Mathematical Analysis of Ivermectin as a Malaria Control Method

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1 Abstract

Malaria epidemics are detrimental to the health of many people and economies of many countries. There exist methods of malaria control, but the fight against the disease is far from being over. The history of mathematical modeling of malaria spread is more than hundred years old. Recently, a model was proposed in the literature that captures the dynamics of malaria transmission by taking into account the behavior and life cycle of the mosquito and its interaction with the human population. We modify this model by including the effect of an anti-parasitic medication, ivermectin, on several threshold parameters, which can determine the spread of malaria. The modified model takes a form of a system of nonlinear ordinary differential equations. We investigate this model using applied dynamical systems techniques. We were able to show that that exist parameter regimes such that careful use of ivermectin can curtail the spread of malaria without harming the mosquito population. Otherwise, the ivermectin either eradicates the mosquito population, or has little to no effect on the spread of malaria. We suggest that ivermectin can be very effective when used as a malaria control method in conjunction with other methods such as reduction of breeding sites.

2 Introduction

2.1 Background

Malaria, a disease caused by a mosquito-borne parasite, results in hundreds of thousands of deaths each year, primarily in sub-Saharan Africa. According to the 2014 WHO report there were about 198 million cases of malaria in 2013, resulting in approximately 584,000 deaths, 90% of which occurred in sub-Saharan Africa. Roughly 78% of malaria related deaths were in children under five years of age. In addition to causing a large number of deaths, malaria can also damage the active and potential work force in a country,
hindering economic growth. Malaria is seen predominantly in areas with poor economic conditions to begin with, making it challenging for the economy to flourish. Because of the detrimental effects of malaria, it is clear that ongoing research for control methods for malaria can save future lives and boost the economies of nations at risk. Malaria has been a recurring issue since as early as 1324 BC when it was said to have played part in the death of the boy Pharaoh Tutankhamen [2]. Although the number of malaria infections a year have dropped from 227 million in 2000 to 198 million in 2013 [3], there are still many areas where malaria is prevalent.

As a response to this epidemic, several mathematicians have developed models in search of understanding of malaria dynamics. The research began as early as 1911, when the Ross-Macdonald was the first to create a model demonstrating the interaction between mosquitoes and humans which perpetuates malaria. Although we will not go into depth about the history of malaria models, those interested may see [4] - [6] for details. In 2012, as a part of this ongoing research, a Susceptible-Infectious-Susceptible model for malaria that accounts for the interactions between the human and mosquito populations was created in [7] to account for the complex dynamics of the disease. This model was among the first models which consider the population dynamics of the mosquito population. Other models which consider the population dynamics of the mosquito include [8], [9]. Specifically, the model in [7] considers factors related to local carrying capacity of the mosquito population, as well as mosquito birth rates, that ultimately affect how the disease spreads through the human population. The new, rich dynamics of the system provide valuable insight into what factors most directly affect the spread of malaria, and make it possible to study many additional control strategies.

In [7] the existence of zero, one, or two endemic steady states, Hopf bifurcations, and backwards (subcritical) bifurcations were shown. Furthermore, the effect of certain parameters, such as the carrying capacity and birth rate mentioned above, on these phenomena was studied. Here we adapt the model used by [7] account for the use of another control strategy in the form of medication. In particular, we investigate the pharmaceutical drug ivermectin, a widely accepted broad-spectrum antiparasitic drug. Ivermectin has been identified in [10] to cause infertility and death in the anopheles mosquito. When a mosquito bites a human who has recently ingested ivermectin, it will die within 48-72 hours. If the concentration of ivermectin is too weak, the mosquito will not die, but its eggs will not be fertile. Some recent studies [11]-[13] suggest that ivermectin could be used as an additional control method for malaria. Here we study the possible effects of ivermectin on malaria control and the mosquito population. We show that the medication can eradicate malaria in certain cases without detrimental effects to the mosquito population. Although some
may argue that this complete eradication of mosquitoes is a viable solution, from an ecological stand point, such action could be quite dangerous. Mosquitoes are a food source for predators and provide pollination in any environments in which they reside, thus, their total disappearance could have a negative effect on an ecological system. Although this effect could be studied further, we assume in this paper that the eradication of mosquitoes is not desirable.

2.2 Ideas behind the Model

Malaria is caused by the parasite *Plasmodium* and is not transmissible by human to human contact. However, a mosquito biting an infected human becomes infected and therefore can spread the disease to other humans. Diseases such as malaria which are spread by a secondary source are referred to as *vector-borne* disease. In the case of malaria, the female mosquito is the vector which spreads the disease. Since the female mosquitoes rely on blood meals to reproduce, the transmission of malaria is driven by the life cycle of the mosquito. The vector-borne transmission of malaria is of great importance in regards to understanding, and hopefully controlling, the spread of the disease. In particular, the female *Anopheles* mosquito transmits or receives the parasite while biting a human as part of the mosquito’s reproductive cycle [14]. This is an important distinction from many other diseases, as both mosquitoes and humans are intimately tied to one another in both reception and transmission of the parasite. Thus, understanding the life cycle of the parasite-bearing mosquito population directly influences the understanding of the dynamics of malaria in the human population. Accordingly, a mathematical model for malaria must take into account the dynamics of the disease, as well as the life cycles of mosquitoes, and their interaction with the human population.

It is important that only the life cycles of the female mosquitoes is relevant, as only the females transmit the disease to humans. To model the spread of Malaria, the life of the mosquito can be split into three stages; resting, questing, and fed. The life cycle of the mosquito starts in the resting stage, enters the questing stage upon maturity where it begins searching for a blood-meal to reproduce, and if a meal is successfully taken, enters into the fed stage. Examining the life of a mosquito, and specifically the reproduction process, it is apparent that mosquitoes reproduce only after taking a blood-meal. After reproducing, the mosquitoes re-enter the resting stage, and the cycle continues. It should also be noted that a mosquito is not guaranteed a blood-meal while questing. It is possible for a mosquito to fail to take a meal, and live to attempt another meal, and also to die within the questing stage.

Relating ivermectin to the life cycle structure introduced above, the drug would affect mosquitoes during the transition from the questing stage to the fed stage. We focus here on the effect of the drug killing
mosquitoes that take a blood-meal from a medicated human. Essentially, ivermectin creates a break in the life cycle of the mosquito, removing a mosquito from the system between the questing and fed stages. It should also be noted that using ivermectin does not directly prevent disease transmission to people who have taken the drug, or help cure infected individuals. Rather, the medication kills the mosquito, stopping it from transmitting the disease after biting a person with ivermectin in their blood.

3 The Model

3.1 The Model, Variables, and Parameters

The mathematical model used here is a nonlinear system of ordinary differential equations. The primary feature of the model is its focus on the life cycles of the mosquito vectors in the transmission of malaria. The model itself is based on the model in [7], but includes additional features related to the administration of the drug ivermectin, and its effect on the spread of the disease. The inclusion of the intricate life cycle of the mosquitoes within the model allows for a realistic interpretation of the effects the drug would have if administered in areas of the world struggling with the disease. The original model by [7] takes into account the three stages of mosquito life described above; resting, questing, and fed. Further, each stage of mosquito as well as the human population can be either susceptible or infected. The model utilizes parameters such as flow rates of mosquitoes to and from human habitats, probabilities of mosquitoes successfully taking blood from a human, and birth and death rates to capture the dynamics of the disease as accurately as possible.

For the portion of the model related to humans, birth and death are constant and transitions between susceptible and infected are considered. Susceptible humans that have blood taken by an infected mosquito become infected, and infected humans can also naturally recover at a slow rate. Within the mosquito population, the vectors are born and die, and also transfer between each of the three life cycles, as well as being either infected or susceptible. Susceptible mosquitoes can become infected by feeding on an infected human. The variables and parameters used in the model are described in the Tables 1 and 2 respectively. For a more technical, in depth description of the model, see [7].

