An optimal control strategy to reduce the spread of malaria resistance

Fatmawati, Hengki Tasman

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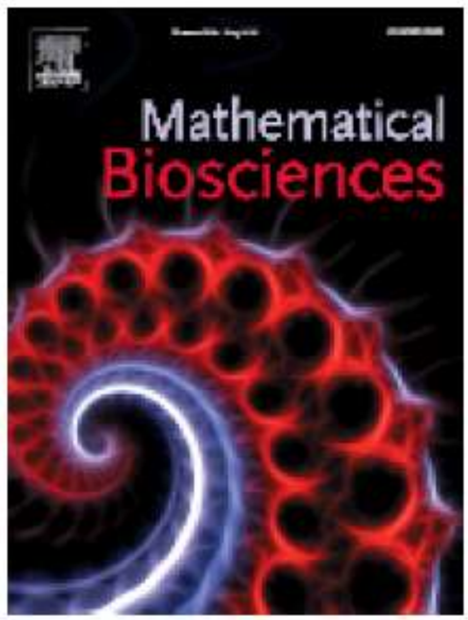

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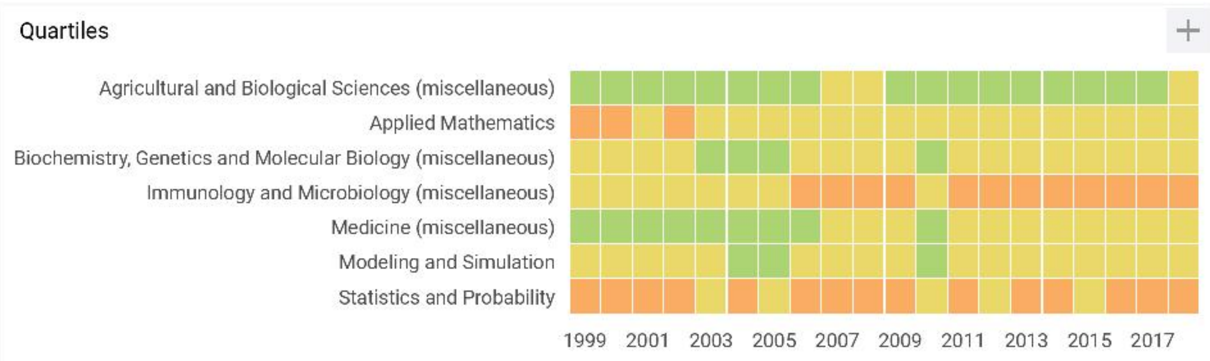

