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NUMERICAL SIMULATION OF MALARIA TRANSMISSION MODEL CONSIDERING SECONDARY INFECTION

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Abstract. Malaria is an infectious disease caused by Plasmodium and transmitted through the bite of female Anopheles mosquitoes. This article constructs a mathematical model to understand the spread of malaria by considering the vector–bias phenomenon in the infection process, secondary infection, and fumigation as a means of malaria control. The model is constructed as a SIRI-UV model based on six-dimensional non-linear ordinary differential equations. Analysis of the equilibrium points with their local stability and sensitivity analysis of the basic reproduction number \mathcal{R}_0 is shown analytically and numerically. Based on the analytical studies, two types of equilibrium points were obtained, namely the disease-free equilibrium points and the endemic equilibrium points. We find that the disease-free equilibrium is locally stable if $\mathcal{R}_0 < 1$. Our proposed model shows the possibility of a forward bifurcation, backward bifurcation, or forward bifurcation with hysteresis. To support the interpretation of the model, a numerical simulation for the sensitivity of \mathcal{R}_0 and some autonomous simulations conducted to see how the change of parameter will affect the dynamics of our model. Simulation results show that the increasing of mortality rate on mosquitoes due to fumigation will increase the probability that malaria is eliminated.

Keywords: malaria; fumigation; vector-bias; bifurcation; reproduction number

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1. INTRODUCTION

Malaria is a mosquito-borne disease caused by protozoan parasites in the genus *Plasmodium* which infect humans through the bites of infected female genus *Anopheles* mosquitoes. According to the World Health Organization's report, there were an estimated 219 million cases of malaria in 2017, compared to 217 million cases the year before. The total funding for malaria control and elimination reached an estimated of US\$ 3.1 billion in 2017 [1]. The rate of malaria incidents is highest in the following five countries: Nigeria (25%), Congo Democratic Republic (11%), Mozambique (5%), India (4%) and Uganda (4%).

Five species of *Plasmodium* parasites can infect humans: (1) *P. falciparum*, (2) *P. vivax*, (3) *P. ovale*, (4) *P. malariae*, and (5) *P. knowlesi*. Clinically, *P. falciparum* and *P. vivax* are the biggest threat to humans compared to the other species. The common symptoms include fever, headache, shivering, cold sweat, aches, nausea and vomiting. Infection of *P. falciparum* can lead to other complications such as severe anemia, acute respiratory distress syndrome, kidney failure, and cerebral malaria [2].

Various efforts to prevent and control the spread of malaria have been carried out to reduce the prevalence of the disease. Some of these efforts include insecticide-treated mosquito nets and indoor spraying with residual insecticides [1]. In Indonesia, the government has implemented several programs to control mosquito vectors in the form of a week of anti-mosquito nets ("pekan kelambu anti nyamuk massal") and monitoring its use, training workers against malaria, and provision of diagnostic tools and anti-malarial drugs [3].

A mathematical model for malaria transmission was first introduced in 1916 [4] and further extended by Macdonald [5, 6]. Models with acquired immunity were studied later [7, 8, 9]. Since the resistance to malaria is not fully acquired and declines through time, without new exposures, individuals may lose immune memory and become infected again [10]. Here, we use the SIS model to describe the dynamics of malaria in the human population. For a mosquito population, we use the SI model under the assumption that mosquitoes do not recover from malaria parasites, and also, the malaria parasites do not harm the host. This type of model is based on the Ross-Macdonald model [6]. Several blood-seeking mosquitoes search for their meals by the use of host odors, breath, and sweat [11, 12, 13].

A vector-bias model in malaria was first introduced in [14]. This model is an extension of the Ross-Macdonald model by considering the greater attractiveness of infectious humans to mosquitoes [5, 6]. Following Kingsolver's work [15] incorporates an extrinsic incubation time in mosquitoes to study the dynamics of the disease in terms of a reproduction number. Chamchod and Britton combined a vector-bias term into the malaria transmission model and showed that the greater vector-bias affects greater attractiveness of infectious humans to mosquitoes affected malaria transmission [16].

After recovery, humans with primary infection of malaria can be infected malaria for the second time as a secondary infection. Generally, with a secondary infection, humans do not show clinical symptoms (asymptomatic). However, this infection may be fatal. Therefore, we include the compartment of secondary infection in our malaria transmission model by also considering vector-bias, which is the tendency of mosquitoes to bite humans. In detail, we discretized humans in our model into four compartments: Humans with primary infection (I_1) represents humans who received first-time infections and show clinical symptoms; humans with secondary infection (I_2) describes humans with re-infection without clinical symptoms; susceptible individuals (S), and individuals who have just recovered from malaria (R) [17].

The next section of this paper discusses the construction of malaria transmission model, which is followed by mathematical analysis of the model. The analysis is the existence and local stability of DF , basic reproduction number (\mathcal{R}_0), endemic equilibrium EE , and bifurcation. Section 4 explains the numerical simulations that are carried out on the model. The numerical simulations consist of sensitivity of \mathcal{R}_0 relative to some parameters, and an autonomous simulations. Finally, the last section is the conclusion.

2. THE CONSTRUCTION OF MATHEMATICAL MODEL

To begin our construction, let us divide the human population into four classes based on their health status: susceptible (S); clinical symptomatic malaria individuals resulting in a susceptible individual after the first infection (I_1); recovered (R); asymptomatic infection resulting from recovered individuals (I_2); while the mosquito population is divided into two classes: susceptible (U) and infected (V). I_2 compartment is only for non-primary infections, while the primary infection individuals are included in I_1 . In this paper, we assume that individuals who have

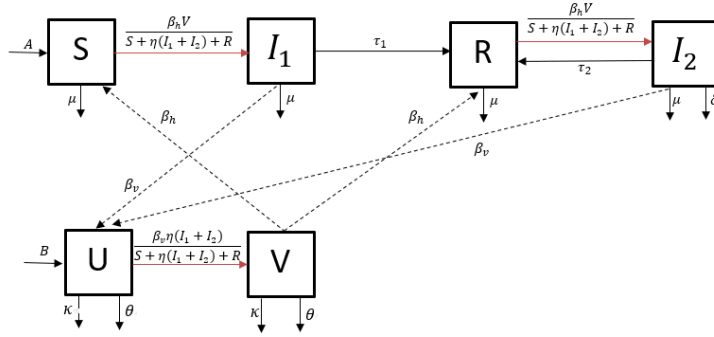


FIGURE 1. The transmission diagram of malaria with secondary infection.

recovered from the first malaria infection may instantly get infected again by mosquito bites. The vector-bias phenomenon occurs when mosquitoes are more attracted to infected individuals, and this vector-bias is included in our model. Variables N and M are the total number of individuals and mosquitoes, respectively. The malaria transmission diagram with the secondary infection is given in Fig.1.