As described above, the effect of ivermectin on the transmission of malaria is that mosquitoes which take a blood meal from a medicated human will die before returning to the breeding site and successfully reproducing. We assume that staggered doses of ivermectin will be given consistently to some portion $M$ of the population, thus that portion of the population will always have a large enough concentration of the
Table 1: The variables for systems (1) and (5).

<table>
<thead>
<tr>
<th>Description</th>
<th>Original Variable</th>
<th>Dimensionless Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total human population</td>
<td>( N_h(t) )</td>
<td></td>
</tr>
<tr>
<td>Susceptible humans</td>
<td>( S_h(t) )</td>
<td></td>
</tr>
<tr>
<td>Infected humans</td>
<td>( I_h(t) )</td>
<td>( i_h )</td>
</tr>
<tr>
<td>Susceptible resting mosquitoes</td>
<td>( S_r(t) )</td>
<td>( s_r )</td>
</tr>
<tr>
<td>Susceptible questing mosquitoes</td>
<td>( S_q(t) )</td>
<td>( s_q )</td>
</tr>
<tr>
<td>Susceptible fed mosquitoes</td>
<td>( S_f(t) )</td>
<td>( s_f )</td>
</tr>
<tr>
<td>Infected resting mosquitoes</td>
<td>( I_r(t) )</td>
<td>( i_r )</td>
</tr>
<tr>
<td>Infected questing mosquitoes</td>
<td>( I_q(t) )</td>
<td>( i_q )</td>
</tr>
<tr>
<td>Infected fed mosquitoes</td>
<td>( I_f(t) )</td>
<td>( i_f )</td>
</tr>
<tr>
<td>Total mosquito population</td>
<td>( N_m(t) )</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: The parameter descriptions for system (1).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a_v )</td>
<td>Fed mosquitoes rate of return to the breeding site.</td>
</tr>
<tr>
<td>( \alpha_v(N_h) )</td>
<td>Rate of mosquito attraction to humans.</td>
</tr>
<tr>
<td>( \mu_h, \mu_u, \mu_v, \mu_w )</td>
<td>Human and mosquito death rates.</td>
</tr>
<tr>
<td>( \lambda_v(S_r) )</td>
<td>birth rate of the resting mosquitoes (note: no other mosquitoes give birth).</td>
</tr>
<tr>
<td>( r_h )</td>
<td>Human recovery rate from malaria.</td>
</tr>
<tr>
<td>( \beta_v )</td>
<td>Flow rate of susceptible and questing mosquitoes to humans.</td>
</tr>
<tr>
<td>( \beta_h )</td>
<td>Flow rate of infectious and questing mosquitoes to humans.</td>
</tr>
<tr>
<td>( p )</td>
<td>Probability of blood being taken from a susceptible human by a susceptible mosquito.</td>
</tr>
<tr>
<td>( q )</td>
<td>Probability of blood being taken from an infected human by a susceptible mosquito.</td>
</tr>
<tr>
<td>( p_1 )</td>
<td>Probability of blood being taken from an infected human by an infectious mosquito.</td>
</tr>
<tr>
<td>( q_1 )</td>
<td>Probability of blood being taken from an susceptible human by an infectious mosquito.</td>
</tr>
<tr>
<td>( M )</td>
<td>The portion of humans which have mosquito killing levels ivermectin in their blood.</td>
</tr>
<tr>
<td>( L )</td>
<td>The mosquito carrying capacity in the local environment.</td>
</tr>
</tbody>
</table>

The result is the following model,

\[
\begin{align*}
\dot{S}_h &= \mu_h N_h + r_h I_h - \beta_h S_h I_f - \mu_h S_h, \quad (1a) \\
\dot{I}_h &= \beta_h S_h I_f - (\mu_h + r_h) I_h, \quad (1b) \\
\dot{S}_r &= p \beta_v S_h S_f (1 - M) - (a_v + \mu_v) S_r, \quad (1c) \\
\dot{S}_q &= a_v \lambda_v(S_r) S_v + a_v \lambda_v(I_r) I_r + a_v S_r - (\mu_v + \alpha_v(N_h)) S_q, \quad (1d) \\
\dot{S}_f &= \alpha_v(N_h) S_q - (\mu_v + \beta_v N_h) S_f, \quad (1e) \\
\dot{I}_r &= (p_1 \beta_h N_h I_f + q \beta_h I_f S_f) (1 - M) - (a_v + \mu_v) I_r, \quad (1f) \\
\dot{I}_q &= a_v I_r - (\mu_v + \alpha_v(N_h)) I_q, \quad (1g) \\
\dot{I}_f &= \alpha_v(N_h) I_q - (\mu_v + \beta_h N_h) I_f. \quad (1h)
\end{align*}
\]
with the equations for the total populations of mosquitoes and humans

\[
\begin{align*}
\dot{N}_h &= 0, \\
\dot{N}_m &= p \beta_v S_h S_f (1 - M) + a_v (\lambda_v S_r) S_r + \lambda_v (I_r) I_r \\
&\quad - ((1 - p_1) (\beta_h N_h I_f) + (1 - q) (\beta_v N_h S_f)) (1 - M) - \mu_v N_m.
\end{align*}
\]

The effect of ivermectin is captured through the scaling of the questing mosquitoes which successfully take a blood meal by ratio of the humans medicated with the drug. In the system, the two terms in which are scaled are \(p \beta_v S_h S_f\) in Equation (1c) and \(p_1 \beta_h N_h I_f + q \beta_v N_h S_f\) in Equation (1f). Ultimately, we assume that any mosquito taking blood from a medicated human dies before reaching the next stage of the life cycle. So we change the original model by scaling the mosquitoes entering the fed life stage by a constant \((1 - M)\).

In this constant, \(M\) represents a proportion of the human population which are medicated with the drug ivermectin.

The system (1) also requires appropriate initial conditions in the form

\[(S_h(0), I_h(0), S_r(0), S_q(0), S_f(0), I_r(0), I_q(0), I_f(0)).\]

### 3.2 Positivity, Uniqueness of Solution, and Boundedness

Since the variables in this model represent populations, their values are non-negative. Therefore, we use a reasonable domain \(D \subset \mathbb{R}^8\),

\[
D = \{(S_h, I_h, S_r, S_q, S_f, I_r, I_q, I_f) : S_h \geq 0, I_h \geq 0, N_h \geq S_h + I_h \geq 0, S_r \geq 0, S_q \geq 0, S_f \geq 0, \\
I_r \geq 0, I_q \geq 0, I_f \geq 0, N_m \geq S_r + S_q + S_f + I_r + I_q + I_f \geq 0\}.
\]

Since the right hand side of the equations in (1) and (2) and their partial derivatives are continuous in \(D\), it can be verified by standard techniques as in [15] that for any initial condition in \(D\) with

\[S_r(0) + S_q(0) + S_f(0) + I_r(0) + I_q(0) + I_f(0) = N_m(0)\] and \(S_h + I_h = N_h\),

there exists a unique solution to the system for all \(t\). Also note that if \(N_m(0) > 0\) then \(N_m(t) > 0\) for all \(t\) and if \(N_m(0) = 0\) then \(N_m(t) = 0\) for all \(t\). The same holds for the human population, \(N_h\). Additionally we
note the following result for the mosquito population.

**Theorem 3.1.** The closed set $\Phi = \{(S_r, S_q, S_f, I_r, I_q, I_f) \in \mathbb{R}^6 : N_m = S_r + S_q + S_f + I_r + I_q + I_f \leq \frac{2\mu_v \lambda_0 L}{\mu_v} \}$ is positively invariant and attracting with respect to the system (1).

