\partial p_j} \right) + \sum_{l=1}^{16} \left(\frac{\partial g_k}{\partial p_l} \frac{\partial p_l}{\partial p_j} \right) = 0 \tag{3.4}$$

for k going from 1 to 7 and j going from 1 to 16. However, $\partial p_l/\partial p_j = 0$ if $l \neq j$ so each equation in (3.4) reduces to

$$\sum_{i=1}^{7} \frac{\partial g_k}{\partial x_i} \frac{\partial x_i}{\partial p_j} = -\frac{\partial g_k}{\partial p_j}. \tag{3.5}$$

These equations are decoupled in terms of the parameters, p_j, but are coupled in terms of the function, g_k. The equations (3.4) are thus 16 linear systems of 7 coupled equations. They may be written as

$$Az^{(j)} = b^{(j)} \tag{3.6}$$

where A is the (7×7) Jacobian of the malaria model (2.12) with $A_{ki} = \partial g_k/\partial x_i$; $z^{(j)}$ is the unknown (7×1) vector with the i^{th} term of $z^{(j)}$ given by $\partial x_i/\partial p_j$; and $b^{(j)}$ is a (7×1) vector with the k^{th} term given by $-\partial g_k/\partial p_j$. The matrix A is known because we can evaluate the Jacobian (2.21) 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 16 linear systems of equations (3.6) for $z^{(j)}$ gives us what we want: $\partial x_i/\partial p_j$ for $1 \le i \le 7$ and $1 \le j \le 16$. Finally, we multiply $\partial x_i/\partial p_j$ by p_j/x_i, as in the definition of the sensitivity index (3.1), to find the sensitivity of each state

Table 3.16: The sensitivity indices, $(\partial x_i/\partial p_j) \times (p_j/x_i)$, 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 3.1, 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	$+0.056$	$+0.044$	-0.021	$+0.31$	$+0.016$	$+0.017$	0
ψ_h	$+0.092$	$+0.071$	-0.034	$+0.51$	$+0.027$	$+0.027$	0
ψ_v	$+0.00044$	$+0.00044$	$+0.00045$	-0.000030	-0.32	-1.3	$+1.3$
σ_{vh}	$+0.046$	$+0.045$	$+0.046$	-0.0031	$+0.77$	$+0.77$	0
β_{hv}	$+0.026$	$+0.026$	$+0.027$	-0.0018	$+0.019$	$+0.019$	0
β_{vh}	$+0.013$	$+0.013$	$+0.013$	-0.00089	$+0.50$	$+0.50$	0
$\widetilde{\beta}_{vh}$	$+0.0064$	$+0.0063$	$+0.0064$	-0.00044	$+0.25$	$+0.25$	0
ν_h	-1.0	$+0.0062$	$+0.0063$	-0.00043	$+0.0046$	$+0.0046$	0
ν_v	$+0.015$	$+0.015$	$+0.016$	-0.0011	-0.40	$+0.60$	0
γ_h	$+0.10$	-0.84	$+0.15$	$+0.058$	-0.38	-0.38	0
δ_h	$+0.011$	-0.010	$+0.0037$	-0.068	-0.0042	-0.0042	0
ρ_h	$+0.62$	$+0.62$	-0.14	-0.043	$+0.27$	$+0.27$	0
μ_{1h}	$+0.0090$	$+0.0076$	$+0.00064$	-0.075	$+0.0039$	$+0.0039$	0
μ_{2h}	$+0.082$	$+0.070$	$+0.0059$	-0.69	$+0.036$	$+0.036$	0
μ_{1v}	-0.0089	-0.0089	-0.0090	$+0.00061$	-0.0066	-0.0066	-0.34
μ_{2v}	-0.026	-0.026	-0.027	$+0.0018$	-0.019	-0.019	-1

variable in the endemic equilibrium point, x_i, to the parameter, p_j.

We show the sensitivity indices of the state variables at the endemic equilibrium point, x_{ee}, to the parameters for areas of high and low transmission in Tables 3.16 and 3.17 respectively. All sensitivity indices are shown to 2 significant figures because that was the accuracy of the parameters. However, 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 these results for N_v in §3.3.2.1.

In interpreting the sensitivity indices, it is important to first note two points.

1. Keeping all other factors fixed, increasing disease prevalence will lead to a decrease in the human population size — because of disease-induced death in infectious humans. Similarly, reducing the disease prevalence will lead to an increase in the human population size.

Table 3.17: Sensitivity indices of the endemic equilibrium to parameters for baseline parameter values given in Table 3.1 for areas of low transmission.

	e_h	i_h	r_h	N_h	e_v	i_v	N_v
Λ_h	-1.5	-1.5	-1.5	$+0.39$	-1.5	-1.5	0
ψ_h	-1.1	-1.2	-1.2	$+0.30$	-1.1	-1.1	0
ψ_v	-0.87	-0.88	-0.88	$+0.0069$	-1.4	-2.4	$+1.3$
σ_{vh}	$+7.4$	$+7.6$	$+7.6$	-0.059	$+8.2$	$+8.2$	0
β_{hv}	$+3.8$	$+3.9$	$+3.9$	-0.030	$+3.7$	$+3.7$	0
β_{vh}	$+3.2$	$+3.3$	$+3.3$	-0.026	$+4.0$	$+4.0$	0
$\tilde{\beta}_{vh}$	$+0.40$	$+0.41$	$+0.41$	-0.0032	$+0.50$	$+0.50$	0
ν_h	-0.98	$+0.019$	$+0.019$	-0.00015	$+0.018$	$+0.018$	0
ν_v	$+2.3$	$+2.4$	$+2.4$	-0.018	$+1.9$	$+2.9$	0
γ_h	-2.8	-3.8	-2.8	$+0.030$	-3.5	-3.5	0
δ_h	$+0.017$	$+0.012$	$+0.012$	-0.0079	$+0.012$	$+0.012$	0
ρ_h	$+0.065$	$+0.066$	-0.89	-0.00052	-0.037	-0.037	0
μ_{1h}	$+0.18$	$+0.18$	$+0.18$	-0.049	$+0.17$	$+0.17$	0
μ_{2h}	$+2.3$	$+2.3$	$+2.3$	-0.64	$+2.2$	$+2.2$	0
μ_{1v}	-1.3	-1.3	-1.3	$+0.010$	-1.3	-1.3	-0.34
μ_{2v}	-3.8	-3.9	-3.9	$+0.030$	-3.7	-3.7	-1

2. Keeping all other factors fixed, reducing the human population size will lead to an increase in disease prevalence — because the number of mosquito bites per human per unit time will increase. Similarly increasing the human population size will lead to a decrease in disease prevalence.

   The equilibrium value of the size of the mosquito population is decoupled from the rest of the system and every mosquito has a fixed number of bites on humans per unit time. As the human population decreases and the total number of mosquito bites on humans remains constant, the number of bites per human per unit time increases, leading to an increase in disease prevalence.

In areas of low transmission, the order of the relative sensitivity of the different parameters for R_0 is largely similar to that for the equilibrium value of i_h. 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_{vh}, followed by the mosquito to human disease transmission probability, β_{hv}, and the density-dependent mosquito death rate, μ_{2v}. Other important parameters include the human recovery rate, γ_h, the human to mosquito disease transmission probability, β_{vh}, the mosquito rate of progression from the latent state, ν_v, and the human density-dependent death and emigration rate, μ_{2h}.

The direction of change of the endemic equilibrium with respect to most of the parameters, for areas of low transmission, agrees with an intuitive expectation. The parameters that perhaps require some explanation are the human disease-induced death rate, δ_h, and the rate of loss of immunity, ρ_h. As δ_h increases, disease prevalence increases. We believe that this is true because an increase in δ_h reduces the equilibrium human population, N_h and the effect of this reduction is stronger than the effect of the reduction on i_h and R_0, resulting in an overall increase in disease prevalence. As ρ_h increases, r_h decreases, which would tend to reduce disease prevalence. However, as a significant 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 quite different from the sensitivity of R_0 to the parameters. As 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. We believe this is 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 over 97% 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 80% 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, μ_{2h} and Λ_h, also result in large increases in i_h. Increasing μ_{2h} causes a significant reduction in the human population size and thus leads to an increase in disease prevalence. The effects of the human birth rate, ψ_h, and the immigration rate, Λ_h, are a little more complicated. Increasing these parameters increases the total human population size which would tend to decrease disease prevalence. 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 are the mosquito biting rate, σ_{vh}, followed by the mosquito to human disease transmission probability, β_{hv}, and the density-dependent mosquito death rate, μ_{2v}. These were the most important parameters for R_0 and for the endemic equilibrium in areas of low transmission.