Hence, based on transmission diagram in Fig.1, the dynamics of malaria with secondary infection is written as follows:

$$\begin{aligned}
 \frac{dS}{dt} &= A - \frac{\beta_h SV}{S + \eta(I_1 + I_2) + R} - \mu S, \\
 \frac{dI_1}{dt} &= \frac{\beta_h SV}{S + \eta(I_1 + I_2) + R} - \tau_1 I_1 - \mu I_1, \\
 \frac{dR}{dt} &= \tau_1 I_1 + \tau_2 I_2 - \frac{\beta_h RV}{S + \eta(I_1 + I_2) + R} - \mu R, \\
 \frac{dI_2}{dt} &= \frac{\beta_h RV}{S + \eta(I_1 + I_2) + R} - \tau_2 I_2 - \mu I_2 - \delta I_2, \\
 \frac{dU}{dt} &= B - \frac{\beta_v \eta U (I_1 + I_2)}{S + \eta(I_1 + I_2) + R} - \kappa U - \theta U, \\
 \frac{dV}{dt} &= \frac{\beta_v \eta U (I_1 + I_2)}{S + \eta(I_1 + I_2) + R} - \kappa V - \theta V,
 \end{aligned}
 \tag{1}$$

where all parameters are positive and described as in Table 1. Denote $\eta \geq 1$, and η is called a bias parameter. When $\eta = 1$, there is no vector-bias effect in the model.

TABLE 1. List of parameters for malaria transmission in model (1).

Par	Description	Value	Unity	References
A	The number of human births	0.4215	$\frac{\text{human}}{\text{day}}$	assumed
μ	Natural death rate of humans	0.000039	$\frac{1}{\text{day}}$	[18]
δ	Natural death rate from asymptomatic infections	0.1	$\frac{1}{\text{day}}$	assumed
β_h	Transmission rate in humans	0.0084	$\frac{\text{human}}{\text{mosquito} \times \text{day}}$	[18]
β_v	Transmission rate in mosquitoes	0.084	$\frac{1}{\text{day}}$	[18]
τ_1	Recovery rate from clinical infections	0.14	$\frac{1}{\text{day}}$	assumed
τ_2	Recovery rate from asymptomatic infections	0.0714	$\frac{1}{\text{day}}$	assumed
η	Bias parameter	2	—	assumed
B	The number of adult mosquitoes	4761.9	$\frac{\text{mosquito}}{\text{day}}$	assumed
κ	Natural death rate of mosquitoes	0.0476	$\frac{1}{\text{day}}$	[19]
θ	Fumigation death rate of mosquitoes	0.1	$\frac{1}{\text{day}}$	assumed

For the system in model (1) to be epidemiological meaningful, we have to prove that all of its state variables are always non-negative. In this case, we have to prove the positivity and boundedness of solutions, and also an invariant region of solutions.

2.1. Positivity and boundedness of solutions.

Theorem 1. *Given the initial conditions of model (1) is*

$$(S(0), I_1(0), R(0), I_2(0), U(0), V(0)) \geq 0,$$

then the solution $(S(t), I_1(t), R(t), I_2(t), U(t), V(t))$ of the malaria model (1) is non-negative for all $t \geq 0$. Furthermore

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{A}{\mu}, \quad \limsup_{t \rightarrow \infty} M(t) \leq \frac{B}{\kappa + \theta},$$

where

$$N(t) = S(t) + I_1(t) + R(t) + I_2(t), \quad M(t) = U(t) + V(t).$$

Proof. Consider the first equation in model (1), i.e. $\frac{dS}{dt} + S(\frac{\beta_h V}{S + \eta(I_1 + I_2) + R} + \mu) = A$. If $S(t) \rightarrow 0$, then $\lim_{S(t) \rightarrow 0} \frac{dS}{dt} = A \geq 0$, it means $S(t)$ is a non decreasing function. Therefore $S(t) \geq S(0)$ for $t \geq 0$. In the similar way, it can be proven that $R(t) > 0, I_2(t) > 0, U(t) > 0, V(t) > 0$. Then $(S(t), I_1(t), R(t), I_2(t), U(t), V(t)) \geq 0$ for $t \geq 0$. Next, the rate of change in the total of human population over time is

$$\begin{aligned} \frac{dN}{dt} &= A - \mu N - \delta I_2, \\ &\leq A - \mu N. \end{aligned}$$

By the variable separation method, we have $N \leq \frac{A - e^{-\mu(t+C)}}{\mu}$. While $t \rightarrow \infty$, then $N \rightarrow \frac{A}{\mu}$. Previously it is known that $N \leq \frac{A - e^{-\mu(t+C)}}{\mu}$, then $N \leq \frac{A}{\mu} - \frac{e^{-\mu(t+C)}}{\mu} \leq \frac{A}{\mu}$. So we have

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{A}{\mu}.$$

Similarly, the rate of change in the mosquito population is

$$\frac{dM}{dt} = B - (\kappa + \theta)M.$$

By the variable separation method, we have $M = \frac{B - e^{-(\kappa + \theta)(t+C)}}{\kappa + \theta}$. When $M = \frac{B - e^{-(\kappa + \theta)(t+C)}}{\kappa + \theta}$, then $M = \frac{B}{\kappa + \theta} - \frac{e^{-(\kappa + \theta)(t+C)}}{\kappa + \theta} \leq \frac{B}{\kappa + \theta}$.

For $t \rightarrow \infty$, then

$$\begin{aligned} M &= \frac{B - e^{-(\kappa + \theta)(t+C)}}{\kappa + \theta}, \\ M &\rightarrow \frac{B}{\kappa + \theta}. \end{aligned}$$

This result can be written as

$$\limsup_{t \rightarrow \infty} M(t) \leq \frac{B}{\kappa + \theta}.$$

Hence, N is bounded by $\frac{A}{\mu}$ and M is bounded by $\frac{B}{\kappa + \theta}$. \square

2.2. Invariant regions. The malaria model (1) can be stated in a biologically-feasible region as follows. Consider the region

$$\Omega = \Omega_h \times \Omega_v \subset \mathbb{R}_+^4 \times \mathbb{R}_+^2,$$

where

$$\Omega_h = \left\{ (S, I_1, R, I_2) \in \mathbb{R}_+^4 : N(t) \leq \frac{A}{\mu} \right\},$$

$$\Omega_v = \left\{ (U, V) \in \mathbb{R}_+^2 : M(t) \leq \frac{B}{\kappa + \theta} \right\}.$$

Based on subsection 2.1, the region Ω in model (1) is positively-invariant with non-negative initial conditions in \mathbb{R}_+^6 .

3. MODEL ANALYSIS

This section discusses the analysis of the deterministic model (1), that consists of: the existence and local stability of disease-free equilibrium (DF), basic reproduction number (\mathcal{R}_0) and the endemic equilibrium points (EE).