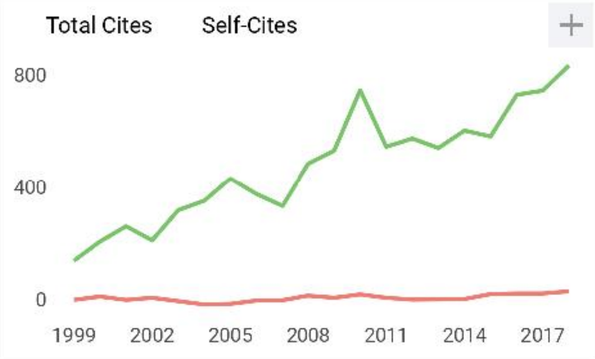

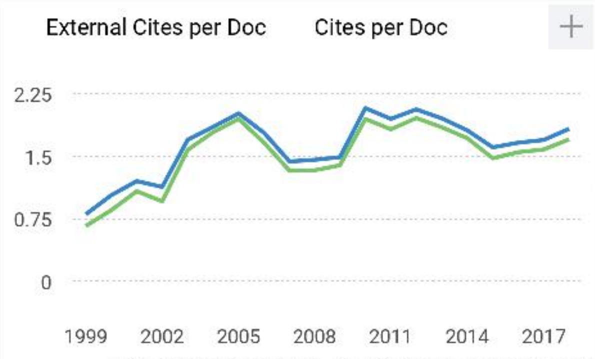

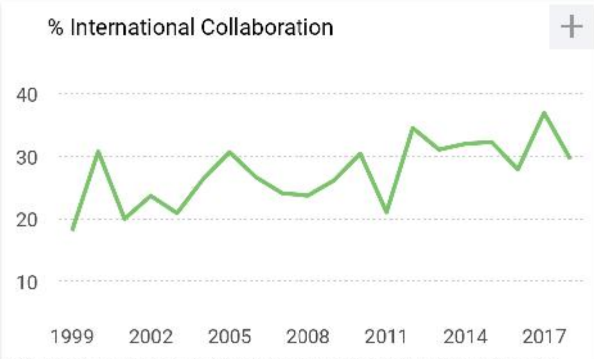

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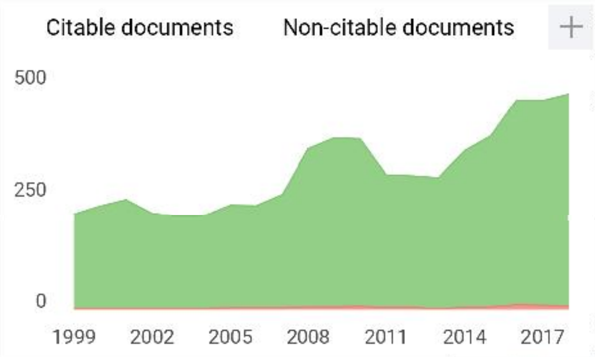

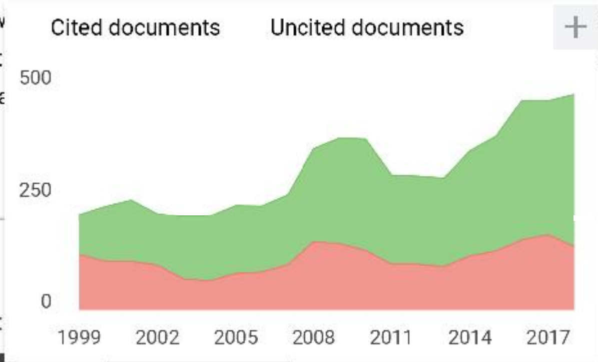

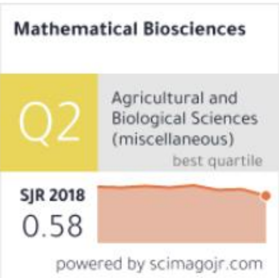

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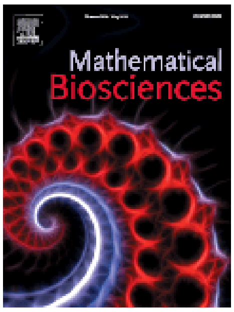

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An optimal control strategy to reduce the spread of malaria resistance

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ABSTRACT

This paper presents a mathematical model of malaria transmission considering the resistance of malaria parasites to the anti-malarial drugs. The model also incorporates mass treatment and insecticide as control strategies. We consider the sensitive and resistant strains of malaria parasites in human and mosquito populations. First, we investigated the existence and stability of equilibria of the model without control based on two basic reproduction ratios corresponding to the strains. Then, the Pontryagins Maximum Principle is applied to derive the necessary conditions for optimal control. Simulation results show the effectiveness of the optimal control to reduce the number of infected hosts and vectors.

1. Introduction

Malaria is still an endemic disease in many countries. This disease is caused by *Plasmodium* parasites and transmitted to humans by the female Anopheles mosquitoes. An estimated 3.4 billion people are at risk on malaria, of which 1.2 billion are at high risk. In the malaria high-risk areas, more than one malaria case occur per 1000 hosts. In 2012, it is estimated there were about 207 million cases of malaria, causing 627,000 deaths, mostly among African children [14]. In recent decades, resistance of *Plasmodium* parasites to the anti-malarial drugs have emerged in many areas. This resistance is generated by improper usage of anti-malarial drugs. A comprehensive analysis and planning is needed to control the spread of malaria resistance.

Mathematical models could be used to understand the dynamic of the spread of malaria resistance. In [1,7], the models was developed by assuming two types of malaria strains, the sensitive strain and the full resistant strain. In [13], the authors proposed a model with partial resistance of malaria parasites. Studies of mathematical models with optimal control considering malaria resistance also have been done. A simple model to control the spread of malaria resistance was proposed in [9]. The model focuses on the effect of treatment by assuming the full resistance of malaria parasites to anti-malarial drugs. In [5], the authors proposed a mathematical model of the spread of malaria considering mass treatment and insecticide as controls. In this paper, the model in [5] is developed by adding the factor of malaria resistance.

The organization of this paper is as follows. In Section 2, we propose a model of malaria transmission with controls on treatment and insecticide. The model is analyzed in Section 3. In Section 4, we give some numerical simulations. The conclusion of this paper could be seen in Section 5.