3.3.2.1 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. Remember at equilibrium,

$$N_v = \frac{\psi_v - \mu_{1v}}{\mu_{2v}}. \tag{2.36}$$

As N_v depends on only three parameters, the sensitivity indices of N_v to all other parameters is 0. We evaluate the nonzero sensitivity indices below:

1. Sensitivity of N_v to μ_{2v}:

$$\begin{aligned}\Upsilon_{\mu_{2v}}^{N_v} &= \frac{\partial N_v}{\partial \mu_{2v}} \cdot \frac{\mu_{2v}}{N_v} \\ &= -\left(\frac{\psi_v - \mu_{1v}}{\mu_{2v}^2}\right) \cdot \mu_{2v} \cdot \left(\frac{\mu_{2v}}{\psi_v - \mu_{1v}}\right) \\ &= -1\end{aligned}$$

2. Sensitivity of N_v to ψ_v:

$$\begin{aligned}\Upsilon_{\psi_v}^{N_v} &= \frac{\partial N_v}{\partial \psi_v} \cdot \frac{\psi_v}{N_v} \\ &= \frac{1}{\mu_{2v}} \cdot \psi_v \cdot \left(\frac{\mu_{2v}}{\psi_v - \mu_{1v}}\right) \\ &= \frac{\psi_v}{\psi_v - \mu_{1v}}\end{aligned}$$

   For the baseline parameter values given in Table 3.1, for areas of high and low transmission, $\Upsilon_{\psi_v}^{N_v} = 1.3$.

3. Sensitivity of N_v to μ_{1v}:

$$\begin{aligned}\Upsilon_{\mu_{1v}}^{N_v} &= \frac{\partial N_v}{\partial \mu_{1v}} \cdot \frac{\mu_{1v}}{N_v} \\ &= -\frac{1}{\mu_{2v}} \cdot \mu_{1v} \cdot \left(\frac{\mu_{2v}}{\psi_v - \mu_{1v}}\right) \\ &= -\frac{\mu_{1v}}{\psi_v - \mu_{1v}}\end{aligned}$$

   For the baseline parameter values given in Table 3.1, for areas of high and low transmission, $\Upsilon_{\mu_{1v}}^{N_v} = -0.34$.

3.4 Control strategies

In 1998, the World Health Organization (WHO), in conjunction with the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), and the World Bank, launched the Roll Back Malaria Global Partnership (RBM), with the goal of halving the worldwide burden of malaria by 2010. Of the numerous anti-malarial activities and research efforts supported by RBM and others, we describe some of the control strategies, and their effects on the parameters of our model, here. As we know the sensitivity indices of R_0 and the endemic equilibrium point to these parameters, we can use them to compare the effectiveness of the control strategies.

Larval control: This strategy includes methods such as the destruction of breeding sites which aim to reduce the number of mosquitoes. Decreasing the number of breeding sites lowers the mosquito birth rate, ψ_v, and probably also increases the mosquito death rates, μ_{1v} and μ_{2v}. Although sensitivity analysis shows that reducing ψ_v would increase R_0, in areas of high transmission reducing ψ_v would reduce the fraction of infectious humans at equilibrium, i_h. In areas of high transmission, a 10% reduction in ψ_v would approximately increase R_0 by 1.2% and reduce i_h by 0.0044%. In areas of low transmission, a 10% reduction in ψ_v would approximately increase R_0 by 1.4% and increase i_h by 8.8%. This is not useful for a control strategy, but methods used for larval control would also affect μ_{1v} and μ_{2v} (though to lesser degrees) which would have more beneficial effects. In areas of high transmission, a 10% increase in μ_{2v} would approximately reduce R_0 by 5% and reduce i_h by 0.26%. In areas of low transmission, a 10% increase in μ_{2v} would approximately reduce R_0 by 5% and reduce i_h by 39%.

Indoor residual spraying (IRS): Spraying reduces mosquito longevity (and perhaps also fertility). This strategy is also likely to kill mosquitoes that rest indoors after feeding so it would increase the chances of killing infected

mosquitoes. IRS increases the mosquito death rate and reduces the number of mosquitoes — increasing μ_{1v} and μ_{2v}. As described above, increasing μ_{2v} can be effective in reducing malaria burden.

Insecticide-treated bed nets (ITN): RBM has been promoting the use of insecticide treated bed nets in many countries and regions of Africa to reduce the transmission of malaria; and has succeeded in doing so in many regions. As some recent studies have shown [30], ITN's have had a significant impact on disease prevalence and mortality. Increasing the number of bed nets reduces the number of human-mosquito contacts, and to a lesser extent increases the mosquito death rates, μ_{1v} and μ_{2v}. Preventing mosquito-human contacts would reduce the number of bites per mosquito, σ_{vh}. This would translate into the mosquitoes biting other animals or not biting at all. Reducing the number of blood meals that each female mosquito gets, would also lower the mosquito birth rate, ψ_v, and perhaps reduce the number of mosquitoes. In areas of high transmission, a 10% reduction in σ_{vh} would approximately reduce R_0 by 10% and reduce i_h by 0.45%. In areas of low transmission, a 10% reduction in σ_{vh} would approximately reduce R_0 by 10% and reduce i_h by 76%. This seems to be the most effective strategy for control in areas of low transmission, and the most effective in reducing disease transmission in areas of high transmission.

Insecticide-treated livestock: There are studies underway in regions that have zoophilic mosquitoes to treat cattle and other livestock close to homesteads with insecticides. Insecticide-treated livestock has similar effects to IRS, although treating livestock with insecticide has been shown to be more cost-effective in areas where the mosquitoes are mostly zoophilic [29] and [63]. It increases μ_{1v}, μ_{2v} and to a lesser degree reduces σ_{vh}. Like IRS, insecticide-treated livestock is an effective strategy.

Intermittent prophylactic treatment (IPT): This is a new area of research that involves administering antimalarial drugs at regular intervals, even to those who are not sick, to reduce parasitemia load. This is essentially similar

to the treatment taken by travellers from malaria-free regions when visiting malaria-endemic countries. This form of control would most likely be applied in areas of high transmission where almost everyone has some *Plasmodium* in their blood.

Intermittent prophylactic treatment in pregnancy (IPTp): As the name suggests, IPTp involves giving malarial medicine to pregnant women, regardless of whether or not they have clinical malaria. Initial tests are now in progress.

Intermittent prophylactic treatment for infants (IPTi): Initial studies have started in this area and have shown significant effects in reducing infant mortality.

As our model shows no distinction between infants, adults and pregnant women, we can only model this strategy as a general reduction in the probability of transmission of infection from an infectious mosquito to a susceptible human, β_{hv}. The treatment also probably causes a slight increase in the human recovery rate, γ_h, as it may result in some infectious people beginning treatment before becoming aware of their infection. In areas of high transmission, a 10% reduction in β_{hv} would approximately reduce R_0 by 5% and reduce i_h by 0.26%. In areas of low transmission, a 10% reduction in β_{hv} would approximately reduce R_0 by 5% and reduce i_h by 39%.

Prompt and effective case management (PECM): This strategy involves the quick identification and treatment of malaria cases. Although it may seem obvious, PECM is not always possible in many places because of poor health infrastructure and a lack of resources. This strategy is more commonly practiced in areas of low transmission because these areas usually have more resources and identifying malarial infections is easier. Quick treatment is doubly effective because it directly reduces the suffering and lack of productivity due to malaria; and it reduces the transmission of infection to mosquitoes. PECM

increases the human recovery rate, γ_h, and to a lesser extent reduces the disease-induced death rate, δ_h. In areas of high transmission, a 10% increase in γ_h would approximately reduce R_0 by 3% and reduce i_h by 8.4%. In areas of low transmission, a 10% increase in γ_h would approximately reduce R_0 by 4.3% and reduce i_h by 38%. This appears to be the most effective strategy for reducing disease burden in areas of high transmission.

Gametocytocidal drugs: These drugs kill gametocytes in humans, reducing human-to-mosquito disease transmission. This is useful in areas like South-East Asia where there is low transmission and most sick people can be reached. This would not be useful in many parts of Africa where there are high levels of transmission and there are not sufficient resources to allow the drugs to be dispensed to all people with parasite loads. These drugs reduce the disease transmission probability from infectious and recovered humans to susceptible mosquitoes, β_{vh} and $\tilde{\beta}_{vh}$. In areas of high transmission, a 10% reduction in β_{vh} would approximately reduce R_0 by 3.4% and reduce i_h by 0.13%. In areas of low transmission, a 10% reduction in β_{vh} would approximately reduce R_0 by 4.4% and reduce i_h by 33%.

Transmission blocking vaccine: Research on a vaccine that blocks malaria transmission has so far appeared promising. Like the gametocytocidal drugs, the vaccine reduces the disease transmission probability from infectious and recovered humans to susceptible mosquitoes, β_{vh} and $\tilde{\beta}_{vh}$. However, the coverage of the vaccine would be far greater than that of the drugs and so the vaccine would have a stronger effect than the gametocytocidal drugs. Although the vaccine would be more expensive to develop, the cost per dose would be lower than that of the drugs.