3.1. Existence and local stability of disease-free equilibrium. The malaria model (1) has a disease-free equilibrium point given by

$$(2) \quad DF = (S, I_1, R, I_2, U, V) = \left(\frac{A}{\mu}, 0, 0, 0, \frac{B}{\kappa + \theta}, 0 \right).$$

This steady state presents the extinction of malaria in both populations, human and mosquito. One should note that the total of human population in (2) is absorbed in the susceptible population, likewise as in mosquito population. Next, we analyze the local stability of DF by linearizing the system (1) using the Jacobian matrix. The Jacobian matrix of system (1) is given

by

$$(3) \quad J_{DF} = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & -\beta_h \\ 0 & -\mu & \tau_1 & \tau_2 & 0 & 0 \\ 0 & 0 & -\tau_1 - \mu & 0 & 0 & \beta_h \\ 0 & 0 & 0 & -\tau_2 - \mu - \delta & 0 & 0 \\ 0 & 0 & -\frac{\beta_v \eta B \mu}{(\kappa + \theta)A} & -\frac{\beta_v \eta B \mu}{(\kappa + \theta)A} & -\kappa - \theta & 0 \\ 0 & 0 & \frac{\beta_v \eta B \mu}{(\kappa + \theta)A} & \frac{\beta_v \eta B \mu}{(\kappa + \theta)A} & 0 & -\kappa - \theta \end{bmatrix}.$$

The corresponding eigenvalues are $\lambda_1 = \lambda_2 = -\mu$, $\lambda_3 = -\theta - \kappa$, $\lambda_4 = -\delta - \mu - \tau_2$, while the other two eigenvalues are determined from the second degree polynomial as follows:

$$\lambda^2 + a_1 \lambda + a_0 = 0,$$

where $a_1 = (\kappa + \mu + \tau_1 + \theta) > 0$, $a_0 = (1 - \mathcal{R}_0^2)A(\mu + \tau_1)(\kappa + \theta)^2$, and

$$\mathcal{R}_0 = \frac{\sqrt{A(\mu + \tau_1)\beta_v \eta B \mu \beta_h}}{A(\mu + \tau_1)(\kappa + \theta)}.$$

Based on the Routh-Hurwitz criterion, the following result holds:

Theorem 2. *The malaria free steady state (DF) of system (1) always exists and is locally asymptotically stable (LAS) if $\mathcal{R}_0 < 1$.*

3.2. Basic reproduction number (\mathcal{R}_0). In this section, the basic reproduction number of the system (1) is discussed. In many mathematical models, the disease will always die out whenever the basic reproduction number is less than one [20, 21, 22, 23, 24]. The basic reproduction number (\mathcal{R}_0) is determined from the system (1) by using the next generation matrix approach [25]. For that purpose, we define the transmission matrix (\mathcal{F}) and the transition matrix (\mathcal{V}) of

system (1), respectively, as follows:

$$\mathcal{F} = \begin{bmatrix} -\frac{\beta_h SV \eta}{(S+\eta(I_1+I_2)+R)^2} & -\frac{\beta_h SV \eta}{(S+\eta(I_1+I_2)+R)^2} & \frac{\beta_h S}{S+\eta(I_1+I_2)+R} \\ -\frac{\beta_h RV \eta}{(S+\eta(I_1+I_2)+R)^2} & -\frac{\beta_h RV \eta}{(S+\eta(I_1+I_2)+R)^2} & \frac{\beta_h R}{S+\eta(I_1+I_2)+R} \\ \frac{\beta_v \eta U}{S+\eta(I_1+I_2)+R} - \frac{\beta_v \eta^2 U(I_1+I_2)}{(S+\eta(I_1+I_2)+R)^2} & \frac{\beta_v \eta U}{S+\eta(I_1+I_2)+R} - \frac{\beta_v \eta^2 U(I_1+I_2)}{(S+\eta(I_1+I_2)+R)^2} & 0 \end{bmatrix},$$

$$\mathcal{V} = \begin{bmatrix} -\tau_1 - \mu & 0 & 0 \\ 0 & -\tau_2 - \mu - \delta & 0 \\ 0 & 0 & -\kappa - \theta \end{bmatrix}.$$

By using both matrices above, the basic reproduction number of system (1) is given by:

$$(4) \quad \mathcal{R}_0 = \rho(-FV^{-1}) = \frac{\sqrt{A(\mu + \tau_1) \beta_v \eta B \mu \beta_h}}{A(\mu + \tau_1)(\kappa + \theta)},$$

where ρ is the spectral radius operator. Please note that according to Theorem (2), and the form of basic reproduction number in (4), we have the following corollary.

Corollary 1. *Malaria will be eradicated and disappear from population whenever the basic reproduction number is less than unity, and unstable otherwise.*

The basic reproduction number (\mathcal{R}_0) presents the number of secondary malaria infection in a completely susceptible population, due to infection from one primary infected malaria individual in one infection period.

3.3. Endemic equilibrium and bifurcation. The endemic equilibrium of system (1), that is EE , is difficult to determine explicitly. Therefore, we show this equilibrium as a function of I_1 , which is given by

$$(5) \quad EE = (S, I_1, R, I_2, U, V) = (S^*, I_1^*, R^*, I_2^*, U^*, V^*),$$

where

$$\begin{aligned}
S^* &= \frac{(A + I_1(-\mu - \tau_1))}{\mu}, \\
R^* &= \frac{\tau_1((-\mu - \tau_1)I_1 + A)I_1(\mu + \delta + \tau_2)}{(-\tau_2(\mu + \tau_1)I_1 + A(\mu + \delta + \tau_2))\mu}, \\
I_2^* &= \frac{I_1^2 \tau_1(\mu + \tau_1)}{((-\mu - \tau_1)I_1 + A)\tau_2 + A(\mu + \delta)}, \\
U^* &= \frac{B((\mu k_1 k_5 - \delta \tau_1)(\mu + \tau_1)I_1^2 + A(k_1 \mu^2 + (\delta k_1 + k_2 \tau_2)\mu - \tau_1 \tau_2)I_1 + A^2(\mu + k_6))}{k_4(k_5 b_1 \mu - \delta \tau_1 k_3)I_1^2 + A(b_1 \mu^2 + (b_2 \kappa + b_2 \theta + \beta_v \eta k_6)\mu - \tau_1 \tau_2 k_3)I_1 + A^2 k_3(\mu + k_6)}, \\
V^* &= \frac{I_1((\mu k_1 k_5 - \delta \tau_1)k_4 I_1^2 + A(k_1 \mu^2 + (\delta k_1 + k_2 \tau_2)\mu - \tau_1 \tau_2)I_1 + A^2(\mu + k_6))k_4}{((-\mu - \tau_1)I_1 + A)(-\tau_2(\mu + \tau_1)I_1 + A(\mu + \delta + \tau_2))\beta_h},
\end{aligned}$$

and $k_1 = \eta - 1, k_5 = \tau_1 - \tau_2, k_2 = \eta - 2, k_6 = \delta + \tau_2, k_3 = \kappa + \theta, b_1 = k_1 \kappa + k_1 \theta + \beta_v \eta, k_4 = \mu + \tau_1$, and $b_2 = \delta k_1 + k_2 \tau_2$, with I_1^* is taken from the positive root of the following polynomial

$$(6) \quad a_4 I_1^4 + a_3 I_1^3 + a_2 I_1^2 + a_1 I_1 + a_0 = 0,$$

with coefficients a_0, a_1, a_2, a_3, a_4 can be seen in Appendix 1.

To determine the number of positive roots in (6), first we show that a_0 as a function of \mathcal{R}_0 . From Appendix (1), we have that

$$\begin{aligned}
a_0 &= A^3(\delta + \mu + \tau_2)^2(A(\kappa + \theta)^2(\mu + \tau_1) - B\mu\beta_h\beta_v\eta), \\
&= A^3(\delta + \mu + \tau_2)^2(\mathcal{R}_0 - 1).
\end{aligned}$$

Hence, it is easy to see that $a_0 > 0 \Leftrightarrow \mathcal{R}_0 > 1$.

Next, we can determine the number of possible positive real roots of the polynomial in equation (6) using the Descartes Rule of Signs in Table 2.