2. Model formulation

We assume the host population is constant and we consider two types of malaria parasite, these are, the sensitive parasite and the full resistant parasite. The host population is classified into the susceptible class (S_H), the host infected by sensitive parasite class (I_{Hs}), the host infected by resistant parasite class (I_{Hr}) and the recovered host with temporary immunity class (R_H).

The mosquito population is also classified into the larvae or pupa class (L_V), the susceptible class (S_V), the vector infected by sensitive parasite class (I_{Vs}), and the vector infected by resistant parasite class (I_{Vr}). For controlling mosquito population, we incorporate larvacide and insecticide terms in the model.

The control functions u_1 and u_2 represent time dependent efforts of mass treatment and insecticide intervention respectively. The control functions u_1 and u_2 are defined on interval $[0, t_f]$, where $0 \le u_i(t) \le 1$, $t \in [0, t_f]$, $i = 1, 2$ and t_f denotes the end time of the controls.

We use the transmission diagram as in Fig. 1 for deriving our model, where $N_H = S_H + I_{Hs} + I_{Hr} + R_H$ denotes the total population size of host. The model is as follows.

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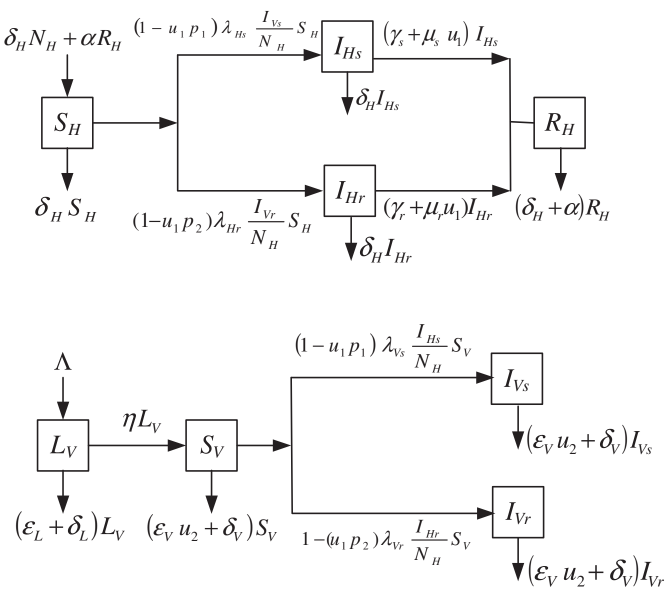

Fig. 1. Malaria transmission diagram.

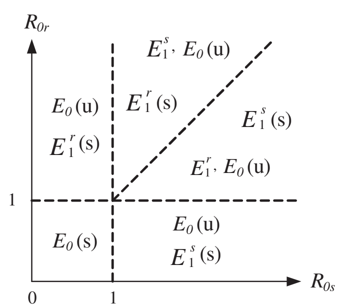

Fig. 2. Bifurcation diagram of model (1). The alphabets *s* and *u* in the parentheses stand for locally asymptotically stable and unstable respectively.

$$
\begin{aligned}
\frac{dS_H}{dt} &= \delta_H N_H - (1-u_1 p_1)\lambda_{Hs}\frac{I_{Vs}}{N_H}S_H \\
&\quad -(1-u_1 p_2)\lambda_{Hr}\frac{I_{Vr}}{N_H}S_H - \delta_H S_H + \alpha R_H, \\
\frac{dI_{Hs}}{dt} &= (1-u_1 p_1)\lambda_{Hs}\frac{I_{Vs}}{N_H}S_H - (\delta_H + \gamma_s + \mu_s u_1)I_{Hs}, \\
\frac{dI_{Hr}}{dt} &= (1-u_1 p_2)\lambda_{Hr}\frac{I_{Vr}}{N_H}S_H - (\delta_H + \gamma_r + \mu_r u_1)I_{Hr}, \\
\frac{dR_H}{dt} &= (\gamma_s + \mu_s u_1)I_{Hs} + (\gamma_r + \mu_r u_1)I_{Hr} - (\delta_H + \alpha)R_H, \\
\frac{dL_V}{dt} &= \Lambda - (\eta + \varepsilon_L + \delta_L)L_V, \\
\frac{dS_V}{dt} &= \eta L_V - (1-u_1 p_1)\lambda_{Vs}\frac{I_{Hs}}{N_H}S_V \\
&\quad -(1-u_1 p_2)\lambda_{Vr}\frac{I_{Hr}}{N_H}S_V - (\varepsilon_V u_2 + \delta_V)S_V, \\
\frac{dI_{Vs}}{dt} &= (1-u_1 p_1)\lambda_{Vs}\frac{I_{Hs}}{N_H}S_V - (\varepsilon_V u_2 + \delta_V)I_{Vs}, \\
\frac{dI_{Vr}}{dt} &= (1-u_1 p_2)\lambda_{Vr}\frac{I_{Hr}}{N_H}S_V - (\varepsilon_V u_2 + \delta_V)I_{Vr},
\end{aligned}
\tag{1}
$$

where $0 \le p_1 + p_2 \le 1$. Parameters used in model (1) could be seen in Table 1.