*Proof.* See [7, Theorem 2.1].

### 3.3 Reparameterization and Nondimensionalization

We now scale the model by introducing dimensionless variables. Noting that $S_h = N_h - I_h$, we introduce the new variables:

\[
\begin{align*}
    s_r &= \frac{S_r}{L}, \\
    s_q &= \frac{p\beta_v N_h \alpha(N_h)}{L(a_v + \mu_v)(\mu_v + \beta_v N_h)} S_q, \\
    s_f &= \frac{p\beta_v N_h}{L(a_v + \mu_v)} S_f, \\
    \tau &= (a_v + \mu_v)t,
\end{align*}
\]

(3)

and the dimensionless parameter groupings:

\[
\begin{align*}
    \beta &= \frac{a_v \alpha_v (N_h) \beta_h L}{(a_v + \mu_v)(\mu_v + \alpha_v(N_h))(\mu_v + \beta_h N_h)}, \\
    \delta &= \frac{a_v \alpha_v (N_h) \beta_h N_h p_1}{(a_v + \mu_v)(\mu_v + \alpha_v(N_h))(\mu_v + \beta_h N_h)}, \\
    \mu &= \frac{\mu_h + \rho_h}{a_v + \mu_v}, \\
    \sigma &= \frac{q}{p}, \\
    \alpha &= \frac{a_v \alpha_v (N_h) \beta_h N_h \rho}{(a_v + \mu_v)^2(\mu_v + \beta_v N_h)}, \\
    \gamma &= \frac{\mu_v + \beta_v N_h}{a_v + \mu_v}, \\
    \rho &= \frac{\mu_v + \alpha_v(N_h)}{a_v + \mu_v}, \\
    \epsilon &= \frac{\mu_v + \beta_h N_h}{a_v + \mu_v},
\end{align*}
\]

(4)

to yield new parameters for the model. System (1) now takes the form:

\[
\begin{align*}
    \dot{i}_h &= \beta (1 - i_h) i_f - \mu i_h, \\
    \dot{s}_r &= (1 - i_h) s_f (1 - M) - s_r, \\
    \dot{s}_q &= \alpha \lambda_0 (s_r (1 - s_r) + i_r (1 - i_r)) + \alpha s_r - \rho s_q, \\
    \dot{s}_f &= \gamma (s_q - s_f), \\
    \dot{i}_r &= (\delta i_f + \sigma I s_f) (1 - M) - i_r, \\
    \dot{i}_q &= \rho (i_r - i_q), \\
    \dot{i}_f &= \epsilon (i_q - i_f),
\end{align*}
\]

(5)

where the dots now represent the derivative with respect to $\tau$. A feasible region for the parameter space is
\[ \Gamma = \{ 0 \leq \beta < L/N_h, \mu > 0, 0 < \alpha < \rho < 1, 0 \leq \delta < 1, \epsilon > 0, \rho > \gamma > 0, \lambda_0 > 0 \}, \] for details see \[7\]. The system \([5]\) requires an initial condition in the form \((i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0))\).

4 The Existence and Linear Stability of Steady States

4.1 The Disease Free System

In the absence of malaria, \(i_h = 0, i_r = 0, i_q = 0, i_f = 0\), and our model \([5]\) reduces to:

\[
\begin{align*}
\dot{s}_r &= s_f(1 - M) - s_r, \quad (6a) \\
\dot{s}_q &= \alpha \lambda_0 s_r (1 - s_r) + \alpha s_r - \rho s_q, \quad (6b) \\
\dot{s}_f &= \gamma (s_q - s_f). \quad (6c)
\end{align*}
\]

We identify a threshold parameter \(R^*\) with the properties stated in the Theorems \([4.1]\) and \([4.2]\), where

\[
R^* = \frac{\alpha \lambda_0}{\rho - M - \alpha}. \quad (7)
\]

**Theorem 4.1.** The threshold parameter \(R^*\) has the following properties:

- If \(R^* \leq 1\), there exists only the trivial steady state, \(E_0 = (s^*_r, s^*_q, s^*_f) = (0, 0, 0)\).
- If \(R^* > 1\), there exists, in addition to the trivial steady state \(E_0\), a non-trivial steady state

\[
E_1 = (s^*_r, s^*_q, s^*_f) = \left(1 - \frac{1}{R^*}, \frac{1}{1 - M}, \frac{1}{1 - M}\right). \quad (8)
\]

**Proof.** We find the steady state solutions to system \([6]\) by setting the right hand side of that system equal to zero and solving the resulting system of equations. It is straightforward calculation to verify that the existence of realistic steady state solutions as given by \([7]\) and that if \(R^* > 1\) then \(E_1\) as given in \([8]\) exists.

When \(R^* = 1\), \(E_1\) reduces to the trivial steady state \(E_0\), and when \(R^* < 1\), \(E_1\) is not a realistic steady state. \(\square\)

**Remark 4.1.** From a biological standpoint, Theorem \([4.1]\) states that the threshold parameter \(R^*\) has the following effect on the mosquito population. If \(R^* < 1\), the mosquito population will die out over time. If
\( R^* = 1 \), the mosquito population will remain constant. Finally, when \( R^* > 1 \) the mosquito population will grow to the carrying capacity of the environment.

**Theorem 4.2.** The trivial steady state always exists and is linearly stable to small perturbations. Let

\[
Y = \gamma + \rho + 1 > 0, \quad Z = \gamma + \rho + \gamma \rho > 0, \quad X = \gamma (\rho - \alpha (1 - M)) > 0 \quad \text{since} \quad \rho > \alpha, M < 1.
\]  

Then when \( R^* > 1 \), the non-trivial steady state \( E_1 \) is linearly stable to small perturbations whenever

\[
YZ - X(R^* - 1) > 0
\]

and can be driven to instability via a Hopf bifurcation at the point in the parameter space where

\[
YZ - X(R^* - 1) = 0.
\]

**Proof.** Stability of steady state solutions to the system (5) is determined by the signs of the eigenvalues of the linearized system at the steady state, namely

\[
\begin{pmatrix}
\dot{s}_r \\
\dot{s}_q \\
\dot{s}_f
\end{pmatrix}
= J(s_r^*, s_q^*, s_f^*)
\begin{pmatrix}
s_r \\
s_q \\
s_f
\end{pmatrix}
= \begin{pmatrix}
-1 & 0 & 1 - M \\
\alpha(\lambda_0 + 1) - 2\alpha\lambda_0 s_r^* & -\rho & 0 \\
0 & \gamma & -\gamma
\end{pmatrix}
\begin{pmatrix}
s_r \\
s_q \\
s_f
\end{pmatrix},
\]

where \( J(s_r^*, s_q^*, s_f^*) \) is the Jacobian matrix of the system evaluated at the steady state. If \( k \) is an eigenvalue of \( J(s_r^*, s_q^*, s_f^*) \) then \( k \) is a solution to the characteristic equation

\[
k^3 + Yk^2 + Zk + \rho\gamma + 2\gamma\alpha\lambda_0 s_r^*(1 - M) - \gamma\alpha(\lambda_0 + 1)(1 - M) = 0,
\]

where \( Y \) and \( Z \) are as stated in Equation (9). It then follows that at \( E_0, s_r^* = 0 \), and all solutions to Equation (10) have negative real parts when \( R^* \leq 1 \). Additionally, when \( R^* > 1 \) the solution to (10) has positive real parts, so perturbations grow exponentially and at \( E_1, s_r^* = 1 - \frac{1}{R^*} \). Routh - Hurwitz stability criterion tells us that solutions of Equation (10) have negative real parts when \( YZ - X(R^* - 1) > 0 \), and a Hopf Bifurcation occurs where \( X(R^* - 1) = YZ \).