Based on Table 2 and $a_0 > 0 \Leftrightarrow \mathcal{R}_0 < 1$, we have:

- (1) If $a_0 > 0 \Leftrightarrow \mathcal{R}_0 < 1$, and $a_4 > 0$ whereas for a_1, a_2 and a_3 can be positive or negative then the eq.(6) has 0, 2, or 4 positive roots.
- (2) If $a_0 < 0 \Leftrightarrow \mathcal{R}_0 > 1$, and $a_4 > 0$ whereas for a_1, a_2 and a_3 can be positive or negative then the eq.(6) has one or three positive roots.

Note that all variables in eq.(5), depend on I_1 . When the solution of (6), that is I_1^* , and $I_1^* > 0$, then all other variables will also be positive. So, based on the result of point 2, we have the

TABLE 2. Descartes rule of signs for polynomial (6).

a_4	>0															
a_3	>0							<0								
a_2	>0			<0			>0			<0						
a_1	>0	<0	>0	<0	>0	<0	>0	<0	>0	<0	>0	<0	>0	<0		
a_0	>0	<0	>0	<0	>0	<0	>0	<0	>0	<0	>0	<0	>0	<0	>0	<0
Maximum	0	1	2	1	2	3	2	1	2	3	4	3	2	3	2	1
positive																
roots																

system (1) has one or three endemic equilibrium points if $\mathcal{R}_0 > 1$. Based on point 1, the system (1) may have some endemic equilibrium points even though $\mathcal{R}_0 < 1$. To illustrate the existence of the endemic equilibrium point using polynomial (6), we substitute the parameter values in Table 1, except β_h which we choose as the bifurcation parameter. The results can be seen in Fig. 2

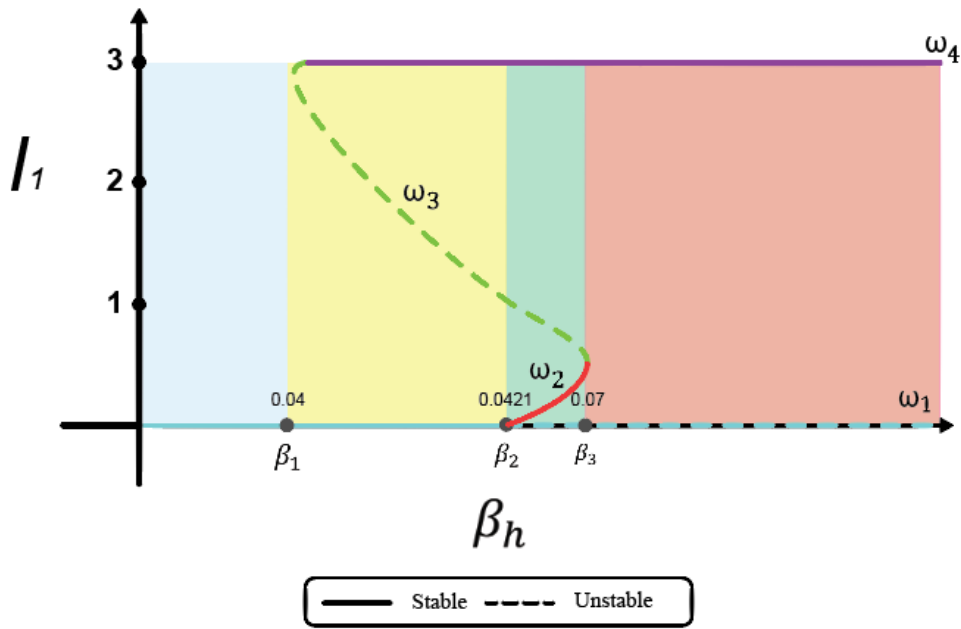


FIGURE 2. Bifurcation diagram of system (1) using polynomial (6).

The relation between β_h and I_1 can be distinguished based on the value of β_h . Note that Fig. 2 has two fold points, namely at β_{h1} and β_{h3} . Furthermore, we have that $\mathcal{R}_0 = 1$ when $\beta_h = \beta_{h2}$. From numerical calculation, we have the following results: If $\beta_h < \beta_{h1}$, then system (1) has no endemic equilibrium. If $\beta_h \in [\beta_1, \beta_2]$, (see Table 3 by taking $\beta_h = 0.042$), we get two I_1^* values associated with two endemic points (EE_1 and EE_2). In addition, there is always a stable DF based on Theorem 2. The stability of two endemic points is determined by eigenvalues from the correspondent Jacobian matrix. The eigenvalues of EE_1 (ω_3 at Fig. 2) are $(-0.30898, -0.15359, 0.00497, -0.00505, -0.00223, -0.14761)$ which shows that EE_1 is unstable. On the other hand, the eigenvalues of EE_2 on ω_4 are $(-13.45736, -13.53472, -0.09738, -0.14428, -0.22887, -0.14761)$ which shows that EE_2 is stable.

Using a similar approach with the previous description on the yellow region, the green region has an unstable DF , three endemic equilibria: one (in the curve of ω_3) is unstable, and the other two (small (in the curve ω_2) and large one (in the curve ω_4)) are stable. Finally, the red region, which $\mathcal{R}_0 > 1$, has one endemic equilibrium which is stable. The dashed line shows that the endemic equilibrium point is unstable, and the solid line shows that the endemic equilibrium point is stable. We summarized our numerical experiments in Table 3. It indicates how sensitive is β_h is to the stability of the equilibrium point.

TABLE 3. Equilibrium point stability based on Fig. 2.

Domain	ω_1	ω_2	ω_3	ω_4
$\beta_h \in [0, \beta_1]$	Stable	-	-	-
$\beta_h \in (\beta_1, \beta_2)$	Stable	-	Unstable	Stable
$\beta_h \in (\beta_2, \beta_3]$	Unstable	Stable	Unstable	Stable
$\beta_h \in (\beta_3, \infty)$	Unstable	-	-	Stable

We close our analytical section with the following remark.

Remark 1. *Our proposed malaria model shows the usual behavior regarding the relationship between the disease-free equilibrium and \mathcal{R}_0 , i.e., it will always be stable when $\mathcal{R}_0 < 1$. An interesting feature occurs when our model shows the possibility of the existence of endemic equilibrium even though the disease-free stable. Hence, bistability phenomena appear, which*

makes the long time behavior of our model highly dependent on the initial condition. On the other hand, it is also possible that our model shows the existence of multiple stable endemic equilibrium, especially when \mathcal{R}_0 is larger but close to one.

4. NUMERICAL SIMULATIONS

In this section, a sensitivity analysis is conducted to find how sensitive \mathcal{R}_0 is to the robustness of parameters in system (1). Also, some numerical simulations for the autonomous system will be carried out from the mathematical model of malaria transmission in system (1) for several possible scenarios that might appear in the field.