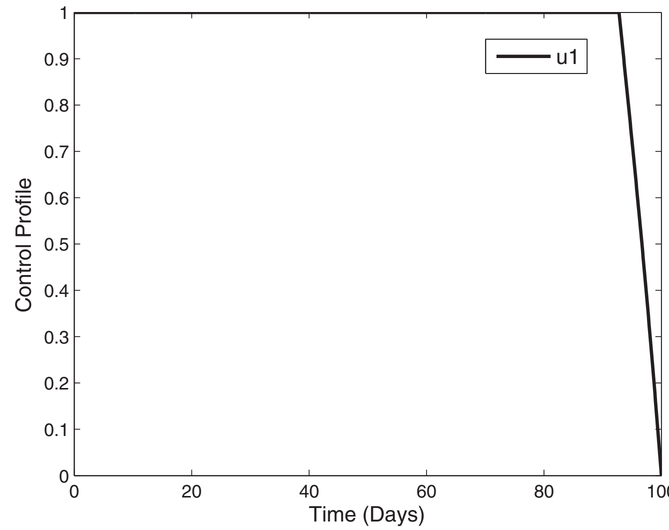

Fig. 3. The profile of the optimal treatment control u_1^*.

Table 1
Parameters of model (1).

Description	Parameter	
Life span of host	$1/\delta_H$	
Immunity lose rate	α	
Oviposition rate	Λ	
Natural death rate of larvae	δ_L	
Larvae death rate from larvacide	ε_L	
Maturation rate of larvae	η	
Vector death rate from insecticide	ε_V	
Natural death rate of vector	δ_V	
	Sensitive Infection	Resistant Infection
Recovery rate from treatment	μ_s	μ_r
Infection rate for vector	λ_{Vs}	λ_{Vr}
Infection rate for host	λ_{Hs}	λ_{Hr}
Natural recovery period of host	$1/\gamma_s$	$1/\gamma_r$
Proportion of success treatment	p_1	p_2

Table 2
Parameter values for simulations.

Parameter	Value	Ref.	Parameter	Value	Ref.
δ_H	0.00003914/day	[13]	δ_V	0.07142/day	[16]
α	0.00274/day	[15]	ε_V	0.1/day	[16]
μ_s	0.25/day	[13]	λ_{Vs}	0.27/day	[2]
μ_r	0.048/day	[13]	λ_{Vr}	0.27/day	[2]
Λ	1000	–	λ_{Hs}	0.3/day	[2]
δ_L	0.4/day	[16]	λ_{Hr}	0.3/day	[2]
ε_L	0.4/day	[16]	γ_s	0.01/day	[2]
η	0.07142/day	[16]	γ_r	0.01/day	[2]

The region of biological interest of model (1) is

$$\Omega = \{(S_H, I_{Hs}, I_{Hr}, R_H, L_V, S_V, I_{Vs}, I_{Vr}) \in \mathbb{R}^8_+ : S_H + I_{Hs} + I_{Hr} + R_H = N_H\},$$

where N_H is constant.

Model (1) is well-posed in the non-negative region $\mathbb{R}^8_+$ because the vector field on the boundary does not point to the exterior. So, if it is given an initial condition in the region, then the solution is defined for all time $t \ge 0$ and remains in the region.