Transgenetically modified mosquitoes: As there are some species of *Anopheles* mosquitoes that have an immune response to kill the *Plasmodium* parasites, there is hope that genetically modified mosquitoes could be introduced into the wild that would be incapable of transmitting malaria. This is a promis-

ing area of research, although still in its early stages. There would need to be strict controls to ensure that the new mosquitoes created are not accidentally given the capability of transmitting other diseases such as influenza or AIDS. As these mosquitoes would be immune to malaria, having a population of only transgenetically modified mosquitoes would result in $\beta_{vh} = 0$ and $\tilde{\beta}_{vh} = 0$. However, we would expect some wild-type mosquitoes to persist in the population so the control strategy would reduce the two transmission probability terms, β_{vh} and $\tilde{\beta}_{vh}$. Li (2004) [46] and (2005) [47] has examined some population models for the introduction of transgenic mosquitoes.

3.5 Conclusion and comparison of control strategies

We divide the parameters of the malaria model, by two criteria, into four categories. The first criterion is whether the sensitivity analysis shows them to be important in disease transmission and prevalence (whether the sensitivity index of R_0 or x_{ee} to the parameter is high). The second criterion is whether we have control over the parameter through the intervention strategies listed in §3.4. In the first category, we include the parameters that are important for disease transmission and spread, that we have control over: σ_{vh}, β_{hv}, β_{vh}, γ_h, and μ_{2v}. In the second category, we include the parameters that are important, but that we do not have control over: Λ_h, ψ_h, ρ_h, μ_{2h}, and ν_v (which though important, is not as important as the others). The third category are the parameters that we have control over but do not seem to be important: ψ_v, $\tilde{\beta}_{vh}$, and μ_{1v}. The fourth category are the parameters that are not important and that we do not have control over: ν_h and μ_{1h}. One parameter, δ_h, falls outside these four categories. Although δ_h would fit in the third category because we have control over it and it is not important for disease transmission and spread, it is still an extremely important parameter from a social point of view as it is directly related to malaria mortality and human suffering.

It is reassuring to note that the most sensitive parameters for R_0 and x_{ee} are in the first category and not in the second category. As Table 3.15 shows for R_0, the

three most sensitive parameters in high transmission areas, and five most sensitive parameters in low transmission areas, — all parameters with sensitivity indices greater than 0.35 — can be controlled through intervention. As Tables 3.16 and 3.17 show for i_h in x_{ee}, the most sensitive parameter in high transmission areas is controllable and the five most sensitive parameters in low transmission areas are controllable.

The most sensitive parameter for R_0, in both high and low transmission, and for i_h in low transmission areas is σ_{vh}. This suggests that the use of ITN's is very effective, as has been shown by field studies conducted by the Centers for Disease Control and Prevention (CDC) and the Kenya Medical Research Institute (KEMRI) in western Kenya [30]. The equilibrium fraction of infectious humans, i_h, in areas of high transmission is most sensitive to γ_h, which we can control with PECM, suggesting that this would also be an effective strategy, especially in areas of high transmission. PECM also reduces the disease-induced death rate, lowering malaria mortality.

Among the parameters that we can control, the most sensitive parameters after σ_{vh} and γ_h are β_{hv} and μ_{2v} whose sensitivity indices are equal in magnitude for R_0 and i_h in high and low transmission. These can be controlled by IPT, and by larval control, IRS, and insecticide-treated livestock. The only other important parameter that we have control over is β_{vh}, which we can control with gametocytocidal drugs, a transmission blocking vaccine, and transgenetically modified mosquitoes.

There are some important parameters that we cannot control. Most of these are the human demographic parameters, μ_{2h}, Λ_h, and ψ_h, which also vary from region to region. The rate of loss of immunity, ρ_h, is another important parameter that we have little control over. In reality, this rate represents a nonlinear process that depends on the transmission rate so it remains an important simplification of the model. Although the mosquito rate of progression from the latent period, ν_v, is an important parameter that we have no control over, the magnitudes of its sensitivity indices are not as high as the other important parameters.

We had expected the mosquito demographic parameters, ψ_v and μ_{1v}, to be more

important than the model showed them to be. These are parameters that some commonly used control strategies target. We assume that the low sensitivity indices are due to the density dependence of the per capita mosquito death rate. As we demonstrated earlier in an example, there are regimes of parameter values where the magnitudes of the sensitivity indices for ψ_v and μ_{1v} are high. As expected, the probability of disease transmission from recovered humans to susceptible mosquitoes, $\tilde{\beta}_{vh}$, is not important. However, control strategies that reduce β_{vh} also reduce $\tilde{\beta}_{vh}$.

We note here that all the control strategies in §3.4, with the possible exception of larval control which targets ψ_v, have a strong effect on at least one important parameter so they are effective. However, according to our model there are situations where larval control may not be effective in, and possibly even detrimental to, malaria control.

So far, we only have a qualitative relationship between the control strategies and the parameters. A future goal is to quantitatively relate the control strategies to the parameters and to include the cost of the control strategies to directly relate the reduction in disease prevalence and transmission to the cost involved.

CHAPTER 4

CONCLUSION

We derived and analyzed a mathematical model to better understand the transmission and spread of malaria. We used this model to compare intervention strategies for malaria control for two representative areas of high and low transmission to show that the most effective strategies are the use of insecticide-treated bed nets and prompt and effective diagnosis and treatment of infected individuals.

Mathematically, we modeled malaria as a 7-dimensional system of ordinary differential equations. We first showed that there exists a domain where the model is epidemiologically and mathematically well-posed. We showed the existence of two equilibrium points without disease: one with only humans and no mosquitoes, x_{mfe}, and one with both humans and mosquitoes, x_{dfe}. The equilibrium point with no mosquitoes, x_{mfe}, is locally asymptotically stable if the mosquito birth rate, ψ_v, is less than the density-independent mosquito death rate, μ_{1v}.

We defined a reproductive number, R_0, that is epidemiologically accurate in that it provides the expected number of new infections (in mosquitoes or humans) from one infectious individual (human or mosquito) over the duration of the infectious period given that all other members of the population are susceptible. We showed that, assuming $\psi_v > \mu_{1v}$, if $R_0 < 1$ then the disease-free equilibrium point, x_{dfe}, is locally asymptotically stable; and if $R_0 > 1$ then x_{dfe} is unstable.

We also proved that an endemic equilibrium point exists for all $R_0 > 1$ with a transcritical bifurcation at $R_0 = 1$. The analysis and the numerical simulations showed that with no, or little, disease-induced death ($\delta_h = 0$ or some small positive values of δ_h), there is a supercritical (forward) transcritical bifurcation at $R_0 = 1$ with an exchange of stability between the disease-free equilibrium and the endemic equilibrium. For larger values of δ_h, there is a subcritical (backward) transcritical bifurcation at $R_0 = 1$, with an exchange of stability between the endemic equilibrium

and the disease-free equilibrium; and there is a saddle-node bifurcation at $R_0 = R_0^*$ for some $R_0^* < 1$.

While we do not have any analytical results on the stability of the endemic equilibrium for large values of R_0, numerical results suggest that the equilibrium is stable. However, we showed that that all orbits of the system of equations describing the malaria model (2.12) are bounded. Thus, if there are no stable endemic equilibria, then there would exist a nonequilibrium attractor (such as a limit cycle or strange attractor), though for this model we have no evidence for nonequilibrium attractors. Also, although we cannot prove in general that the endemic equilibrium point is unique for $R_0 > 1$, numerical results for particular parameter sets seem to suggest that there is a unique endemic equilibrium point for $R_0 > 1$.

The possible existence of a subcritical (backward) bifurcation at $R_0 = 1$, and a saddle-node bifurcation at some $R_0^* < 1$, can have strong implications for public health. Simply reducing R_0 to a value below 1 is not always sufficient to eradicate the disease; it is now necessary to reduce R_0 to a value less than R_0^* to ensure that there is no endemic equilibrium. The existence of a saddle-node bifurcation also implies that in some areas with endemic malaria, it may be possible to significantly reduce prevalence or eradicate the disease with small increases in control programs (a small reduction in R_0 so that it is less than R_0^*). Note that it may also be possible in some areas where malaria has been eradicated, for a slight disruption, like a change in environmental or control variables or an influx of infectious humans or mosquitoes, for the disease to reestablish itself in the population with a significant increase in disease prevalence (increasing R_0 above R_0^* or moving the system into the basin of attraction of the endemic equilibrium).

Following the mathematical analysis, we compiled two reasonable sets of baseline values for the parameters in the model: one for areas of high transmission ($R_0 = 7.0$) and one for areas of low transmission ($R_0 = 1.1$). We computed the sensitivity indices of the reproductive number, R_0, and the endemic equilibrium, x_{ee}, to the parameters around these baseline values. The sensitivity indices allowed us to compare the effectiveness of different control strategies, as each strategy affects

different parameters to different degrees.

We noted that the most sensitive parameters for R_0 and x_{ee} are controllable through intervention strategies. The most sensitive parameter for R_0, in both high and low transmission, and for i_h in low transmission areas is the mosquito biting rate, σ_{vh}. This suggests that the use of ITN's can be very effective, as has been demonstrated by field studies [30]. The equilibrium fraction of infectious humans, i_h, in areas of high transmission is most sensitive to the human recovery rate, γ_h, which we can control with PECM, suggesting that this would also be an effective strategy, especially in areas of high transmission. PECM also reduces the disease-induced death rate, reducing malaria mortality.