4.1. Sensitivity of \mathcal{R}_0 . In this section, numerical simulations are performed to investigate the sensitivity of \mathcal{R}_0 related to controllable parameters such as recovery rate (τ_1) fumigation rate (θ) and infection rate (β_h). Taking the derivative of \mathcal{R}_0 with respect to these parameters will yield the following:

$$\begin{aligned}\frac{\partial \mathcal{R}_0}{\partial \theta} &= -\frac{\sqrt{A(\mu + \tau_1)B\eta\mu\beta_h\beta_v}}{A(\mu + \tau_1)(\kappa + \theta)^2}, \\ \frac{\partial \mathcal{R}_0}{\partial \tau_1} &= 1/2 \frac{B\eta\mu\beta_h\beta_v}{\sqrt{A(\mu + \tau_1)B\eta\mu\beta_h\beta_v}(\mu + \tau_1)(\kappa + \theta)} - \frac{\sqrt{A(\mu + \tau_1)B\eta\mu\beta_h\beta_v}}{A(\mu + \tau_1)^2(\kappa + \theta)}, \\ \frac{\partial \mathcal{R}_0}{\partial \beta_h} &= 1/2 \frac{B\eta\mu\beta_v}{\sqrt{A(\mu + \tau_1)B\eta\mu\beta_h\beta_v}(\kappa + \theta)}, \\ \frac{\partial \mathcal{R}_0}{\partial \eta} &= 1/2 \frac{B\mu\beta_h\beta_v}{\sqrt{A(\mu + \tau_1)B\eta\mu\beta_h\beta_v}(\kappa + \theta)}.\end{aligned}$$

These equations tell us that increasing θ and τ_1 will reduce \mathcal{R}_0 . For the implementation in the field, increasing τ_1 is related to increased quality of medical treatment, drugs, health services, and other forms of intervention in a purpose to accelerate the human recovery rate. Increasing θ is not only related to large-scale fumigation but should also consider the quality of the chemical composition of insecticides. The chosen insecticide should effectively kill the adult mosquito and must not be harmful to the ecosystem. Furthermore, the possibility of resistance to insecticide must be considered carefully, since many reports show the phenomenon of mosquito resistance. On the other hand, reducing infection rate β_h is related to intervention that is not only that intended to protect people from infection but also the genetic modifications of mosquitoes

related to their capability to inject *Plasmodium* should be contemplated. Many means of intervention have massively campaigned to reduce β_h such as the distribution of mosquito bed nets made from insecticide, the use of mosquito repellent, and using Wolbachia.

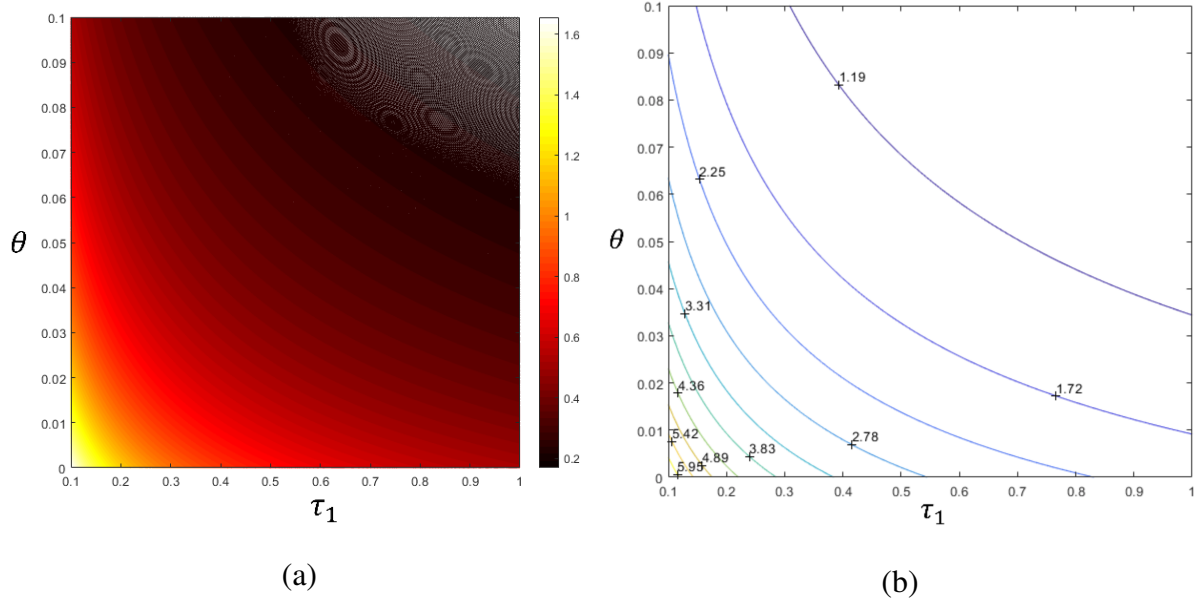


FIGURE 3. Sensitivity of \mathcal{R}_0 respect to τ_1 and θ : continuously (a) and discrete (b).

Fig. 3-4 present the numerical results of the sensitivity of \mathcal{R}_0 related to τ_1, θ and β_h . It can be seen that increasing τ_1 and θ will significantly reduce \mathcal{R}_0 . From our analytical result, to achieve a stable disease-free equilibrium, \mathcal{R}_0 should be as small as possible less than one. Therefore, implementation fumigation needs to be carried out partially with a good quality of medical treatment of malaria. Fig.3 (b) shows that carelessness in choosing a combination between fumigation and medical treatment cannot provide malaria eradication. To be specific, for a constant τ_1 , θ should be larger than its lower bound θ^* (where θ^* fulfill $\mathcal{R}_0(\theta_1^*) = 1$), which depend on τ_1 and is given by :

$$(7) \quad \theta > \theta^* = \frac{10^{-12} \left(2.3 \times 10^9 \sqrt{4.3 \times 10^9 + 1.1 \times 10^{14} \tau_1} - 4.76 \times 10^{16} \tau_1 - 1.85 \times 10^{12} \right)}{39 + 10^6 \tau_1}.$$

On the other hand, for a specific value of θ , τ_1 should be larger from its lower bound τ_1^* (where τ_1^* fulfill $\mathcal{R}_0(\tau_1^*) = 1$) which is given by :

$$(8) \quad \tau_1 > \tau_1^* = \frac{-243.75\theta^2 - 23.25\theta + 3885.56}{(119 + 2500\theta)^2}.$$

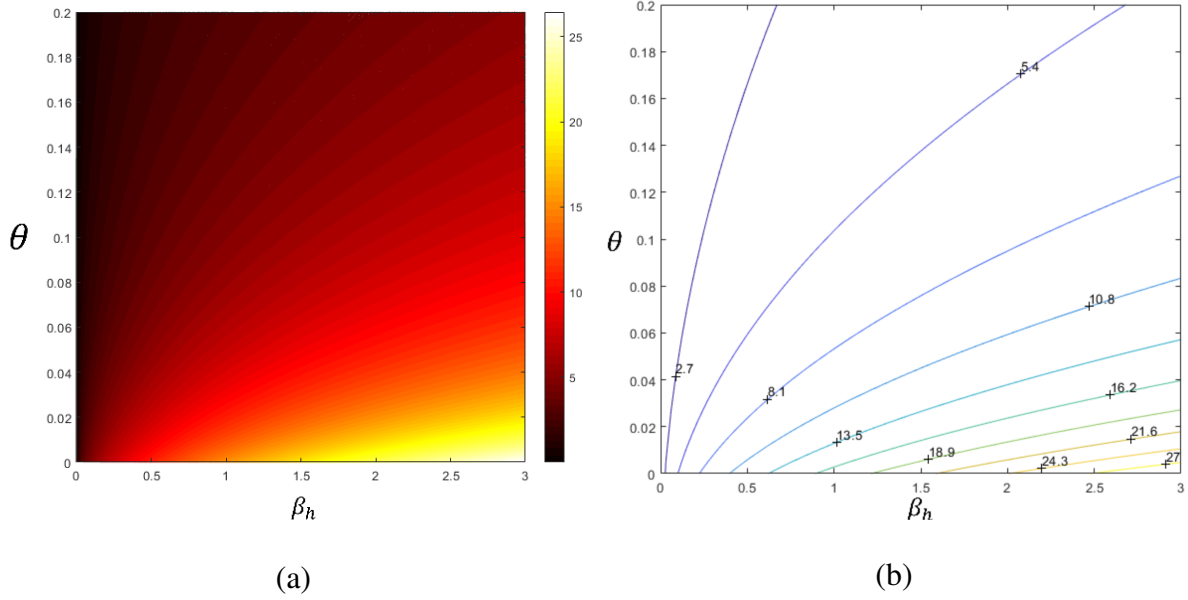


FIGURE 4. Sensitivity of \mathcal{R}_0 respect to β_h and η : continuously (a) and discrete (b).