We seek to minimize the number of malaria infected host and the cost of applying mass treatment and insecticide controls. We consider an optimal control problem with the objective function given by

$$J(u_1, u_2) = \int_0^{t_f} \left(I_{Hs} + I_{Hr} + I_{Vs} + I_{Vr} + \frac{c_1}{2}u_1^2 + \frac{c_2}{2}u_2^2 \right) dt, \tag{2}$$

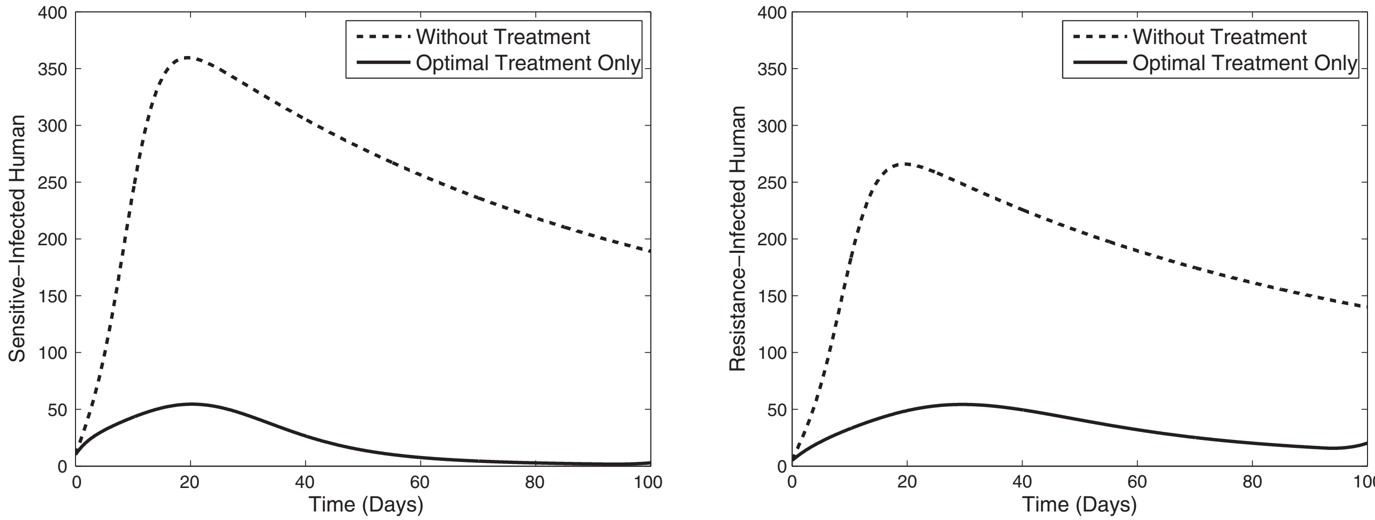

Fig. 4. The dynamics of I_{Hs} and I_{Hr} using control u_1^*.

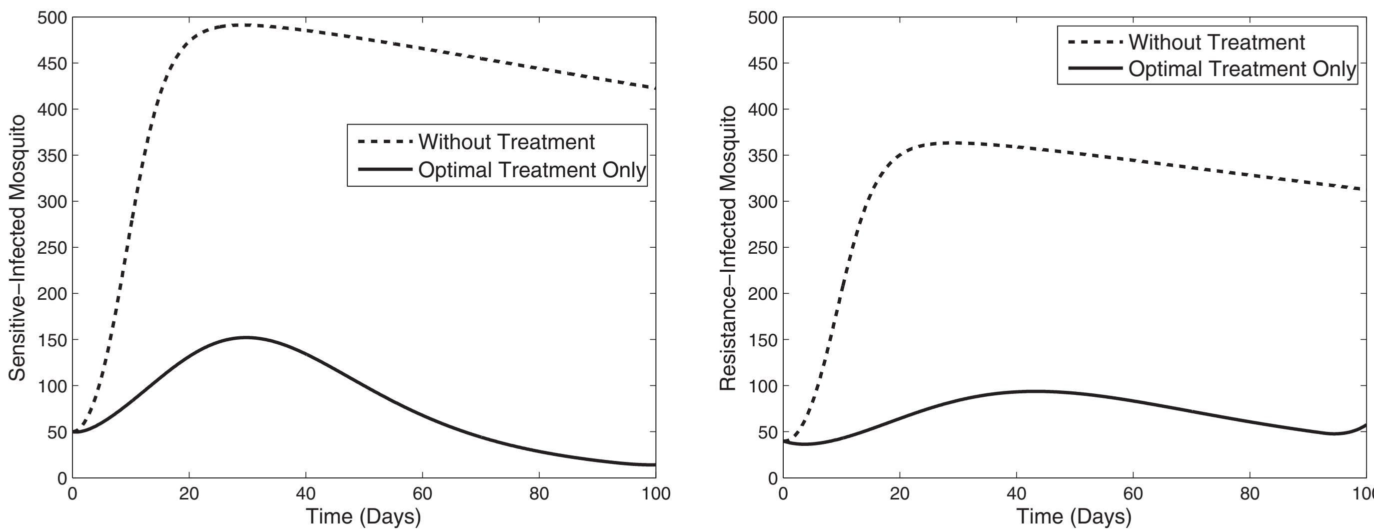

Fig. 5. The dynamics of I_{Vs} and I_{Vr} using control u_1^*.