Among the parameters that we can control, the most sensitive parameters after σ_{vh} and γ_h are the mosquito to human disease transmission probability, β_{hv}, and the density-dependent mosquito death rate, μ_{2v}, whose sensitivity indices are equal in magnitude for R_0 and i_h in high and low transmission. These can be controlled by IPT; and by larval control, IRS, and insecticide-treated livestock. The only other important parameter that we have control over is the human to mosquito disease transmission probability, β_{vh}, which we can control with gametocytocidal drugs, a transmission blocking vaccine, and transgenetically modified mosquitoes.

There are some important parameters that we cannot control. Most of these are the human demographic parameters, μ_{2h}, Λ_h, and ψ_h, which also vary from region to region. The rate of loss of immunity, ρ_h, is another important parameter that we have little control over. In reality, this rate represents a nonlinear process that depends on the transmission rate so it remains an important simplification of the model. Although the mosquito rate of progression from the latent period, ν_v, is an important parameter that we have no control over, the magnitudes of its sensitivity indices are not as high as the other important parameters.

We had expected the mosquito demographic parameters, ψ_v and μ_{1v}, to be more important than the model showed them to be. These are parameters that some commonly used control strategies target. We assume that the low sensitivity indices are due to the density dependence of the per capita mosquito death rate. As ex-

pected, the probability of disease transmission from recovered humans to susceptible mosquitoes, $\tilde{\beta}_{vh}$, is not important. However, control strategies that reduce β_{vh} also reduce $\tilde{\beta}_{vh}$.

All the control strategies that we discussed, with the possible exception of larval control which targets ψ_v, have a strong effect on at least one important parameter so they are effective. However, according to our model there are situations where larval control may not be effective in, and possibly even detrimental to, malaria control.

So far, we only have a qualitative relationship between the control strategies and the parameters. A future goal is to quantitatively relate the control strategies to the parameters and to include the cost of the control strategies to directly relate the reduction in disease prevalence and transmission to the cost involved. Other future goals include improving the model to capture important features of malaria transmission that our model does not include. We list some of these below.

Seasonal effects: Seasonally varying environmental effects, such as rainfall, temperature, and humidity, affect many of the important factors in malaria transmission. These environment-dependent parameters include the mosquito birth rate, ψ_v, the mosquito death rates, μ_{1v} and μ_{2v}, and the mosquito rate of progression from the latent period, ν_v. We can model these seasonal effects by making some of these parameters periodic functions of time. Analyzing this periodically-forced model, including changes in the reproductive number and endemic states, would provide a more accurate picture of malaria transmission than is currently obtained from models using parameter values that are averaged over the seasons.

Mosquito population models: The mosquito life cycle has discrete stages and the development times for these stages are dependent on the environment. We can improve models for mosquito population dynamics by including these separate juvenile stages, while incorporating environmental and seasonal effects. Also, anthropophilic mosquito species, like *An. gambiae*, depend on

humans for their reproduction. We can model this with a mosquito birth rate, ψ_v, that is dependent on the size of the human population, N_h.

Interactions between mosquitoes and humans: We have currently assumed that the number of bites per mosquito is fixed, while the number of bites per human changes depending on the number of mosquitoes. For a more accurate description of mosquito-human interaction, the total number of bites between mosquitoes and humans would need to depend on the densities of both populations.

Superinfection: Similar to other infections caused by macroparasites, malaria displays some properties of superinfection where reinfection when one is already infected can worsen the effects of the disease. We can include this in our model by making the recovery rate, γ_h, a function of the inoculation rate, λ_h.

Transmission-rate dependent period of immunity: Resistance to malaria has been shown to be dependent on prevalent levels of transmission. We include this effect in our model by making the rate of loss of immunity, ρ_h, a function of the inoculation rate, λ_h.

Age structure: Age structure is important in the dynamics of malaria, as most deaths occur in infants and the average parasitemia levels of infected individuals decreases with age. Immune response also changes with age. Adding age structure also allows us to study the effects of the various control strategies on the age distribution of disease prevalence. We can model age structure, either through discrete age groups or continuously through converting the system of equations to partial differential equations.

Spatial Structure: Spatial spread is an important feature in the dynamics of malaria, from local transmission in a given region, to the global spread of drug-resistant strains of *Plasmodium*. We can include spatial dynamics through the replication of the basic model at different nodes, representing various locations, with some human/mosquito migration between the nodes.

Ultimately, we would like to validate this model by applying it to a specific malaria-endemic part of the world. We want to compare predicted endemic states obtained from the model using parameter values for that location to the actual local prevalence data. This will allow us to make informed decisions about the type and level of intervention strategies that provide the most effective coverage in that area.

APPENDIX A

BIOLOGICAL AND MEDICAL BACKGROUND OF MALARIA

A.1 Introduction

In this appendix, we describe the history and some of the medical and biological factors of malaria. The word, malaria, is derived from the Italian phrase, *"mal aria"*, meaning bad air.

A.2 History

Malaria, or malaria-like symptoms, have been described in written history for thousands of years, including ancient Chinese, Indian, Greek and Roman writings. The Chinese writings mention a cure for the disease from a certain Qinghao plant. In 1971, Chinese scientists isolated a chemical, artemisinin, from this plant, that serves among the modern drugs available against malaria today. The Indian writings, *Susruta*, describe the disease as being transmitted by the bites of certain insects. Hippocrates, among the Greeks, writes of the symptoms of the disease. It is likely that malaria was responsible for the decline of the populations of several of the city-states. The Romans noticed a correlation between high prevalence of the disease and proximity to swampland.

The modern history of malaria began in the early 17^{th} Century when Spanish Jesuits in South America discovered, from the local population, that the bark of a certain tree[1] cures malaria. Some highlights of the history of malaria following this discovery are described in Table A.1:

[1]The bark is known as Peruvian bark and the tree is named Cinchona after the Countess of Chinchón (wife of the Viceroy of Peru) who, according to legend, was cured of malarial fever with this bark.

Table A.1: A brief history of malaria.

1880:	Laveran discovered the parasite (*Plasmodium*) responsible for the disease.
1886:	Golgi discovered that there was more than one species of *Plasmodium* that infected humans.
1897:	Ronald Ross[2] discovered that mosquitoes transmit malaria.
WW II:	Chloroquine (kills the parasite) and DDT (kills mosquitoes) synthesized.
1945:	Plan of global[3] malaria eradication begins.
1951:	Malaria considered eradicated from the USA[4].
1978:	Effort to eradicate worldwide malaria considered a failure.
Now:	Resurgence of malaria; with reintroduction into areas where it was previously considered eradicated.

A.3 The malaria parasite

The parasite that causes malaria is of the genus *Plasmodium*. There are four species that affect humans:

- *P. falciparum* — more common in tropical areas
- *P. vivax* — more common in temperate areas
- *P. malariae* — not as common
- *P. ovale* — not as common

There are other species of *Plasmodium* that cause malaria in other animals.

[2]Ronald Ross was also the first person to mathematically model malaria.

[3]The worldwide malaria eradication program did not include many African nations because the problem there was considered too big and the countries were thought to be lacking in the necessary resources.

[4]There were 1,337 reported cases of malaria in the USA in 2002 — of which all but 5 were imported.

A.3.1 Life cycle

The species of *Plasmodium* that infect humans have three main life stages: two of which require a human host (in the liver and blood) and one requiring a mosquito host. Figure A.1 shows the life cycle of the malaria parasite.

When an infectious mosquito bites a human, the parasite, in the form of sporozoites in the saliva of the mosquito, enters the human. The sporozoites then migrate to the liver, invading the hepatic cells. In 5–15 days, the sporozoites develop into schizonts[5]. The schizonts contain thousands of "daughter" merozoite cells. The merozoites invade erythrocytes (red blood cells) and mature into schizonts, rupturing the erythrocytes and releasing more merozoites[6]. It usually takes about 48 hours for the merozoites to reproduce more merozoites for *P. falciparum*, *P. vivax* and *P. ovale*; and about 3 days for *P. malariae*. These merozoites go on to invade more erythrocytes and the cycle continues (until treatment or death).

Some merozoites differentiate into sexual forms, known as gametocytes. These gametocytes then enter a feeding mosquito where they fuse to form a zygote. The zygote matures into an ookinete which penetrates the stomach wall. The ookinete develops into an oocyst which, in a week or more, releases over 10,000 sporozoites. These sporozoites then migrate to the salivary glands. When the mosquito bites again, the sporozoites in the saliva enter a new human host and the cycle continues. It takes about 7–21 days for the gametocytes to form new sporozoites in the mosquito. This incubation time can vary greatly depending on the environmental temperature, humidity and the species of *Plasmodium*. The optimal environmental conditions for sporozoite development are temperatures between 20°C and 30°C; and relative humidity greater than 60%. *P. falciparum* cannot develop if the ambient temperature is below 15°C: largely the reason why the parasite is not prevalent in temperate zones.