**Remark 4.2.** From a biological standpoint, Theorem 4.2 says the following. If there are no mosquitoes in the environment, introducing a small number mosquitoes will have no long term effect on the population of
mosquitoes, they will simply die out again shortly. Similarly, if there is a living population of mosquitoes \((R^* > 1)\) introducing or killing a small number mosquitoes will have no long term effect on the population of mosquitoes unless \(YZ - X(R^* - 1) > 0\). In the later case, introducing or killing some mosquitoes may have a long term effect on the population of mosquitoes.

**Remark 4.3.** We note that the condition \(YZ - X(R^* - 1) > 0\) is equivalent to

\[
1 - \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma \rho) + \gamma \rho}{\gamma \alpha (\lambda_0 + 1)} < M < 1
\]

in terms of \(M\). Additionally, in the case that \(M = 0\), it was found in \([7]\) that \(YZ - X(R^* - 1) > 0\) is equivalent to

\[
0 < \lambda_0(\gamma) < \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma \rho) + \gamma (\rho - \alpha)}{\alpha \gamma}
\]

in the \((\gamma, \lambda_0)\) space. Thus the conditions for a Hopf Bifurcation to occur are both

\[
\lambda_0(\gamma) \geq \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma \rho) + \gamma (\rho - \alpha)}{\alpha \gamma} \quad \text{and} \quad 0 < M = 1 - \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma \rho) + \gamma \rho}{\gamma \alpha (\lambda_0(\gamma) + 1)}.
\]

**Theorem 4.3.** The trivial steady state \(E_1\) is globally and asymptotically stable whenever \(R^* \leq 1\).

**Proof.** See \([18]\). \(\square\)

### 4.2 The Basic Reproduction Number

In a disease model, an essential threshold parameter is the basic reproduction number \(R_0\) which is a measure of the average number of secondary cases of the disease caused by a single infected individual in an otherwise susceptible population \([16]\). It is generally assumed that when \(R_0 < 1\) the disease disappears from a community and when \(R_0 > 1\) the disease remains and spreads throughout the community. The critical case in which \(R_0 = 1\) leaves the community with a constant number of infected individuals. In some cases, there is a possibility of backward bifurcation which complicates disease control because \(R_0 < 1\) may not be enough to curtail the spread of the disease. This phenomena is discussed further in Section 4.5.

To calculate \(R_0\) we use the next generation method where \(R_0\) is the spectral radius of the next generation matrix. The spectral radius is the eigenvalue with the largest absolute value. As in \([16], [17]\) we calculate \(R_0\) to be the spectral radius of the next generation matrix \(M = FY^{-1}\) where
From these we obtain the eigenvalue

\[ \tilde{R}_0 = \sqrt{\frac{\beta_h \beta_h' N_h S_f' (1 - M)}{\mu_v (r_h + \mu_h)} q - \frac{a_v \alpha_v(N_h)}{\alpha_v \alpha_v(N_h)} \left( \frac{1}{1 + \beta_h N_h (1 - p_1M)} \right) + (\mu_v + \beta_h N_h)(a_v + \alpha_v(N_h) + \mu_v)} \]

and, in dimensionless parameters,

\[ \tilde{R}_0 = \sqrt{\frac{s_f' \sigma \beta (1 - M)}{(1 - \delta(1 - M)) \mu \beta}} = \sqrt{\frac{\sigma \beta (R^* - 1)}{(1 - \delta(1 - M)) \mu R^*}} \]

We note here that, since \( R^* > 1 \) and \( 0 \leq \delta(1 - M) < 1 \), \( \tilde{R}_0 \) is a positive real number. Also note that when \( 0 < \tilde{R}_0 \leq 1 \) and \( 1 < \tilde{R}_0 \), \( \tilde{R}_0 \) is a positive real number. Also note that when \( 1 < \tilde{R}_0 \), \( 1 < \tilde{R}_0 \), \( 1 < \tilde{R}_0 \). We use the value \( R_0 = \tilde{R}_0^2 \), which coincides with the value of the basic reproduction number which can be obtained by seeking conditions for the existence of a steady state as in [7]. That is, we use the value

\[ \tilde{R}_0 = \frac{s_f' \sigma \beta (1 - M)}{(1 - \delta(1 - M)) \mu \beta} = \frac{\sigma \beta (R^* - 1)}{(1 - \delta(1 - M)) \mu R^*}. \]  \( (11) \)

The squaring of \( \tilde{R}_0 \) to obtain \( R_0 \) is due to the fact that the transmission of malaria takes place via the mosquito, so the mosquito must bite two humans to transmit the disease. That is, the mosquito must first bite the single introduced infectious individual and then bite one of the susceptible individuals.

### 4.3 Existence of Steady States

**Theorem 4.4.** In the presence of malaria there is a trivial steady state,

\[ E_0 = (0, 0, 0, 0, 0, 0, 0), \]
a disease free steady state,

\[ E_{df} = (i_h^*, s_r^*, s_q^*, i_r^*, i_q^*, i_f^*) = \left( 0, 1 - \frac{1}{R^*}, 1 - \frac{1}{R^*}, 1 - \frac{1}{R^*}, 0, 0, 0 \right), \]

where \( R^* \) is defined in (4) and either zero one or two endemic steady states,

\[ E_e = (i_h^*, s_r^*, s_q^*, u_r^*, i_q^*, i_f^*), \]

whose existence are determined by the size of the threshold parameter \( R_0 \) and the value of the parameters

\[ A_1 = 1 - \frac{\rho \beta s_r^*}{\mu \alpha \lambda_0 (1 - M)} \quad \text{and} \quad A_2 = s_r^*(1 - \frac{1}{R^*} - s_r^*) = s_r^2(R_0 - 1). \]  

When \( E_e \) exists it can be written in terms of \( i_f^* \), the scaled endemic steady state of infectious, fed, mosquitoes.

**Proof.** The steady states of the malaria model are found by setting the right hand side of (5) equal to zero and solving the resulting system of equations. Some algebra shows that the resulting constant solutions, \( i_h^* \), \( s_r^* \), \( s_q^* \), \( i_r^* \), \( i_q^* \), and \( i_f^* \), can be written in terms of \( i_f^* \) as follows.

\[ i_h^*(i_f^*) = \frac{\beta i_f^*}{\beta i_f^* + \mu}, \quad s_r^* = \frac{\mu(1 - \delta(1 - M))}{\sigma \beta}, \quad i_r^* = i_q^* = i_f^*, \]

\[ s_q^*(i_f^*) = s_f^*(i_f^*) = s_r^* \left( \frac{1}{1 - M} \right) \left( 1 + \frac{\beta i_f^*}{\mu} \right), \]  

where \( i_f^* \) is a positive solution to the equation

\[ i_f^*^2 - A_1 i_f^* - A_2 = 0, \]  

with \( A_1 \) and \( A_2 \) given by (12). Solving for \( i_f^* \) we obtain

\[ i_f^{*1,2} = \frac{A_1 \pm \sqrt{A_1^2 + 4A_2}}{2}, \]

whose existence as a real and positive solution is determined by the size and sign of \( A_1 \) and \( A_2 \), leading to the possibility of zero, one, or two solutions.

**Remark 4.4.** From a biological standpoint, Theorem 4.4 states that the following situations are possible.
There can be no mosquitoes and thus no malaria. There can be mosquitoes but no malaria. There can be mosquitoes and malaria. And lastly, when there are mosquitoes and malaria, there are situations in which the infected portion of the human population can fluctuate, sometimes quite a bit, by increasing or decreasing the infected mosquito population. The parameters $A_1$ and $A_2$ determine which of these cases occurs.