where c_1 and c_2 are the weighting constants for mass treatment and insecticide respectively. We choose a quadratic function for measuring the control cost [2,6,10]. The term $c_1 u_1^2$ and $c_2 u_2^2$ describe the cost associated with the mass treatment and insecticide controls respectively. Larger values of c_1 and c_2 will imply more expensive implementation cost for mass treatment and insecticide.

We seek an optimal control u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = \min_{\Gamma} J(u_1, u_2), \tag{3}$$

where $\Gamma = \{(u_1, u_2) \,|\, 0 \le u_i \le 1, i = 1, 2\}$.

3. Model analysis

Consider model (1) without the control functions u_1 and u_2. Let

$$T_s = \frac{\eta\, \Lambda\, \lambda_{Hs}\, \lambda_{Vs}}{N_H\, \delta_V^2\, (\gamma_s + \delta_H)(\delta_L + \varepsilon_L + \eta)} \text{ and}$$

$$T_r = \frac{\eta\, \Lambda\, \lambda_{Hr}\, \lambda_{Vr}}{N_H\, \delta_V^2\, (\gamma_r + \delta_H)(\delta_L + \varepsilon_L + \eta)}.$$

Parameters $R_{0s} = \sqrt{T_s}$ and $R_{0r} = \sqrt{T_r}$ are the basic reproduction ratios for the sensitive infection and the resistant infection respectively. These ratios describe the number of secondary cases of primary case during the infectious period due to the type of parasite [3,4].

With respect to the coordinate $(S_H, I_{Hs}, I_{Hr}, R_H, L_V, S_V, I_{Vs}, I_{Vr})$ and $u_1 = u_2 = 0$, model (1) has the disease-free equilibrium

$$E_0 = \left(N_H, 0, 0, 0, \frac{\Lambda}{\delta_L + \varepsilon_L + \eta}, \frac{\eta\, \Lambda}{\delta_V\, (\delta_L + \varepsilon_L + \eta)}, 0, 0 \right).$$

It also has the sensitive infection endemic equilibrium $E_1^s = (S_H^s, I_{Hs}^s, 0, R_H^s, L_V^*, S_V^s, I_{Vs}^s, 0)$ and the resistant infection endemic equilibrium $E_1^r = (S_H^r, 0, I_{Hr}^r, R_H^r, L_V^*, S_V^r, 0, I_{Vr}^r)$, where

$$S_H^j = \frac{N_H\, \delta_V(\alpha + \gamma_j + \delta_H) + N_H\, \lambda_{Vj}(\alpha + \delta_H)}{T_j\, \delta_V(\alpha + \gamma_j + \delta_H) + \lambda_{Vj}(\alpha + \delta_H)},$$

$$I_H^j = \frac{N_H\, \delta_V(T_j - 1)(\alpha + \delta_H)}{T_j\, \delta_V(\alpha + \gamma_j + \delta_H) + \lambda_{Vj}(\alpha + \delta_H)},$$

$$R_H^j = \frac{N_H\, \gamma_j\, \delta_V(T_j - 1)}{T_j\, \delta_V(\alpha + \gamma_j + \delta_H) + \lambda_{Vj}(\alpha + \delta_H)},$$

$$L_V^* = \frac{\Lambda}{\delta_L + \varepsilon_L + \eta},$$

$$S_V^j = \frac{\eta\, \Lambda[T_j \delta_V(\alpha + \gamma_j + \delta_H) + \lambda_{Vj}(\alpha + \delta_H)]}{T_j\, \delta_V(\delta_L + \varepsilon_L + \eta)[(\alpha + \gamma_j + \delta_H)\, \delta_V + \lambda_{Vj}\, (\alpha + \delta_H)]},$$