[5]It is possible for sporozoites of *P. vivax* and *P. ovale* to remain in the liver for years after the primary infection and cause relapses of malaria in the future.

[6]The rupturing of the red blood cells causes fever and signals the clinical onset of malaria.

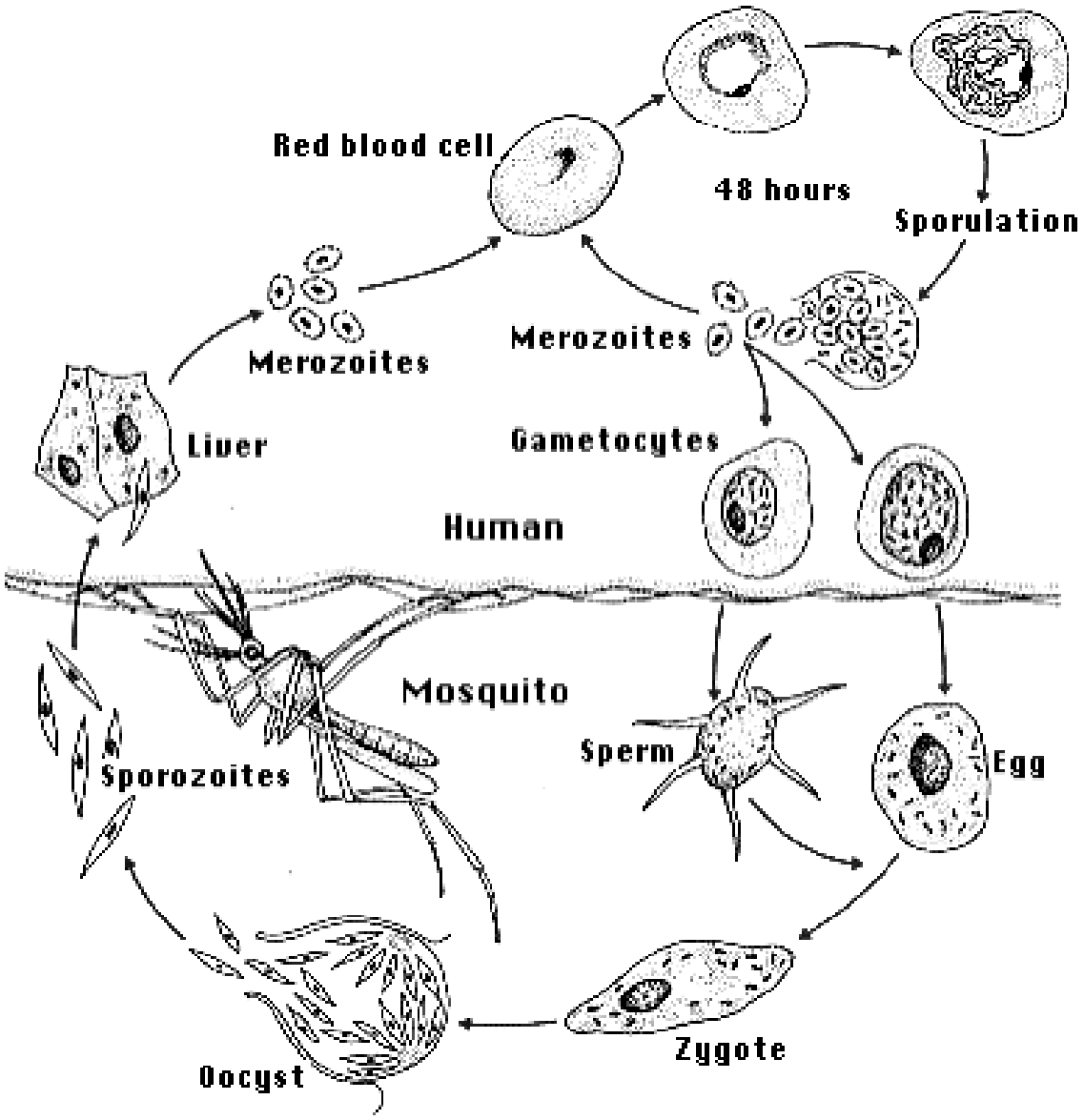


Figure A.1: An illustration of the life cycle of *P. Vivax*. The other species of *Plasmodium* have a similar life cycle, although the time needed to develop from one stage to the next varies. This picture is reproduced, with permission, from Kimball [37].

A.4 The mosquito

There are about 3500 species of mosquito worldwide, of which 430 are in the genus *Anopheles*[7]. Of these 430, only 30–40 species of *Anopheles* are capable of transmit-

[7] *Anopheles* is derived from the Greek word for useless ("without advantage").

ting malaria (they are suitable for the development of the parasite). The *Anopheles* mosquitoes are found worldwide, with the exception of Antarctica and some islands in the Pacific Ocean. The *Anopheles* mosquitoes are easy to recognize because of their characteristic stance: they rest with their head down and their abdomen sticking out, while other mosquitoes usually rest with their body parallel to the resting surface.

A.4.1 Life cycle

The life cycle of the mosquito can be divided into 4 main stages:

Egg: The mosquito eggs usually hatch into larvae in 2–3 days, although this process is temperature-dependent and can take up to 2–3 weeks in cold weather. The eggs are not resistant to drying and require water for successful hatching.

Larva: The larvae require water and prefer clean unpolluted water. They have to frequently rise to the water surface to breathe. They feed on algae, bacteria and other microorganisms.

Pupa: The pupae also require water and need to resurface frequently to breathe.

Adult: The adult males usually feed on nectar and other sources of sugar. Their average lifespan is about a week. Both males and females are sexually active a few days after emerging from the pupal state. At dusk, male mosquitoes form a swarm and females fly into the swarm to mate.

The adult female also feeds on nectar and other sources of sugar, but requires a blood meal for the protein needed to produce eggs. After the blood meal, the female usually rests until the eggs develop. This process too is temperature-dependent and usually takes 2–3 days in tropical conditions. Once she has laid the eggs, the female will mate again and look for another blood meal.

The adult female mosquito can live up to a month (longer in captivity) but

has an expected lifetime of 1–2 weeks in nature. The lifespan of the mosquito also depends on temperature and humidity, among other factors.

The transition from egg to adult usually occurs in 10-14 days in tropical conditions, but can take as little as 5 days or up to a month. The development time for mosquitoes depends on the environmental conditions and on the species of mosquito, with warmer temperatures promoting quicker development.

A.4.2 Other factors related to mosquitoes

The various species of *Anopheles* mosquitoes differ greatly in their preference for breeding sites. For example, *An. stephensi* can breed in tin cans and cisterns, while *An. gambiae* prefer small sunlit pools. Knowing the most prevalent mosquito vector is thus important in designing malaria control strategies that depend on the destruction of mosquito breeding sites.

Some *Anopheles* mosquitoes are anthropophilic (prefer humans) while others are zoophilic (prefer animals). The anthropophilic mosquitoes are more likely to spread malaria because they bite humans more often. The primary vectors in Africa, *An. gambiae* and *An. funestus* are strongly anthropophilic and are thus efficient spreaders of malaria. In areas with higher concentrations of zoophilic mosquitoes, it is possible to devise other malaria prevention strategies such as treating livestock with insecticides.

Most *Anopheles* are crepuscular (active mostly at dusk and dawn) or nocturnal (active mostly at night). Other feeding and resting patterns vary between the different species. Some feed indoors (endophagic), while others feed outdoors (exophagic). Similarly, some rest indoors (endophilic), while others rest outdoors (exophilic). These different preferences require different prevention strategies. It is possible to reduce endophilic mosquitoes by spraying homes with insecticides, while reducing the number of breeding sites is a more effective way of dealing with exophagic and exophilic mosquitoes.

Also, mosquito populations are usually localized because mosquitoes rarely travel

too far from their breeding sites. However, they can get blown around by wind[8]. Mosquitoes usually seek their hosts through various stimuli, including, higher concentrations of CO_2; certain body odors; warmth; and movement. When feeding, the female mosquito first injects some saliva into the host to prevent clotting, allowing the malaria parasite to enter the human host.

Warmer temperatures and rainfall usually result in large increases in mosquito populations. The rainfall provides plenty of breeding grounds, while warmer temperatures speed up most of the developmental processes of the mosquitoes.

Human activities have in many cases aided mosquito populations. Irrigation and agriculture frequently increase the number of breeding sites. Even commonplace human artifacts like tire tracks on muddy roads can provide successful breeding sites for mosquitoes. The abundance of human garbage, such as tin cans and old tires can also serve as breeding grounds to mosquitoes. With warm temperatures and high humidity, even small puddles can last long enough to allow mosquito eggs to develop into adults.

There are many species of *Anopheles* mosquitoes that do not allow the *Plasmodium* parasite to successfully develop. Some mosquitoes even have an immune response that kills the invading parasite. Studying these species could give us some insights into new ways of controlling malaria.

There is some evidence (though not conclusive) that mosquitoes infected with *Plasmodium* have decreased life expectancy, higher mortality rates, lower fertility rates and higher man-biting rates than non-infected mosquitoes [56]. There is also some recent evidence that suggests that the *Plasmodium* parasite, through some unknown mechanism, may increase the attractiveness of infectious humans to the *Anopheles* mosquitoes [45].