Similar interpretations apply for Fig. 4 about how robust is \mathcal{R}_0 to the change of θ and β_h .

Next, we examine which model parameter has the most significant effect on the value of the basic reproduction number (\mathcal{R}_0). Following Chitnis et al. (2008) [26], we calculate the sensitivity index of the basic reproduction number (\mathcal{R}_0), to the parameters in the model. These indices indicate how sensitive \mathcal{R}_0 is to a change in each parameter; in other words, this tells us how crucial each parameter is to malaria transmission. Sensitivity indices allow us to measure the relative change in a state variable when a parameter changes. The normalized forward sensitivity index (NFSI) of the basic reproduction number (\mathcal{R}_0) to a parameter is the relative change in the variable \mathcal{R}_0 to the relative change in a given parameter.

Definition 1. Let $\mathcal{R}_0 : V \rightarrow W$ and $\mathcal{R}_0 \in C^1(V)$, where $V, W \subseteq R^+$. Then, for every parameter $p \in V$, the NFSI of \mathcal{R}_0 is defined as:

$$(9) \quad \gamma_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0}.$$

Using a Definition 1, the sensitivity index of \mathcal{R}_0 with respect to each of the parameters \mathcal{R}_0 is as follows:

$$\begin{aligned}\gamma_A^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial A} \times \frac{A}{\mathcal{R}_0} = -\frac{1}{2}, & \gamma_B^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial B} \times \frac{B}{\mathcal{R}_0} = \frac{1}{2}, & \gamma_{\tau_1}^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \tau_1} \times \frac{\tau_1}{\mathcal{R}_0} = -\frac{\tau_1}{2\mu+2\tau_1}, \\ \gamma_{\beta_h}^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \beta_h} \times \frac{\beta_h}{\mathcal{R}_0} = \frac{1}{2}, & \gamma_{\beta_v}^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \beta_v} \times \frac{\beta_v}{\mathcal{R}_0} = \frac{1}{2}, & \gamma_{\mu}^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \mu} \times \frac{\mu}{\mathcal{R}_0} = \frac{\tau_1}{2\mu+2\tau_1}, \\ \gamma_{\kappa}^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \kappa} \times \frac{\kappa}{\mathcal{R}_0} = -\frac{\kappa}{\kappa+\theta}, & \gamma_{\theta}^{\mathcal{R}_0} &= \frac{\partial \mathcal{R}_0}{\partial \theta} \times \frac{\theta}{\mathcal{R}_0} = -\frac{\theta}{\kappa+\theta}.\end{aligned}$$

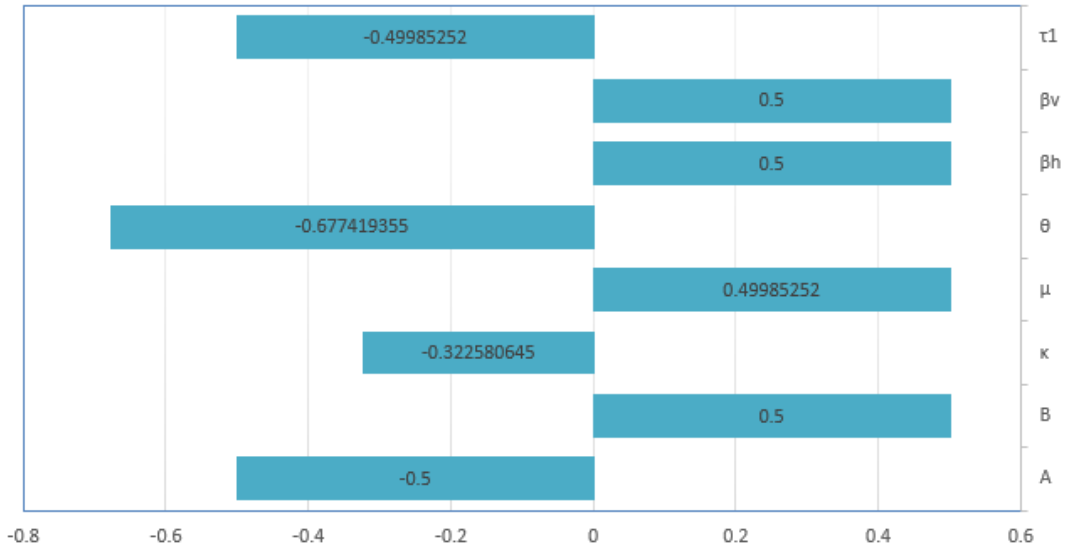


FIGURE 5. Diagram of sensitivity index of \mathcal{R}_0 .

Substitute all parameters in Table 1, we show the sensitivity diagram in Fig. 5. A positive index in Fig. 5 presents the proportional relation to the change of parameters with \mathcal{R}_0 . For example, increasing β_v, β_h, A and β will increase \mathcal{R}_0 . Furthermore, the value of sensitivity present how 1% change of the parameter will change \mathcal{R}_0 . For example, increasing τ_1 for 10% will reduce \mathcal{R}_0 for 4.99%. According to this result, we have the following remark.

Remark 2. *To control the spread of malaria transmission, the best and easiest strategy is to use fumigation in a purpose to control the vector population. However, The use of fumigation on a large scale should consider any other aspect, such as ecology and cost constrain for intervention.*

4.2. Autonomous simulation. Numerical simulations of model system (1) are carried out with a set of parameter values given in Table 1 with the following initial conditions:

$$S(0) = 6500, I_1(0) = 2000, R(0) = 1000, I_2(0) = 500, U(0) = 70.000, V(0) = 30.000.$$

4.2.1. Example 1 : Variations of β_h . In this section, the analysis of autonomous simulation is discussed. In this simulation, it is shown that the different transmission rate in humans can affect the long-term behavior of model (1). The simulation results are in Fig.6 with a table of equilibrium points in Table 4.