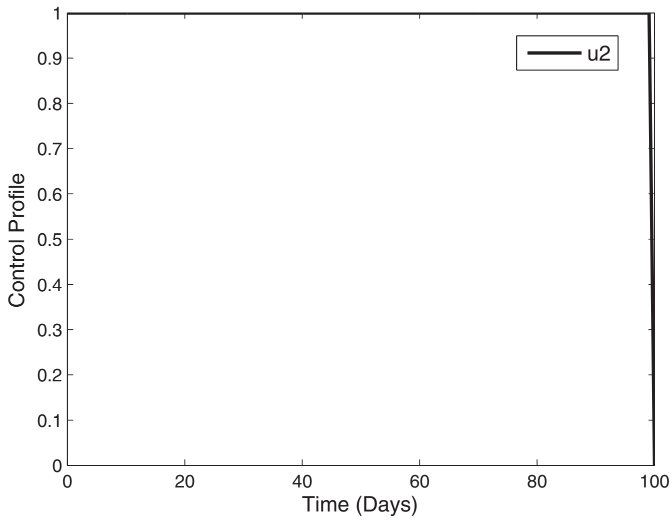

Fig. 6. The profile of the optimal insecticide control u_2^*.

$$I_V^j = \frac{(T_j - 1)(\alpha + \delta_H)\,\eta\,\Lambda\,\lambda_{Vj}}{T_j\,\delta_V(\delta_L + \varepsilon_L + \eta)[(\alpha + \gamma_j + \delta_H)\,\delta_V + \lambda_{Vj}\,(\alpha + \delta_H)]},$$
$$j \in \{s, r\}.$$

The equilibrium E_0 always exists. Moreover, the equilibria E_1^s and E_1^r exist if $R_{0s} > 1$ and $R_{0r} > 1$ respectively.

Theorem 1. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_{0s}, R_{0r} < 1$ and unstable if $R_{0s}, R_{0r} > 1$.*

Proof. Linearizing model (1) near the equilibrium E_0 gives eigen values $-\delta_H$, $-\delta_V$, $-(\alpha + \delta_H)$, $-(\delta_L + \eta + \varepsilon_L)$ and the roots of quadratic equations $x^2 + (\delta_H + \delta_V + \gamma_j)x + \delta_V(\delta_H + \gamma_j)(1 - T_j) = 0$, $j \in \{s, r\}$. Both quadratic equations have negative roots if $T_j < 1$ or equivalently $R_{0j} < 1$. □

Linearizing model (1) near the equilibrium E_1^r gives eigen values $-\delta_V$, $-(\eta + \varepsilon_L + \delta_L)$, the roots of quadratic equation

$$N_H^2\,x^2 + N_H^2\,(\delta_H + \gamma_s + \delta_V)\,x + N_H^2\,\delta_V\,(\delta_H + \gamma_s) - S_H^r\,S_V^r\,\lambda_{Hs}\,\lambda_{Vs} = 0 \quad (4)$$

and the roots of quartic equation $x^4 + a_1\,x^3 + a_2\,x^2 + a_3\,x + a_4 = 0$, where