[8]It is possible for mosquitoes to travel much greater distances through inadvertent human activity. In the summer of 1989, 5 Swiss citizens contracted malaria from mosquitoes that had made the journey to Geneva on a plane from a malaria-endemic country.

A.5 Disease

Malaria is usually transmitted between humans through the bites of female *Anopheles* mosquitoes. It can, however, be directly transmitted from human to human through blood transfusions, needle sharing and vertically from mother to child, but the incidence of direct human to human transmission is significantly lower than that from through mosquitoes.

The incubation period is usually 7–30 days[9] (the time it takes for the sporozoites from a new mosquito bite to travel to the liver and develop into merozoites in the blood stream).

There are 2 types of malaria.

Uncomplicated malaria: Classically, uncomplicated malaria is associated with an attack that lasts 6–10 hours. Although this attack is not observed often, it remains the stereotypical symptom of malaria. The attack involves 3 stages:

1. Cold stage (sensation of cold, shivering)
2. Hot stage (fever, headache, vomiting, seizures in young children)
3. Sweating stage (sweats, tiredness)

These attacks usually occur every second day for *P. falciparum*, *P. vivax* and *P. ovale*; and every third day for *P. malariae*[10]. The usual symptoms of malaria include, fever, chills, sweating, headaches, nausea, vomiting, body aches, and general malaise. For infections with *P. falciparum*, it is also possible for the patient to exhibit more specialized symptoms, including, mild jaundice; enlargement of the liver; and an increased respiratory rate. As most of the usual symptoms of uncomplicated malaria are common to many other diseases

[9]It is possible for the incubation period to last years for infections of *P. vivax* and *P. ovale*.

[10]This cycle corresponds to the the time taken by the merozoites in the blood to develop into schizonts in the erythrocytes and release more merozoites. The reason this cycle is not always seen is that not all merozoites in the blood are synchronized.

(such as influenza and the common cold), malaria is not always an easy disease to diagnose.

Severe malaria: Severe malaria occurs when *P. falciparum* infections are complicated by severe organ failure. This usually occurs in people with little or no immunity and must be treated as a medical emergency. Some of the symptoms of severe malaria are:

- Cerebral malaria (characterized by abnormal behaviour, impaired consciousness or coma)
- Severe anaemia caused by hemolysis (destruction of red blood cells)
- Hemoglobinuria (hemoglobin in the urine) due to hemolysis
- Pulmonary edema (fluid build-up in the lungs) and Acute Respiratory Distress Syndrome (ARDS)
- Thrombocytopenia (decrease in blood platelets) and abnormalities in blood coagulation
- Cardiovascular collapse and shock

A.5.1 Relapse

Sporozoites of *P. vivax* and *P.ovale* can survive in the liver cells of humans for years, releasing merozoites into the bloodstream at arbitrary times. It is thus possible for a person who has contracted and been treated for malaria to have a relapse many years in the future. It is also possible to not show the first symptoms of malaria until many years have passed since the infectious bite.

People infected with *P. falciparum* and *P. malariae* can also show symptoms of malaria some period of time after termination of treatment. This, however, is due to surviving parasites in the bloodstream and is known as recrudescence.

A.6 Diagnosis

As the symptoms for malaria are rather general, it is difficult to derive concrete diagnoses from them. The symptoms should, however, lead to suspicion of malaria and thus to more rigorous tests.

The primary test for malaria remains microscopic diagnosis: involving a technician searching for the parasite in a blood smear under a microscope. As this test depends heavily on the quality of the reagents (used in creating the blood smear), the quality of the microscope and the experience of the laboratorian, the test is not always reliable. Several blood smears may be required to show the presence of the parasite. This test can also determine the species of *Plasmodium* causing the infection. There are also other tests, including antigen detection (accuracy still to be verified) and molecular diagnosis (requires a specialized laboratory) but these are far more expensive and are not commonly available in the areas where malaria is most prevalent. Other sophisticated techniques can be used to measure past infections and resistance of the parasite to anti-malarial drugs.

A.6.1 Problems with diagnosis:

There are two extreme problems with the diagnosis of malaria. In regions where malaria has been eradicated, doctors are not familiar with malaria, and considering the similarities in symptoms to other common diseases, malaria is often overlooked as the responsible disease. This can be dangerous because malaria is a serious life-threatening illness if not treated early. Not recognizing, and hence not treating, people with malaria also increases the risks of reintroduction of malaria into these regions.

On the other side of the spectrum, in regions where malaria is endemic and transmission rates are high, medical workers, when confronted with malaria-like symptoms are likely to presuppose that the disease is malaria. In many of the poorer (and highly malaria-endemic) countries, resources are often lacking to conduct any diagnostic tests, including microscopic diagnosis. To further complicate the issue,

most adults in areas of high malaria transmission continuously have low levels of *Plasmodium* in their blood, without having clinical malaria. Thus, it is likely for a person with some disease other than malaria to be treated only for malaria. This practice can increase the prevalence of drug-resistant strains of the parasite and does not treat people who may have some other potentially life-threatening disease.

A.7 Treatment

Malaria is a curable disease, with good chances of survival, if diagnosed early and given the correct medication. However, severe malaria can be dangerous if not treated early or treated with drugs that the parasite is immune to.

There are various drugs available today that kill blood-borne parasites, including chloroquine; sulfadoxine-pyrimethamine (Fansidar®); mefloquine (Lariam®); atovaquone-proguanil (Malarone®); quinine; doxycycline; and artemisinin (from Qinghao plant).

In many areas of the world (excluding Central America west of the Panama Canal, and many parts of the Middle East), *P. falciparum* is resistant to chloroquine. This is one of the primary reasons for the large number of anti-malarial drugs available today. These other drugs are more expensive and usually have more serious side-effects, including the possibility of neural disorders; so chloroquine remains the primary drug of choice against all *Plasmodium* species that have no chloroquine resistance. *P. vivax* and *P. ovale* are currently resistant to chloroquine only in Papua New Guinea and Indonesia, although there have been some isolated cases of chloroquine-resistant *P. vivax* in Burma, India and South and Central America. *P. malariae* currently has no chloroquine resistance.

The main drug used to kill dormant *P. vivax* and *P. ovale* stages in the liver is primaquine phosphate.

Quinidine gluconate is administered intravenously to treat severe malaria.

A.8 Immunity

Infection with malaria leaves some temporary residual immunity. Inhabitants of areas with high malaria transmission also build up immunity to the disease — and usually have low levels of *Plasmodium* in their blood. Serious malarial illnesses are thus rare in adults and older children, affecting only young children and pregnant women (without this protective immunity). However, immunity to malaria has been shown to be transient [38] and decays in the absence of reinfection. This decay process is not fully understood and some studies in Madagascar have shown protective immunological memory after decades of no malaria transmission [16].

A.9 Problems facing malaria control

There are currently numerous obstacles to malaria control in many parts of the world. Many of these problems were responsible for the failure of the global malaria eradication plan. Some of these obstacles include:

- A serious lack of resources in areas worst hit by malaria. This forms a vicious cycle, as malaria significantly reduces productivity in a region, increasing poverty. Increased poverty then further hinders the fight against malaria.
- The number of drug-resistant strains of *Plasmodium* is increasing quickly: most obviously seen with the ineffectiveness of chloroquine against *P. falciparum* in most parts of the world; and the emergence of chloroquine-resistant *P. vivax* (CRPV).
- There is also an increasing number of insecticide-resistant mosquitoes (including resistance to dichloro-diphenyl-trichloroethane (DDT)[11]). Many mosquitoes have also now learned to altogether avoid insecticide treated surfaces, making their control even harder.

[11] Probably the most effective and inexpensive chemical used to control mosquitoes to date, although now banned in many parts of the world because of environmental concerns.

- Human activities continually create new breeding sites for mosquitoes and human populations have invaded (and continue to invade) mosquito habitats, increasing the number of contacts between mosquitoes and humans.

- Overpopulation and urbanization has significantly increased human population density in many parts of the world, again increasing the number of contacts between humans and mosquitoes.

- As malaria affects some of the poorest countries of the world, there is no large financial incentive for pharmaceutical companies to invest large amounts of money in research and development for malarial medicines and vaccines. Most of the research is done in academic and governmental organizations.

- Global warming promotes quicker development of mosquitoes and of the parasites in the mosquitoes, and increases the lifespan of mosquitoes, greatly increasing the transmission rate of malaria.

A.10 Control Strategies

In 1998, the World Health Organization (WHO), in conjunction with the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), and the World Bank, launched the Roll Back Malaria Global Partnership (RBM), with the goal of halving the worldwide burden of malaria by 2010. Of the numerous anti-malarial activities and research efforts supported by RBM and others, we describe some of the control strategies here.

Larval control: This strategy includes methods such as the destruction of breeding sites which aim to reduce the number of mosquitoes.