Remark 4.5. As can be seen in Figure [1] the various possibilities for the number and sizes of endemic steady states, depending on the signs of our threshold parameters $A_1$, $A_2$, and $\Delta$ where $\Delta = A_1^2 + 4A_2$ are as follows:

1. If $A_2 > 0$, $A_1 < 0$, and $\Delta > 0$ then there is a unique endemic steady state defined by

$$i_h^* = \frac{\alpha \lambda_0 \sigma \beta (1 - M) - \rho \beta (1 - \delta(1 - M)) + \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2}}{\alpha \lambda_0 \sigma \beta (1 - M) - \rho \beta (1 - \delta(1 - M)) + \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2} + 2 \mu \alpha \lambda_0 \sigma (1 - M)},$$

$$s_r^* = \frac{\mu(1 - \delta(1 - M))}{\sigma \beta},$$

$$s_q^* = s_f^* = \frac{\mu(1 - \delta(1 - M))}{\sigma \beta(1 - M)} \left( 1 + \frac{\beta \left( \frac{\sigma \alpha \lambda_0 (1 - M) - \rho (1 - \delta(1 - M)) + \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2}}{2 \mu \alpha \lambda_0 \sigma (1 - M)} \right)}{\frac{\sigma \alpha \lambda_0 (1 - M) - \rho (1 - \delta(1 - M)) + \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2}}{2 \alpha \lambda_0 \sigma (1 - M)}} \right),$$

$$i_r^* = i_q^* = i_f^* = \frac{\sigma \alpha \lambda_0 (1 - M) - \rho (1 - \delta(1 - M)) + \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2}}{2 \alpha \lambda_0 \sigma (1 - M)}.$$

(16)

2. If $A_2 > 0$, $A_1 = 0$, and $\Delta > 0$ the unique endemic steady state is defined by

$$i_h^* = \frac{(1 - \delta(1 - M)) \sqrt{\mathcal{R}_0 - 1}}{(1 - \delta(1 - M)) \sqrt{\mathcal{R}_0 - 1} + \sigma},$$

$$s_r^* = \frac{\mu(1 - \delta(1 - M))}{\sigma \beta},$$

$$s_q^* = s_f^* = \frac{\mu(1 - \delta(1 - M))}{\sigma \beta(1 - M)} \left( 1 + \frac{(1 - \delta(1 - M)) \sqrt{\mathcal{R}_0 - 1}}{\sigma} \right),$$

$$i_r^* = i_q^* = i_f^* = \frac{\mu(1 - \delta(1 - M)) \sqrt{\mathcal{R}_0 - 1}}{\sigma \beta}.$$

(17)

3. If $A_2 > 0$, $A_1 > 0$, and $\Delta > 0$ the unique endemic steady state is represented by the equations in (16), however, the steady state values will differ numerically since there is a change in the sign of $A_1$. 

263
Figure 1: The $A_1, A_2$ parameter space showing the possible number of endemic steady state solutions to Equation (5). Note that $\Delta = A_2^2 + 4A_2$, the discriminant of Equation (15). Lines which are broken contain no realistic endemic steady states, while lines which are solid contain realistic endemic steady states. We note here that the condition $R_0 > 1$ is equivalent to $A_2 > 0$ and $R_0 < 1$ is equivalent to $A_2 < 0$. Here we can see that by changing the signs of $A_1$, $A_2$, and $\Delta$, all of which depend on $M$, we can control the number of realistic endemic steady states. Figure adapted from [7].
4. If \( A_2 = 0, A_1 > 0, \) and \( \Delta > 0 \) the unique endemic steady state is defined by

\[
\begin{align*}
    i_h^* &= \frac{\beta \alpha \lambda_0 \sigma (1 - M) - \beta \rho (1 - \delta (1 - M))}{\beta \alpha \lambda_0 \sigma (1 - M) - \beta \rho (1 - \delta (1 - M)) + \mu \alpha \lambda_0 \sigma (1 - M)}, \\
    s_r^* &= \frac{\mu (1 - \delta (1 - M))}{\sigma \beta}, \\
    s_q^* &= s_f^* = \frac{\mu (1 - \delta (1 - M))}{\sigma \beta (1 - M)} \left( 1 + \frac{\beta (\alpha \lambda_0 \sigma (1 - M) - \rho (1 - \delta (1 - M)))}{\mu \alpha \lambda_0 \sigma (1 - M)} \right), \\
    i_r^* &= i_q^* = i_f^* = \frac{\alpha \lambda_0 \sigma (1 - M) - \rho (1 - \delta (1 - M))}{\alpha \lambda_0 \sigma (1 - M)}. 
\end{align*}
\]

(18)

5. If \( A_2 < 0, A_1 > 0, \) and \( \Delta > 0 \) the model has feasible endemic steady states defined by

\[
\begin{align*}
    i_{h1,2}^* &= \frac{\alpha \lambda_0 \sigma \beta (1 - M) - \rho \beta (1 - \delta (1 - M)) \pm \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2}}{\alpha \lambda_0 \sigma \beta (1 - M) - \rho \beta (1 - \delta (1 - M)) \pm \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2 + 2 \mu \alpha \lambda_0 \sigma (1 - M)}}, \\
    s_{r1,2}^* &= \frac{\mu (1 - \delta (1 - M))}{\sigma \beta}, \\
    s_{q1,2}^* &= s_{f1,2}^* = \frac{\mu (1 - \delta (1 - M))}{\sigma \beta (1 - M)} \left( 1 + \frac{\beta \left( \sigma \mu \alpha \lambda_0 - \rho ((1 - M)^{-1} - \delta) \pm \sqrt{\Delta (\alpha \lambda_0 \sigma)^2} \right)}{2 \mu \alpha \lambda_0 \sigma} \right), \\
    i_{r1,2}^* &= i_{q1,2}^* = i_{f1,2}^* = \frac{\sigma \alpha \lambda_0 (1 - M) - \rho (1 - \delta (1 - M)) \pm \sqrt{\Delta (\alpha \lambda_0 \sigma (1 - M))^2}}{2 \alpha \lambda_0 \sigma (1 - M)}. 
\end{align*}
\]

(19)

6. If \( A_2 < 0, A_1 > 0, \) and \( \Delta = 0 \) the unique endemic steady state is defined by

\[
\begin{align*}
    i_h^* &= \frac{\beta \alpha \lambda_0 \sigma (1 - M) - \beta \rho (1 - \delta (1 - M))}{\sigma \alpha \lambda_0 (1 - M) - \rho (1 - \delta (1 - M)) + 2 \mu \sigma \alpha \lambda_0 (1 - M)}, \\
    s_r^* &= \frac{\mu (1 - \delta (1 - M))}{\sigma \beta}, \\
    s_q^* &= s_f^* = \frac{\mu (1 - \delta (1 - M))}{\sigma \beta (1 - M)} \left( 1 + \frac{\beta (\sigma \alpha \lambda_0 (1 - M) - \rho (1 - \delta (1 - M)))}{2 \sigma \alpha \lambda_0 (1 - M)} \right), \\
    i_r^* &= i_q^* = i_f^* = \frac{\sigma \alpha \lambda_0 (1 - M) - \rho (1 - \delta (1 - M))}{2 \sigma \alpha \lambda_0 (1 - M)}. 
\end{align*}
\]

(20)

Otherwise there exists no endemic steady states. Thus the importance of seeking values of \( M \) between zero and one which can change \( A_1, A_2, \) and \( \Delta \) so that there exists no endemic steady state is clear.

4.4 Stability of Steady States

We now analyze the linear stability of the system in [5]. We linearize the system about the steady state \((i_h^*, s_r^*, s_q^*, s_f^*, i_r^*, i_q^*, i_f^*)\) to obtain:
Proposition 4.1. The trivial steady state is linearly stable to small perturbations whenever $R^* \leq 1$ and unstable when $R^* > 1$.