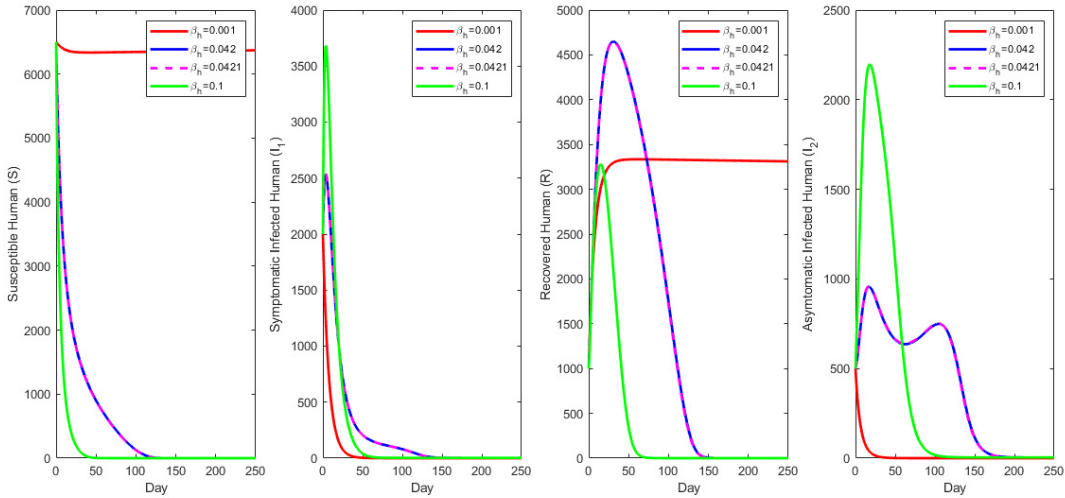


FIGURE 6. The dynamics of the human population with variations in β_h values.

TABLE 4. Autonomous simulation results with variations in the value of β_h in human population.

Case	\mathcal{R}_0	S	I_1	R	I_2
$\beta_h = 0.04$	0.1541	6,415	0	3,279	0
$\beta_h = 0.042$	0.99991	0	3	0	4
$\beta_h = 0.0421$	1.00038	0	3	0	4
$\beta_h = 0.07$	1.5417	0	3	0	4

From the above results, malaria does not cause an epidemic if the success rate for infection from mosquitoes to humans (β_h) is very small at 0.001, this can be seen in Fig.6 (Symptomatic Infected Human) and Table 4. Furthermore, the dynamics will continue to remain endemic when the value of $\beta_h = 0.042$, i.e. $I_1 = 3$. Using similar parameters and initial conditions, the dynamics of mosquitoes is shown in Fig.7 with a table of equilibrium given in Table 5.

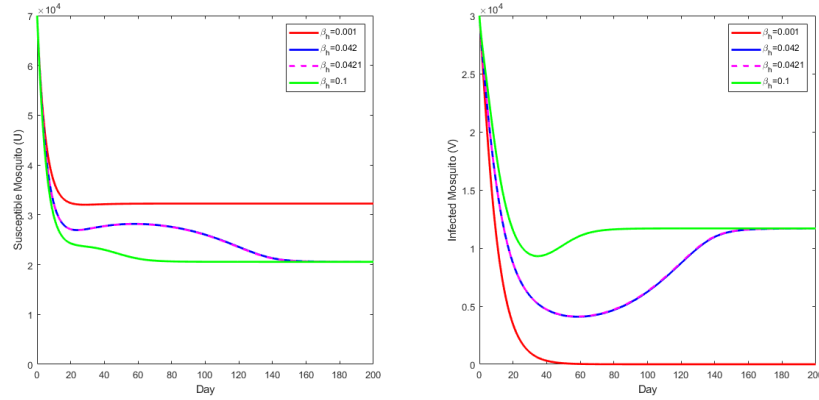


FIGURE 7. The dynamics of the mosquito population with variations in β_h values.

TABLE 5. *Autonomous* simulation results with variations in the value of β_h in mosquito population.

Case	\mathcal{R}_0	U	V
$\beta_h = 0.001$	0.1541	32.258	0
$\beta_h = 0.042$	0.9991	2057.7	1168.1
$\beta_h = 0.0421$	1.00038	2057.7	1168.1
$\beta_h = 0.1$	1.5417	2056.7	1169.2

TABLE 6. *Autonomous* simulation results with variations in the value of θ .

Case	\mathcal{R}_0	V	$I_1 + I_2$
$\theta = 0.9$	0.2148	395	7
$\theta = 0.2$	0.8221	4,860	7
$\theta = 0.08$	4.2749	63,815	7

Similar interpretation given for Fig. 7 that β_h must be reduced as much as possible to find a condition when all infected mosquitoes disappear. Please see Table 5 for the equilibrium point of mosquito with various values of β_h in Fig. 7.

4.2.2. Example 2 : Variation of θ . In this section, the analysis of the autonomous simulation by varying θ is discussed. In this simulation, it is shown that a proper value of the fumigation rate can eradicate the mosquito population from the population. We conduct the simulation using four values of θ , i.e. $\theta = 0.9$ (high intensity); $\theta = 0.2$ (medium intensity); $\theta = 0.08$ (low intensity) and with a value of $\beta_h = 0.08$. The simulation results result are given in Fig. 8 with a table of equilibrium is in Table 6.

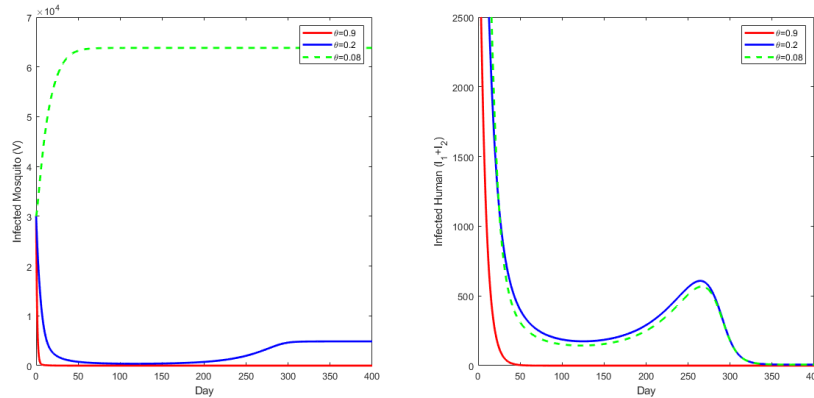


FIGURE 8. The dynamics of the infected mosquito and infected humans with variations in θ values.

Based on our simulation and analytical result in the previous section, there is a minimum rate of fumigation that can make our system tend to the small size of endemic equilibrium. To illustrate this, please see the green and blue curves in Fig. 8, which represents that the fumigation does not cross the minimum threshold of fumigation. The green curve show how a minimum effort of fumigation makes the infected mosquito tend to its endemic equilibrium

point. On the other hand, when the fumigation rate is given in a larger value (0.2), the number of infected mosquitoes decreased significantly even without reaching the disease-free equilibrium. Hence, since $\mathcal{R}_0(\theta = 0.2) = 0.8221 < 1$ still gives a stable endemic equilibrium, we conclude that our system exhibits a backward bifurcation in this scenario. Furthermore, with significant intervention of fumigation given in the field (please see the red curve), the number of infected humans and mosquitoes decreased significantly.

5. CONCLUSIONS

In this paper, the transmission model for malaria by considering secondary infection has been discussed analytically and numerically. The basic reproduction number is calculated using the next-generation matrix approach. The stability of equilibrium points has been shown to be related to the basic reproduction number. We found that malaria can be eradicated if the basic reproduction number is less than unity. However, it is observed that the model might still have a stable endemic equilibrium of malaria, even though the basic reproduction number is less than unity. Hence, the policymakers should not rely solely on the threshold of the basic reproduction number being equal to one. This is because secondary infections could be fatal, leading to backward bifurcation phenomena. Our local sensitivity analysis and numerical experiments indicate that increasing the death rate of mosquitoes is the most effective way to reduce the basic reproduction number.