Indoor residual spraying (IRS): Spraying reduces mosquito longevity (and perhaps also fertility). This strategy is also likely to kill mosquitoes that rest indoors after feeding so it would increase the chances of killing infected mosquitoes.

Insecticide-treated bed nets (ITN): RBM has been promoting the use of insecticide treated bed nets in many countries and regions of Africa to reduce the transmission of malaria; and has succeeded in doing so in many regions. As some recent studies have shown [30], ITN's have had a significant impact on disease prevalence and mortality.

Insecticide-treated livestock: There are studies underway in regions that have zoophilic mosquitoes to treat cattle and other livestock close to homesteads with insecticides. Insecticide-treated livestock has similar effects to IRS, although treating livestock with insecticide has been shown to be more cost-effective in areas where the mosquitoes are mostly zoophilic [29] and [63].

Intermittent prophylactic treatment (IPT): This is a new area of research that involves administering antimalarial drugs at regular intervals, even to those who are not sick, to reduce parasitemia load. This is essentially similar to the treatment taken by travellers from malaria-free regions when visiting malaria-endemic countries. This form of control would most likely be applied in areas of high transmission where almost everyone has some *Plasmodium* in their blood.

Intermittent prophylactic treatment in pregnancy (IPTp): As the name suggests, IPTp involves giving malarial medicine to pregnant women, regardless of whether or not they have clinical malaria. Initial tests are now in progress.

Intermittent prophylactic treatment for infants (IPTi): Initial studies have started in this area and have shown significant effects in reducing infant mortality.

Prompt and effective case management (PECM): This strategy involves the quick identification and treatment of malaria cases. Although it may seem obvious, PECM is not always possible in many places because of poor health infrastructure and a lack of resources. This strategy is more commonly prac-

ticed in areas of low transmission because these areas usually have more resources and identifying malarial infections is easier. Quick treatment is doubly effective because it directly reduces the suffering and lack of productivity due to malaria; and it reduces the transmission of infection to mosquitoes.

Gametocytocidal drugs: These drugs kill gametocytes in humans, reducing human-to-mosquito disease transmission. This is useful in areas like South-East Asia where there is low transmission and most sick people can be reached. This would not be useful in many parts of Africa where there are high levels of transmission and there are not sufficient resources to allow the drugs to be dispensed to all people with parasite loads.

Transmission blocking vaccine: Research on a vaccine that blocks malaria transmission has so far appeared promising. Like the gametocytocidal drugs, the vaccine reduces the transmission probability from infectious and recovered humans to susceptible mosquitoes. However, the coverage of the vaccine would be far greater than that of the drugs and so the vaccine would have a stronger effect than the gametocytocidal drugs. Although the vaccine would be more expensive to develop, the cost per dose would be lower than that of the drugs.

Transgenetically modified mosquitoes: As there are some species of *Anopheles* mosquitoes that have an immune response to kill the *Plasmodium* parasites, there is hope that genetically modified mosquitoes could be introduced into the wild that would be incapable of transmitting malaria. This is a promising area of research, although still in its early stages. There would need to be strict controls to ensure that the new mosquitoes created are not accidentally given the capability of transmitting other diseases such as influenza or AIDS. As these mosquitoes would be immune to malaria, having a population of only transgenetically modified mosquitoes would eliminate the transmission of malaria. However, we would expect some wild-type mosquitoes to persist in the population. Li (2004) [46] and (2005) [47] has examined some population models for the introduction of transgenic mosquitoes.

REFERENCES

[1] R. M. Anderson and R. M. May, *Infectious diseases of humans: dynamics and control*, Oxford Unversity Press, Oxford, 1991.

[2] J. L. Aron, *Mathematical modeling of immunity to malaria*, Mathematical Biosciences, 90 (1988), pp. 385–396.

[3] J. L. Aron and R. M. May, *The population dynamics of malaria*, in The population dynamics of infectious disease: theory and applications, R. M. Anderson, ed., Chapman and Hall, London, 1982, pp. 139–179.

[4] L. M. Arriola and J. M. Hyman, *Forward and adjoint sensitivity analysis: With applications in dynamical systems, linear algebra and optimization*. In Preparation.

[5] J. Arudo, J. E. Gimnig, F. O. ter Kuile, S. P. Kachur, L. Slutsker, M. S. Kolczak, W. A. Hawley, A. S. S. Orago, B. L. Nahlen, and P. A. Phillips-Howard, *Comparison of government statistics and demographic surveillance to monitor mortality in children less than five years old in rural western Kenya*, American Journal of Tropical Medicince and Hygiene, 68 (Suppl. 4) (2003), pp. 30–37.

[6] N. J. T. Bailey, *The mathematical theory of infectious diseases and its application*, Griffin, London, 1975.

[7] J. R. Baker, *Parasitic protozoa*, Hutchinson, London, 1966.

[8] P. B. Bloland, H. A. Williams, Roundtable on the Demography of Forced Migration, and Joseph L. Mailman School of Public Health. Program on Forced Migration and Health, *Malaria control during mass population movements and natural disasters*, National Academies Press, Washington, DC, 2002.

[9] M. F. Boyd, *Malariology*, vol. 1, W. B. Saunders, Philadelphia, 1941, ch. Epidemiology: Factors related to the definitive host, pp. 608–697. Ed. M. F. Boyd.

[10] O. J. T. Briët, *A simple method for calculating mosquito mortality rates, correcting for seasonal variations in recruitment*, Medical and Veterinary Entomology, 16 (2002), pp. 22–27.

[11] C. Castillo-Chavez and B. Song, *Dynamical models of tuberculosis and their applications*, Mathematical Biosciences and Engineering, 1 (2004), pp. 361–404.

[12] Centers for Disease Control and Prevention, *CDC - Malaria*. `http://www.cdc.gov/malaria/index.htm`.

[13] Central Intelligence Agency, *CIA - The World Factbook*. `http://www.cia.gov/cia/publications/factbook/`.

[14] J. M. Cushing, *An introduction to structured population dynamics*, vol. 71 of CBMS-NSF Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, 1998.

[15] G. Davidson and C. C. Draper, *Field study of some of the basic factors concerned in the transmission of malaria*, Transactions of the Royal Society of Tropical Medicine and Hygiene, 47 (1953), pp. 522–535.

[16] P. Deloron and C. Chougnet, *Is immunity to malaria really short-lived?*, Parasitology Today, 8 (1992), pp. 375–378.

[17] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, *On the definition and the computation of the basic reproduction ratio R_0 in models for infectious diseases in heterogeneous populations*, Journal of Mathematical Biology, 28 (1990), pp. 365–382.

[18] K. Dietz, *The estimation of the basic reproductive number for infectious diseases*, Statistical Methods in Medical Research, 2 (1993), pp. 23–41.

[19] K. Dietz, L. Molineaux, and A. Thomas, *A malaria model tested in the African savannah*, Bulletin of the World Health Organisation, 50 (1974), pp. 347–357.

[20] E. J. Doedel, R. C. Paffenroth, A. R. Champneys, T. F. Fairgrieve, Y. A. Kuznetsov, B. Sandstede, and X. Wang, *AUTO 2000: Continuation and Bifurcation Software for Ordinary Differential Equations (with HomCont)*, 0.9.7 ed., June 2002.

[21] C. C. Draper, *Observations on the infectiousness of gametocytes in hyperendemic malaria*, Transactions of the Royal Society of Tropical Medicine and Hygiene, 47 (1953), pp. 160–165.

[22] C. Garrett-Jones and B. Grab, *The assessment of insecticidal impact on the malaria mosquito's vectorial capacity, from data on the population of parous females*, Bulletin of the World Health Organisation, 31 (1964), pp. 71–86.

[23] C. Garrett-Jones and G. R. Shidrawi, *Malaria vectorial capacity of a population of Anopheles gambiae*, Bulletin of the World Health Organisation, 40 (1969), pp. 531–545.

[24] M. T. Gillies and T. J. Wilkes, *Observations on nulliparous and parous rates in a population of A. funestus in East Africa*, Annals of Tropical Medicine and Parasitology, 57 (1963), pp. 204–213.

[25] ——, *A study of the age composition of populations of Anopheles gambiae Giles and A. funestus Giles in north-eastern Tanzania*, Bulletin of Entomological Research, 56 (1965), pp. 237–262.

[26] J. E. Gimnig, M. S. Kolczak, A. W. Hightower, J. M. Vulule, E. Schoute, L. Kamau, P. A. Phillips-Howard, F. O. ter Kuile, B. L. Nahlen, and W. A. Hawley, *Effect of permethrin-treated bed nets on the spatial distribution of malaria vectors in western Kenya*, American Journal of Tropical Medicince and Hygiene, 68 (Suppl. 4) (2003), pp. 115–120.

[27] J. E. Gimnig, J. M. Vulule, T. Q. Lo, L. Kamau, M. S. Kolczak, P. A. Phillips-Howard, E. M. Mathenge, F. O. ter Kuile, B. L. Nahlen, A. W. Hightower, and W. A. Hawley, *Impact of permethrin-treated bed nets on entomologic indices in an area of intense year-round malaria transmission*, American Journal of Tropical Medicince and Hygiene, 68 (Suppl. 4) (2003), pp. 16–22.