Proof. To determine the linear stability of the trivial steady state we find the eigenvalues of the Jacobian matrix evaluated at $E_0 = (0, 0, 0, 0, 0, 0)$,

$$J(E_0) = \begin{pmatrix}
-\mu & 0 & 0 & 0 & 0 & 0 & \beta \\
0 & -1 & 0 & 1 - M & 0 & 0 & 0 \\
0 & \alpha(\lambda_0 + 1) & -\rho & 0 & \alpha\lambda_0 & 0 & 0 \\
0 & 0 & \gamma & -\gamma & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -1 & 0 & \delta(1 - M) \\
0 & 0 & 0 & 0 & \rho & -\rho & 0 \\
0 & 0 & 0 & 0 & \epsilon & -\epsilon & 0
\end{pmatrix}.$$  

If $k$ is an eigenvalue of $J(E_0)$, $k$ is a solution to the characteristic equation

$$(\mu + k) \left( k^3 + Xk^2 + Yk + Z(1 - R^*) \right) \left( k^3 + X_1k^2 + Y_1k + Z_1 \right) = 0,$$  

where $X, Y, Z$ are defined in Equation [9] and

$$X_1 = \epsilon\rho(1 - \delta(1 - M)), \quad Y_1 = \epsilon + \rho + 1, \quad Z_1 = \epsilon\rho + \epsilon + \rho.$$  

Note that $X_1 > 0$ since $0 \leq \delta < 1$ and $M < 1$.

We can see that the characteristic equation takes the form of three polynomials, multiplied together. It
is clear that $Y_1Z_1 - X_1 > 0$ so Routh-Hurwitz tells us that the roots of the right hand cubic in (21) have negative real parts. Additionally, since $\mu > 0$, $(\mu + k)$ has only solutions with negative real parts. Finally, Theorem 4.2 with $s^*_r = 0$ tells us the left cubic in Equation (21) has only negative real parts when $\mathcal{R}^* \leq 1$ but has solutions with positive real parts when $\mathcal{R}^* > 1$. Thus the trivial steady state is unstable to small perturbations whenever $\mathcal{R}^* > 1$, and is stable whenever $\mathcal{R}^* \leq 1$.

**Proposition 4.2.** When $\mathcal{R}^* > 1$, the disease free steady state exists and is linearly stable to small perturbations whenever $YZ - X(\mathcal{R}^* - 1) > 0$ and $\mathcal{R}_0 < 1$ but can become unstable via Hopf Bifurcation, even when $\mathcal{R}_0 > 1$ at the point where $YZ - X(\mathcal{R}^* - 1) = 0$. The disease free steady state is always linearly unstable whenever $\mathcal{R}_0 > 1$.

**Proof.** To determine the linear stability of the disease free steady state we find the eigenvalues of the Jacobian matrix evaluated at $E_{df} = (0, s^*_r, s^*_f, s^*_q, 0, 0, 0)$. If $k$ is an eigenvalue of

$$J(E_{df}) = \begin{pmatrix}
-\mu & 0 & 0 & 0 & 0 & 0 & \beta \\
-s^*_r(1 - M) & -1 & 0 & (1 - M) & 0 & 0 & 0 \\
0 & \alpha\lambda_0(1 - 2s^*_r) + \alpha & -\rho & 0 & \alpha\lambda_0 & 0 & 0 \\
0 & 0 & \gamma & -\gamma & 0 & 0 & 0 \\
\sigma s^*_r(1 - M) & 0 & 0 & 0 & -1 & 0 & \delta(1 - M) \\
0 & 0 & 0 & 0 & \rho & -\rho & 0 \\
0 & 0 & 0 & 0 & 0 & \epsilon & -\epsilon
\end{pmatrix},$$

then $k$ is a solution to the characteristic polynomial

$$(k^3 + Xk^2 + Yk + Z(\mathcal{R}^* - 1)) = 0,$$

or

$$(k^4 + (Y_1 + \mu)k^3 + (\mu Y_1 + Z_1)k^2 + (\mu Z_1 + Y_1)k + X_1\mu(1 - \mathcal{R}_0)) = 0,$$

where $X, Y, Z$ are defined in Equation (9) and $X_1, Y_1, Z_1$ are defined in Equation (22). It can immediately be seen that whenever $\mathcal{R}_0 > 1$, $\mu(1 - \mathcal{R}_0) < 0$ and thus there is at least one sign change in the coefficients.
of the characteristic equation. Hence there is at least one positive real value for $k$ and so $E_{df}$ is linearly unstable to small perturbations whenever $R_0 > 1$. When $R_0 \leq 1$, $\mu(1 - R_0) \geq 0$, thus all the coefficients of Equation (24) are non-negative, so Descartes rule of signs tells us that there are no positive real values $k$ which satisfy the characteristic equation. We now use Routh - Hurwitz criteria to show that all solutions to (24) have negative real parts whenever $R_0 \leq 1$. To do this we must show

\[(Y_1 + \mu)(\mu Y_1 + Z_1)(\mu Z_1 + X_1) > (\mu Z_1 + X_1)^2 + (Y_1 + \mu)^2 \mu X_1(1 - R^*). \quad (25)\]

We subtract the right hand side of Equation (25) from the left hand side and simplify to obtain

\[(\mu Z_1 + X_1)(Y_1 Z_1 - X_1) + (Y_1 + \mu)^2 \mu X_1 R_0 + (Y_1 + \mu) \mu^2(Y_1 Z_1 - X_1) > 0, \text{ since } (Y_1 Z_1 - X_1) > 0. \quad (26)\]

Thus any eigenvalues with positive real parts must be generated by Equation (23). This polynomial is the same as the polynomial in Equation (9) so the relevant results of Theorem 4.2 carry over and $E_{df}$ is unstable to small perturbations even when $R_0 < 1$ whenever

\[\lambda_0(\gamma) \geq \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma \rho) + \gamma(\rho - \alpha)}{\alpha \gamma} \quad \text{and} \quad 0 < M < 1 - \frac{(\gamma + \rho + 1)(\gamma + \rho + \gamma \rho) + \gamma \rho}{\gamma \alpha(\lambda_0(\gamma) + 1)}. \quad (27)\]

Remark 4.6. The endemic steady state $E_e$ studied in [7] can be linearly stable to or unstable to small perturbations and when instabilities occur, they are oscillatory, caused by a Hopf Bifurcation. For details and proof see [7, Proposition 3.10].

4.5 Backward Bifurcation

For $R_0$, there exists a threshold value $R_0^{bb} < 1$ such that when $R_0 < R_0^{bb} < 1$ or $R_0^{bb} < R_0 < 1$ and $A_1 \leq 0$ there exists no endemic steady states, but when $R_0^{bb} < R_0 < 1$ and $A_1 > 0$ there exists two endemic steady states where

\[R_0^{bb} = 1 - \left(\frac{A_1}{2s^*}\right)^2 = 1 - \left(\frac{\beta(\sigma \alpha \lambda_0(1 - M) - \rho(1 - \delta(1 - M)))}{2\mu(1 - \delta(1 - M))\alpha \lambda_0(1 - M)}\right)^2. \quad (27)\]
We compute the value of $R^b_{bb}$ by setting $\Delta = 0$. From here we can see that when $R_0 < R^b_{bb} < 1$, $\Delta < 0$ and thus there are no endemic steady states. Also when $R^b_{bb} < R_0 < 1$ and $A_1 \leq 0$ we can see $\Delta > 0$ but since $A_1 \leq 0$ there are no endemic steady states. Furthermore, when $R^b_{bb} < R_0 < 1$ and $A_1 > 0$ we can see $\Delta > 0$ and $A_2 < 0$. In this case there exist two endemic steady states, even though $R_0 < 1$. Thus a control method focusing solely on driving $R_0$ below one will not always be effective unless $R_0 < R^b_{bb} < 1$. To prove the existence of backwards bifurcation, the techniques of [7, Theorem 3.6] could be used.