However, the existence of the backward bifurcation and/or forward bifurcation with hysteresis in our model suggests that malaria may still exist even though the basic reproduction number is already less than one. Further analysis needs to investigate to understand how to avoid the existence of this type of bifurcation. As another possible improvement for the model in this article, application of optimal control could be used to find the optimal strategy of malaria eradication policy. The optimal control in many epidemiological models intended to minimize number of infected individuals with minimal cost for intervention. This task is usually read as minimizing the following cost function:

$$(10) \quad \mathcal{J}(\mathbf{x}, \mathbf{u}) = \int_0^T (\sum \mathbf{x} + \sum \omega \mathbf{u}) dt$$

where \mathbf{x} and \mathbf{u} are vector values for infected populations, respectively, ω as the weight parameter, and T is the final time simulation. Minimizing this cost function is subject to its respective disease transmission model $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$ with initial condition $\mathbf{x}(0) > 0$. Pontriagin's Maximum principle used to characterize the optimal control problem, and can be solved using the well known forward-backward sweep method [27]. Please see [28, 29, 30, 31] for examples of applications of optimal control problems in a ODE based disease transmission model, PDE in [32], time delay in [33], discrete model in [34], and many more.

6. ACKNOWLEDGMENTS

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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APPENDIX A. THE POLYNOMIAL FOR THE ENDEMIC EQUILIBRIUM

Following are the coefficients in the equation (6). The equation (6) can be written as $a_4 I_1^4 + a_3 I_1^3 + a_2 I_1^2 + a_1 I_1 + a_0 = 0$, with :

$$\begin{aligned}
a_4 &= ((\tau_1 - \tau_2)(\eta - 1)\mu - \delta\tau_1)((\eta - 1)\kappa + (\eta - 1)\theta + \beta_v)(\tau_1 - \tau_2)\mu - \delta\tau_1(\kappa + \theta)(\mu + \tau_1)^3(\kappa + \theta) \\
a_3 &= (2(A(\kappa + \theta)(\eta - 1)(\tau_1 - \tau_2)((\eta - 1)\kappa + (\eta - 1)\theta + \beta_v)\mu^3 + ((\kappa + \theta)((-\eta^2 + 3\eta - 2)\kappa + \\
&\quad (-\eta^2 + 3\eta - 2)\theta - (-3/2 + \eta)\beta_v)\tau_2^2 + (((\eta^2 - 3\eta + 2)\kappa + (\eta^2 - 3\eta + 2)\theta + (-3/2 + \eta)\beta_v)\tau_1 - \\
&\quad \delta(\eta - 1)((\eta - 1)\kappa + (\eta - 1)\theta + \beta_v))\tau_2 + ((\eta^2 - 3\eta + 2)\kappa + (\eta^2 - 3\eta + 2)\theta + (-3/2 + \eta)\beta_v)\tau_1\delta)A - \\
&\quad (1/2)\beta_h\beta_v B\tau_2(\tau_1 - \tau_2))\mu^2 - (1/2)\tau_1((\kappa + \theta)((-2\eta + 2)\kappa + (-2\eta + 2)\theta - \beta_v)\tau_2^2 + \\
&\quad (((2\eta - 2)\kappa + (2\eta - 2)\theta + \beta_v)\tau_1 + \delta((2\eta - 4)\kappa + (2\eta - 4)\theta + \beta_v))\tau_2 + \delta^2((2\eta - 2)\kappa + \\
&\quad (2\eta - 2)\theta + \beta_v))A + \beta_h\beta_v B\tau_2(\tau_1 - \tau_2))\mu + A\delta\tau_1^2\tau_2(\kappa + \theta)^2)(\mu + \tau_1)^2 \\
a_2 &= A(A(\kappa + \theta)(\eta - 1)((\eta - 1)\kappa + (\eta - 1)\theta + \beta_v)\mu^4 + ((2(\kappa + \theta))(\tau_1 + (\eta - 3)\tau_2 + \delta(\eta - 1))(\eta - 1)\kappa + \\
&\quad (\tau - 1 + (\eta - 3)\tau_2 + \delta(\eta - 1))(\eta - 1)\theta + ((1/2)\tau_1 + (\eta - 2)\tau_2 + \delta(\eta - 1))\beta_v)A + \beta_h\beta_v B(\tau_1 - 2\tau_2))\mu^3 + \\
&\quad ((\kappa + \theta)((2\eta - 2)\tau_1^2 + ((-2\eta + 2)\tau_2 + 2\delta(\eta - 2))\tau_1 + (\eta^2 - 6\eta + 6)\tau_2^2 + 2\delta(\eta - 1)(\eta - 3)\tau_2 + \\
&\quad \delta^2(\eta - 1)^2)\kappa + ((2\eta - 2)\tau_1^2 + ((-2\eta + 2)\tau_2 + 2\delta(\eta - 2))\tau_1 + (\eta^2 - 6\eta + 6)\tau_2^2 + 2\delta(\eta - 1)(\eta - 3)\tau_2 + \\
&\quad \delta^2(\eta - 1)^2)\theta + (\tau_1^2 + (\delta - \tau_2)\tau_1 + ((\eta - 3)\tau_2 + \delta(\eta - 1))(\delta + \tau_2))\beta_v A + \beta_h\beta_v B(\delta\tau_1 - \\
&\quad 2\delta\tau_2 + \tau_1\mu^2 - 3\tau_2^2))\mu^2 + \tau_1((\kappa + \theta)((2\eta - 2)\tau_2 + 2\delta(\eta - 2))\tau_1 + (-4\eta + 6)\tau_2^2 + \\
&\quad (-4\eta + 2)\delta\tau_2 - 2\delta^2)\kappa + (((2\eta - 2)\tau_2 + 2\delta(\eta - 2))\tau_1 + (-4\eta + 6)\tau_2^2 + (-4\eta + 2)\delta\tau_2 - 2\delta^2)\theta + \\
&\quad \beta_v(\tau_1 - 2\tau_2)(\delta + \tau_2)A + ((\delta + 2\tau_2)\tau_1 - 2\tau_2\delta - 3\tau_2^2)\beta_h B\beta_v)\mu - 2\tau_1^2 \\
&\quad (\delta^2 + \tau_2\delta - (1/2)\tau_2^2)A(\kappa + \theta)^2)(\mu + \tau_1) \\
a_1 &= (((\kappa + \theta)((2\eta - 2)\kappa + (2\eta - 2)\theta + \beta_v)A + \beta_h\beta_v B)\mu^2 + ((\kappa + \theta)((2\eta - 4)\tau_2 + 2\delta(\eta - 1))\kappa + \\
&\quad ((2\eta - 4)\tau_2 + 2\delta(\eta - 1))\theta + \beta_v(\delta + \tau_2))A + \beta_h\beta_v B(\delta - \tau_1 + 3\tau_2))\mu - 2A\tau_1\tau_2(\kappa + \theta)^2) \\
&\quad (\delta + \mu + \tau_2)A^2(\mu + \tau_1) \\
a_0 &= A^3(\delta + \mu + \tau_2)^2((\kappa + \theta)^2(\mu + \tau_1)A - B\mu\beta_h\beta_v).
\end{aligned}$$