[28] H. Gómez-Acevedo and M. Y. Li, *Backward bifurcation in a model for HTLV-I infection of CD4+ T cells*, Bulletin of Mathematical Biology, 67 (2005), pp. 101–114.

[29] T. Habtewold, A. R. Walker, C. F. Curtis, E. O. Osir, and N. Thapa, *The feeding behaviour and Plasmodium infection of Anopheles mosquitoes in southern Ethiopia in relation to use of insecticide-treated livestock for malaria control*, Transactions of the Royal Society of Tropical Medicine and Hygiene, 95 (2001), pp. 584–586.

[30] W. A. Hawley, F. O. ter Kuike, R. S. Steketee, B. L. Nahlen, D. J. Terlouw, J. E. Gimnig, Y. P. Shi, J. M. Vulule, J. A. Alaii, A. W. Hightower, M. S. Kolczak, S. K. Kariuki, and P. A. Phillips-Howard, *Implications of the western Kenya permethrin-treated bed net study for policy, program implementation, and future research*, American Journal of Tropical Medicince and Hygiene, 68 (Suppl. 4) (2003), pp. 168–173.

[31] J. A. P. Heesterbeek, R_0, PhD thesis, University of Leiden, Leiden, the Netherlands, 1992.

[32] ——, *A brief history of R_0 and a recipe for its calculation*, Acta Biotheoretica, 50 (2002), pp. 189–204.

[33] J. A. P. Heesterbeek and K. Dietz, *The concept of R_0 in epidemic theory*, Statistica Neerlandica, 50 (1996), pp. 89–110.

[34] H. W. Hethcote, *The mathematics of infectious diseases*, SIAM Review, 42 (2000), pp. 599–653.

[35] J. M. Hyman and J. Li, *An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations*, Mathematical Biosciences, 167 (2000), pp. 65–86.

[36] A. Q. Khan and S. A. Talibi, *Epidemiological assessment of malaria transmission in an endemic area of East Pakistan and the significance of congenital immunity*, Bulletin of the World Health Organisation, 46 (1972), pp. 783–792.

[37] J. W. Kimball, *The protists.* `http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/P/Protists.html`.

[38] S. M. Kinyanjui, P. Bull, C. I. Newbold, and K. Marsh, *Kinetics of antibody responses to Plasmodium falciparum-infected erythrocyte variant surface antigens*, Journal of Infectious Diseases, 187 (2003), pp. 667–674.

[39] J. C. Koella, *On the use of mathematical models of malaria transmission*, Acta Tropica, 49 (1991), pp. 1–25.

[40] J. C. Koella and R. Antia, *Epidemiological models for the spread of anti-malarial resistance*, Malaria Journal, 2 (2003).

[41] J. C. Koella and C. Boëte, *A model for the coevolution of immunity and immune evasion in vector-borne disease with implications for the epidemiology of malaria*, The American Naturalist, 161 (2003), pp. 698–707.

[42] G. A. Korn and T. M. Korn, *Mathematical handbook for scientists and engineers: definitions, theorems, and formulas for reference and review*, Dover Publications, Mineola, New York, 2000.

[43] E. S. Krafsur and J. C. Armstrong, *An integrated view of entomological and parasitological observations on falciparum malaria in Gambela, Western Ethiopian Lowlands*, Transactions of the Royal Society of Tropical Medicine and Hygiene, 72 (1978), pp. 348–356.

[44] E. S. Krafsur and C. Garrett-Jones, *The survival of Wuchereria infected Anopheles funestus Giles in north-eastern Tanzania*, Transactions of the Royal Society of Tropical Medicine and Hygiene, 71 (1977), pp. 155–160.

[45] R. Lacroix, W. R. Mukabana, L. C. Gouagna, and J. C. Koella, *Malaria infection increases attractiveness of humans to mosquitoes*, PLoS Biology, 3 (2005), pp. 1590–1593.

[46] J. Li, *Simple mathematical models for interacting wild and transgenic mosquito populations*, Mathematical Biosciences, 189 (2004), pp. 39–59.

[47] ——, *Heterogeneity in modeling of mosquito populations with transgenic mosquitoes*, Journal of Difference Equations and Applications, 2 (2005), pp. 443–457.

[48] J. Li, R. M. Welch, U. S. Nair, T. L. Sever, D. E. Irwin, C. Cordon-Rosales, and N. Padilla, *Dynamic malaria models with environmental changes*, in Proceedings — Thirty-Fourth Southeastern Symposium on System Theory, Huntsville, AL, USA, 2002, pp. 396–400.

[49] G. Macdonald, *The epidemiology and control of malaria*, Oxford University Press, London, 1957.

[50] L. Molineaux and G. Gramiccia, *The Garki Project*, World Health Organization, Geneva, 1980.

[51] L. Molineaux, G. R. Shidrawi, J. L. Clarke, J. R. Boulzaguet, and T. S. Ashkar, *Assessment of insecticidal impact on the malaria mosquito's vectorial capacity, from data on the man-biting rate and age-composition*, Bulletin of the World Health Organisation, 57 (1979), pp. 265–274.

[52] R. C. Muirhead-Thomson, *The malarial infectivity of an African village population to mosquitoes (Anopheles gambiae): A random xenodiagnostic survey*, American Journal of Tropical Medicince and Hygiene, 6 (1957), pp. 971–979.

[53] J. Nedelman, *Inoculation and recovery rates in the malaria model of Dietz, Molineaux and Thomas*, Mathematical Biosciences, 69 (1984), pp. 209–233.

[54] ——, *Introductory review: Some new thoughts about some old malaria models*, Mathematical Biosciences, 73 (1985), pp. 159–182.

[55] G. A. Ngwa, *Modelling the dynamics of endemic malaria in growing populations*, Discrete and Continuous Dynamical Systems—Series B, 4 (2004), pp. 1173–1202.

[56] G. A. Ngwa and W. S. Shu, *A mathematical model for endemic malaria with variable human and mosquito populations*, Mathematical and Computer Modelling, 32 (2000), pp. 747–763.

[57] S. C. Oaks Jr., V. S. Mitchell, G. W. Pearson, and C. C. J. Carpenter, eds., *Malaria: obstacles and opportunities*, National Academy Press, Washington, D.C., 1991.

[58] W. Peters and H. A. Standfast, *Studies on the epidemiology of malaria in New Guinea. II. Holoendemic malaria, the entomological picture*, Transactions of the Royal Society of Tropical Medicine and Hygiene, 54 (1960), pp. 249–260.

[59] J. H. Pull and B. Grab, *A simple epidemiological model for evaluating the malaria inoculation rate and the risk of infection in infants*, Bulletin of the World Health Organisation, 51 (1974), pp. 507–516.

[60] P. H. Rabinowitz, *Some global results for nonlinear eigenvalue problems*, Journal of Functional Analysis, 7 (1971), pp. 487–513.

[61] M. G. Roberts and J. A. P. Heesterbeek, *A new method for estimating the effort required to control an infectious disease*, Proceedings of the Royal Society of London Series B, 270 (2003), pp. 1359–1364.

[62] R. Ross, *The prevention of malaria*, John Murray, London, 1911.

[63] M. Rowland, N. Durrani, M. Kenward, N. Mohammed, H. Urahman, and S. Hewitt, *Control of malaria in Pakistan by applying deltamethrin insecticide to cattle: a community-randomised trial*, The Lancet, 357 (2001), pp. 1837–41.

[64] C. P. Simon and J. A. Jacquez, *Reproduction numbers and the stability of equilibria of SI models for heterogeneous populations*, SIAM Journal on Applied Mathematics, 52 (1992), pp. 541–576.

[65] R. Slooff and J. Verdrager, *Anopheles balabacensis Baisas 1936 and malaria transmission in south-eastern areas of Asia.* WHO/MAL/72.765, 1972.

[66] M. E. Smalley and R. E. Sinden, *Plasmodium falciparum gametocytes: Their longevity and infectivity*, Parasitology, 74 (1977), pp. 1–8.

[67] P. van den Driessche and J. Watmough, *A simple SIS epidemic model with a backward bifurcation*, Journal of Mathematical Biology, 40 (2000), pp. 525–540.

[68] ——, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission*, Mathematical Biosciences, 180 (2002), pp. 29–48.

[69] World Health Organization, *WHO: Malaria.* `http://www.who.int/health_topics/malaria/en/`.

[70] H. M. Yang, *Malaria transmission model for different levels of acquired immunity and temperature-dependent parameters (vector)*, Revista de Saúde Pública, 34 (2000), pp. 223–231.

[71] H. M. Yang and M. U. Ferreira, *Assessing the effects of global warming and local social and economic conditions on the malaria transmission*, Revista de Saúde Pública, 34 (2000), pp. 214–222.

[72] A. R. Zahar, *Review of the ecology of malaria vectors in the WHO Eastern Mediterranean region*, Bulletin of the World Health Organisation, 50 (1974), pp. 427–440.