### 4.6 Finding Critical M Values

If $M = 0$, the model regresses to its original form in [7]. Additionally, the realistically non-feasible case of $M = 1$ is trivial, because it most certainly causes the mosquito population to die out, resulting in the trivial steady state. We now develop the following Theorems and Remarks to search for critical values of $0 < M < 1$ such that the mosquito population is not destroyed (i.e. $R^* > 1$) but the disease will die out ($R_0 < 1$ or $R_0 < R^b_{bb} < 1$).

**Remark 4.7.** By setting $A_1, A_2$, and $\Delta$ each equal to zero, we can solve for $M$ to find the critical values $0 < M_{A_1}, M_{A_2}, M_{\Delta} < 1$ such that $A_1, A_2$, and $\Delta$ change signs. Note that it is possible for $A_2$ and $\Delta$ to change signs multiple times. From there we can easily determine the values of $M$ such that $A_1, A_2$, and $\Delta$ are positive, negative, or zero. This method is used in Section 5 where we do some numerical simulations.

**Theorem 4.5.** There is a threshold parameter

$$M_{R^*} = 1 - \frac{\rho}{(1 + \lambda_0)\alpha}$$

such that when $M \geq M_{R^*}$, there exists only the trivial steady state $E_0$.

**Proof.** Setting $R^* = 1$ in Equation (7), we then solve the resulting equation for $M$ to obtain (28). It is then clear that $M \geq 1 - \frac{\rho}{(1 + \lambda_0)\alpha}$ is equivalent to $R^* \leq 1$ and thus only the trivial steady state exists when $M \geq M_{R^*}$. \qed

**Theorem 4.6.** There is a threshold parameter

$$M_{R_0} = 1 - \frac{\mu}{s_j \sigma \beta + \delta \mu}.$$ such that whenever $M > M_{R_0}$, $R_0 < 1$ and whenever $M < M_{R_0}$, $R_0 > 1$.  

269
### Table 3: Realistic parameter values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_h$</td>
<td>$\frac{1}{60+365}$</td>
</tr>
<tr>
<td>$r_h$</td>
<td>$\frac{1}{80}$</td>
</tr>
<tr>
<td>$\mu_v$</td>
<td>$\frac{1}{21}$</td>
</tr>
<tr>
<td>$a_v$</td>
<td>$.5$</td>
</tr>
<tr>
<td>$\alpha_v(N_h)$</td>
<td>$.5$</td>
</tr>
<tr>
<td>$p$</td>
<td>$.8$</td>
</tr>
<tr>
<td>$q$</td>
<td>$.9$</td>
</tr>
<tr>
<td>$p_1$</td>
<td>$.9352$</td>
</tr>
<tr>
<td>$\beta_h$</td>
<td>$4.4524\times10^{-6}$</td>
</tr>
<tr>
<td>$\beta_v$</td>
<td>$3.8221\times10^{-6}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>[19] [20] [21]</td>
</tr>
</tbody>
</table>

### Table 4: Nondimensionalized parameter values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>$.0377$</td>
</tr>
<tr>
<td>$\delta$</td>
<td>$.7043$</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>$.9$</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>$1.125$</td>
</tr>
<tr>
<td>$\alpha_v$</td>
<td>$.1276$</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>$.7849$</td>
</tr>
<tr>
<td>$\rho$</td>
<td>$1$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$.0229$</td>
</tr>
</tbody>
</table>

### Proof.

Setting $R_0 = 1$ in Equation (11), we then solve the resulting equation for $M$ to obtain (29). From here it is clear that whenever $M > M_{R_0}$, $R_0 < 1$ and whenever $M < M_{R_0}$, $R_0 > 1$. 

### Remark 4.8.

Whenever $A_1 > 0$, the model (5) undergoes a backward (subcritical) bifurcation at $R_0 = 1$. Due to this, it is not so simple to find a bound on $M$ such that malaria is cured. We can find a critical value of $M$ as stated in Theorem 4.6 such that $R_0$ is less than 1, but that does not guarantee the disease goes away in all cases. The result of Theorem 4.6 are still helpful because whenever $R_0 > 1$, malaria will surely persist. Additionally, when $A_1 \leq 0$, we are in the region with no backwards bifurcation, so driving $R_0$ below 1 cures the disease. Thus, when $M > max(M_{A_1}, M_{R_0})$, there exists no endemic steady states. We also note that when $A_2 = 0$, $R_0 = 1$ thus $M_{R_0} = M_{A_2}$.

### Remark 4.9.

In the case in which $M_{R_0} < M < M_{A_1}$, the number of endemic steady states depends on the sign of $\Delta$. When $\Delta < 0$ there exist no endemic steady states, and when $\Delta > 0$, and $A_2 < 0$ the persistence or resolution of malaria depends on the initial values $i_h(0)$ and $i_f(0), i_r(0), i_q(0)$.

### 5 Numerical Simulations

To illustrate the capabilities of ivermectin we now give an example using realistic values for the original and dimensionless parameters in Tables 3 and 4 respectively. In addition, we fix $L = 5000$, $N_h = 100000$, and vary $\lambda_0$. For each $\lambda_0$, we find the critical values $M_{A_1}, M_{A_2} = M_{R_0}, M_{R^*}$, and $M_{\Delta}$, thus determining whether the disease spreads, based on the value of $M$.

Figure 2 displays the persistence of the mosquito population and the lack of disease when $\lambda_0 = 8$. Thus, if $\lambda_0$ is low enough, the disease is not present in the community. However, raising $\lambda_0$ to 12 results in a high level of disease as in Figure 3.
Figure 2: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 8$ and $M = 0$ we get the values $R_0 = 0.6956$ and $R^* = 1.1340$. Thus the mosquitoes survive and there is no disease, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (0, 1, 1, 0, 0, 0)$.

Figure 3: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 12$ and $M = 0$ we get the values $R_0 = 2.6948$ and $R^* = 1.7552$. Thus the mosquitoes survive and malaria is prevalent, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (0.1, 1, 1, 0.1, 0.1, 0.1)$.

When $\lambda_0 = 12, 18,$ and $100$, Figures 4, 5, and 6 respectively display the regions in the $M$ space for which ivermectin can curtail the spread of malaria with or without killing the mosquito population. The signs of $A_1$, $A_2$, and $\Delta$ as well as the size of $R^*$ in each region can be seen in Table 5.
Table 5: The resulting steady states when \( M \) is in the region listed in the first columns. For a given \( \lambda_0 \), the values of \( A, B, C, D, \) and \( E \) can be seen in Figures 4, 5, and 6.

<table>
<thead>
<tr>
<th>Region</th>
<th>( A_1 )</th>
<th>( A_2 )</th>
<th>( \Delta )</th>
<th>( R^* )</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0,A)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>&gt; 1</td>
<td>Unique endemic steady state</td>
</tr>
<tr>
<td>(A,B)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>&gt; 1</td>
<td>Backward Bifurcation zone</td>
</tr>
<tr>
<td>(B,C)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&gt; 1</td>
<td>No endemic steady states</td>
</tr>
<tr>
<td>(C,D)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&lt; 1</td>
<td>Only trivial steady state</td>
</tr>
<tr>
<td>(D,E)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>&lt; 1</td>
<td>Only trivial steady state</td>
</tr>
<tr>
<td>(E,1)</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>&lt; 1</td>
<td>Only trivial steady state</td>
</tr>
</tbody>
</table>

Figure 4: The parameters are as in Tables 3 and 4 with \( \lambda_0 = 12, A = .2219, B = .3538, C = .3972, D = .588, \) and \( E = .8644. \) The signs of \( A_1, A_2, \) and \( \Delta \) as well as the size of \( R^* \) in each region can be seen in Table 5. The thick region between \( A \) and \( C \) is the region in which curing malaria with ivermectin may be possible, without killing the mosquitoes.

Figure 5: The parameters are as in Tables 3 and 4 with \( \lambda_0 = 18, A = .4112, B = .5037, C = .5875, D = .6959, \) and \( E = .9069. \) The signs of \( A_1, A_2, \) and \( \Delta \) and the size of \( R^* \) in each region are as in Table 5. When \( M < F \), the model displays oscillatory instability in the steady states due to the Hopf Bifurcation. However, when \( M > F \), the Hopf Bifurcation does not occur, and the steady state is stable.

The region represented by the thick line between \( A \) and \( C \) is the region in which eliminating malaria with ivermectin may be possible, without killing the mosquitoes. The region to the right of \( C \) is the area in which...
which ivermectin can curtail the spread of malaria, but only by killing all the mosquitoes. The area to the
left of A is the region in which ivermectin will have no effect on the spread of malaria. In Figure 6, F is the
point in the M space at which a Hopf bifurcation occurs when λ₀ = 100.

Figures 7-10 demonstrate the possible effects of ivermectin in the presence of disease when λ₀ = 12.

Figure 7: When the parameters are as in Tables 3 and 4 with λ₀ = 12 and M = .3 we get the values
R₀ = .5493 and R* = 1.177. Although R₀ < 1, there is still an endemic steady state, as demonstrated in
the plot generated by the initial condition (iₜh(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, .1, .1).

Figure 8: When the parameters are as in Tables 3 and 4 with λ₀ = 12 and M = .3 we get the values
R₀ = .5493 and R* = 1.177. Although R₀ did not change from Figure 7, there is no endemic steady state, as demonstrated in the plot generated by the initial condition (iₜh(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.01, 1, 1, .01, .01, .01). We find the threshold for the initial conditions of iₜh(0), i_r(0), i_q(0), and i_f(0) to be about .081 when M = .3. That is, when iₜh(0), i_r(0), i_q(0), i_f(0) > .081, the disease flourishes. However, when iₜh(0), i_r(0), i_q(0), i_f(0) < .081, the disease dies out over time.
When the parameters are as in Tables 3 and 4 with \( \lambda_0 = 12 \) and \( M = .36 \) we get the values \( R_0 = .2121 \) and \( R^* = 1.0671 \). Thus, the malaria outbreak is curtailed without killing of the entire mosquito population. It is however, important to note that the mosquito population is reduced in size, as demonstrated in the plot generated by the initial condition \( (i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, 1, 1, 1) \).

Figure 9: When the parameters are as in Tables 3 and 4 with \( \lambda_0 = 12 \) and \( M = .36 \) we get the values \( R_0 = .2121 \) and \( R^* = 1.0671 \). Thus, the malaria outbreak is curtailed without killing of the entire mosquito population. It is however, important to note that the mosquito population is reduced in size, as demonstrated in the plot generated by the initial condition \( (i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, 1, 1, 1) \).

Figure 10: When the parameters are as in Tables 3 and 4 with \( \lambda_0 = 12 \) and \( M = .45 \) we get the values \( R_0 = -.3147 \) and \( R^* = .9057 \). Thus, the malaria outbreak is curtailed at the cost of killing of the entire mosquito population, as demonstrated in the plot generated by the initial condition \( (i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (.1, 1, 1, 1, 1, 1) \).

When \( \lambda_0 = 100 \), numerical simulations demonstrating the oscillations caused by the Hopf bifurcation at \( M_{Hopf} = .2149 \) can be seen in Figures 11 and 12.
Figure 11: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 100$ and $M = .2$ there are oscillatory solutions as a result of a Hopf bifurcation at $\lambda_0 = 78.2939$, as demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (0, 1, 1, 0, 0, 0)$. Here we calculate the eigenvalues of Equation (10) to be $-2.7994, 0.0072 + 1.6157i$, and $0.0072 - 1.6157i$, so we have a periodic orbit.

Figure 12: When the parameters are as in Tables 3 and 4 with $\lambda_0 = 100$ and $M = .3$, the oscillatory solutions are curtailed because when $\lambda_0 = 100$, $M_{Hopf} = .2149$ and $M > .2149$. This is demonstrated in the plot generated by the initial condition $(i_h(0), s_r(0), s_q(0), s_f(0), i_r(0), i_q(0), i_f(0)) = (0, 1, 1, 0, 0, 0)$. Here we calculate the eigenvalues of Equation (10) to be $-2.6975, -0.0437 + 1.5271i$ and $-0.0437 + 1.5271i$, so we have a stable equilibrium.
6 Biological Implications, and Conclusions

From our system analysis and numerical simulations, we can conclude that there are potentially realistic situations in which ivermectin can be used to curtail the spread of malaria. We suggest that ivermectin would be particularly useful when combined with other methods of malaria control, such as the reduction of breeding sites and use of mosquito nets, since lowering $\lambda_0$ not only lowers the amount of medication needed, but also widens the range of values of $M$ that can be used to cure malaria, without killing the local population of mosquitoes. In addition, the existence of backwards bifurcation suggests that early intervention may be particularly important when using ivermectin to fight malaria. Our numerical simulations showed that in some cases it doesn’t take much medication to curtail the spread of the disease when the initial conditions are small enough, but higher levels are needed once the disease has taken hold of a population.

Our results also suggest that a drug similar to ivermectin, but with a longer half life, could be particularly useful. The parameter $M$ loosely represents the percentage of the population with ivermectin present in their body at any given time. Ivermectin only stays in a human’s blood at a concentration strong enough to kill mosquitoes for about two weeks. Due to this, even keeping as little as 30% of the population medicated at anytime would be logistically challenging. Thus, if a drug with a similar effect, but a longer half life were to be discovered, it would be substantially easier to keep higher percentages of people medicated.

The presence of osculations in the steady states, which are not produced by seasonal forces, was first discovered in [7]. Our adapted model with consideration of the drug ivermectin, shows that there is the possibility of eliminating the occurrence of the Hopf bifurcation, and thus eliminating the oscillatory solutions. In fact, we find that relatively low levels of ivermectin are required to eliminate the occurrence of these oscillations.

The analysis in [7] noted the importance of the parameter $\lambda_0$ in the control of malaria. The parameter $\lambda_0$ is able to move the solutions to our equation through the $A_1, A_2$ parameter space, changing the number of endemic steady states to be 0, 1 or 2. We now note, that even in cases where $\lambda_0$ cannot be changed, or lowered sufficiently, certain levels of $M$ can also move us through the $A_1, A_2$ space to areas with no endemic steady states. Perhaps the most important thing to note is that in some cases we are able to do this without lowering $R^*$ below zero, killing the mosquitoes. Thus we conclude that ivermectin may be use useful tool in combating the spread of malaria, particularly in conjunction with other methods, and can curtail the spread of malaria without annihilating the local mosquito population.
6.1 Further Investigation

The parameter space of this model is so vast that one could spend substantial time exploring the possible outcomes in regards to $\lambda_0$ and $M$. In particular, one could search for specific regions in the parameter space where malaria can be eliminated by changes in $\lambda_0$ and $M$ and regions in which it cannot. In addition to further numerical study of the parameter space, one could make modifications to the model to make it more accurate or study different scenarios. For example, one may wish to investigate a model in which disease related deaths are considered in the human population, or in which multiple populations of humans interact. In addition, as an anonymous reviewer suggested, one could modify the current model to take into account the waning efficiency of the drug over time. The authors of [7] have already written an additional paper [8] in which a more intricate model is studied. These modifications could be made to either model, or the model in this paper.

6.2 Acknowledgments

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References