$$\begin{aligned}
a_1 &= \alpha + 3\delta_H + \delta_V + \gamma_r + \frac{\delta_V\,\lambda_{Vr}\,(\alpha + \delta_H)(T_r - 1)}{\delta_V\,(\alpha + \gamma_r + \delta_H)\,T_r + \lambda_{Vr}\,(\alpha + \delta_H)} \\
&\quad + \frac{\eta\,\Lambda\,\lambda_{Hr}\,\lambda_{Vr}\,(\alpha + \delta_H)(T_r - 1)}{\delta_V\,T_r\,N_H\,(\delta_L + \varepsilon_L + \eta)[\delta_V\,(\alpha + \gamma_r + \delta_H) + \lambda_{Vr}\,(\alpha + \delta_H)]}, \\
a_2 &= 3\,\delta_H(\delta_H + \delta_V) + \gamma_r\,(2\,\delta_H + \delta_V) + \alpha\,(\gamma_r + 2\,\delta_H + \delta_V) - \frac{\eta\,\Lambda\,\lambda_{Hr}\,\lambda_{Vr}}{N_H\,T_r\,\delta_V\,(\delta_L + \varepsilon_L + \eta)} \\
&\quad + \frac{(T_r - 1)\,(\alpha + \delta_H)(\alpha + \gamma_r + 3\delta_H)\,\delta_V\,\lambda_{Vr}}{T_r\,(\alpha + \gamma_r + \delta_H)\,\delta_V + (\alpha + \delta_H)\,\lambda_{Vr}} \\
&\quad + \frac{(T_r - 1)(\alpha + \delta_H)(\alpha + \gamma_r + 2\delta_H + \delta_V)\,\eta\,\Lambda\,\lambda_{Hr}\,\lambda_{Vr}}{N_H\,T_r\,\delta_V\,(\delta_L + \varepsilon_L + \eta)[\gamma_r\,\delta_V + \alpha\,(\delta_V + \lambda_{Vr}) + \delta_H\,(\delta_V + \lambda_{Vr})]} \\
&\quad + \frac{(T_r - 1)^2\,(\alpha + \delta_H)^2\,\eta\,\Lambda\,\lambda_{Hr}\,\lambda_{Vr}^2}{N_H\,T_r\,(\delta_L + \varepsilon_L + \eta)[(\alpha + \gamma_r + \delta_H)\delta_V + (\alpha + \delta_H)\lambda_{Vr}][T_r(\alpha + \gamma_r + \delta_H)\delta_V + (\alpha + \delta_H)\lambda_{Vr}]}, \\
a_3 &= \delta_H\,(\alpha + \delta_H)(\gamma_r + \delta_H) + [\alpha\,\gamma_r + 2(\alpha + \gamma_r)\delta_H + 3\delta_H^2]\,\delta_V - \frac{(\alpha + 2\delta_H)\,\eta\,\Lambda\,\lambda_{Hr}\,\lambda_{Vr}}{T_r\,N_H\,\delta_V\,(\delta_L + \varepsilon_L + \eta)} \\
&\quad + \frac{(T_r - 1)\,(\alpha + \delta_H)\,[\alpha\gamma_r + 2(\alpha + \gamma_r)\delta_H + 3\delta_H^2]\delta_V\,\lambda_{Vr}}{T_r\,\delta_V(\alpha + \gamma_r + \delta_H) + (\alpha + \delta_H)\lambda_{Vr}} \\
&\quad + \frac{(T_r - 1)\,(\alpha + \delta_H)\,[\delta_H\,(\alpha + \gamma_r + \delta_H) + (\alpha + \gamma_r + 2\delta_H)\,\delta_V]\,\eta\,\Lambda\,\lambda_{Hr}\,\lambda_{Vr}}{T_r\,N_H\,\delta_V\,(\delta_L + \varepsilon_L + \eta)[(\alpha + \gamma_r + \delta_H)\,\delta_V + (\alpha + \delta_H)\,\lambda_{Vr}]} \\
&\quad + \frac{(T_r - 1)^2(\alpha + \delta_H)^2(\alpha + \gamma_r + 2\delta_H)\eta\Lambda\lambda Hr\lambda_{Vr}^2)}{T_r\,N_H(\delta_L + \varepsilon_L + \eta)[(\alpha + \gamma_r + \delta_H)\delta_V + (\alpha + \delta_H)\lambda_{Vr}][T_r(\alpha + \gamma_r + \delta_H)\delta_V + (\alpha + \delta_H)\lambda_{Vr}]}, \\
a_4 &= \delta_H\,\delta_V\,(\delta_H + \gamma_r)(\delta_H + \alpha)(T_r - 1).
\end{aligned}$$

The product of the roots of equation (4) is given by

$$\frac{\eta\,\Lambda\,\lambda_{Hs}\,\lambda_{Vs}\,(T_r - T_s)}{N_H\,\delta_V\,(\eta + \varepsilon_L + \delta_L)T_r\,T_s},$$

and the sum of the roots is $-(\delta_H + \gamma_s + \delta_V)$. Hence, both of the roots of equation (4) are negative if $T_r > T_s$ or equivalently $R_{0r} > R_{0s}$.

It is clear that $a_1, a_4 > 0$ if $T_r > 1$ or equivalently $R_{0r} > 1$. Using *Mathematica*, we obtain that if $T_r > 1$, then $a_1\,a_2 > a_3$ and $a_3(a_1\,a_2 - a_3) > a_1^3\,a_4$. Hence, we get following theorem.

Theorem 2. *The endemic equilibrium E_1^r is locally asymptotically stable if $1 < R_{0s} < R_{0r}$. The endemic equilibrium E_1^s is locally asymptotically stable if $1 < R_{0r} < R_{0s}$. .*

The existence and stability of equilibria of model (1) could be summarized in a bifurcation diagram in Fig. 2.

Next, we analyze model (1) with its control functions u_1 and u_2. Consider the objective function (2) for model (1). The sufficient conditions to determine the optimal controls u_1^* and u_2^* such that condition (3) with constraint model (1) could be obtained using the Pontryagin Maximum Principle [12]. The principle transforms Equations (1)–(3) into minimizing Hamiltonian function H problem with respect

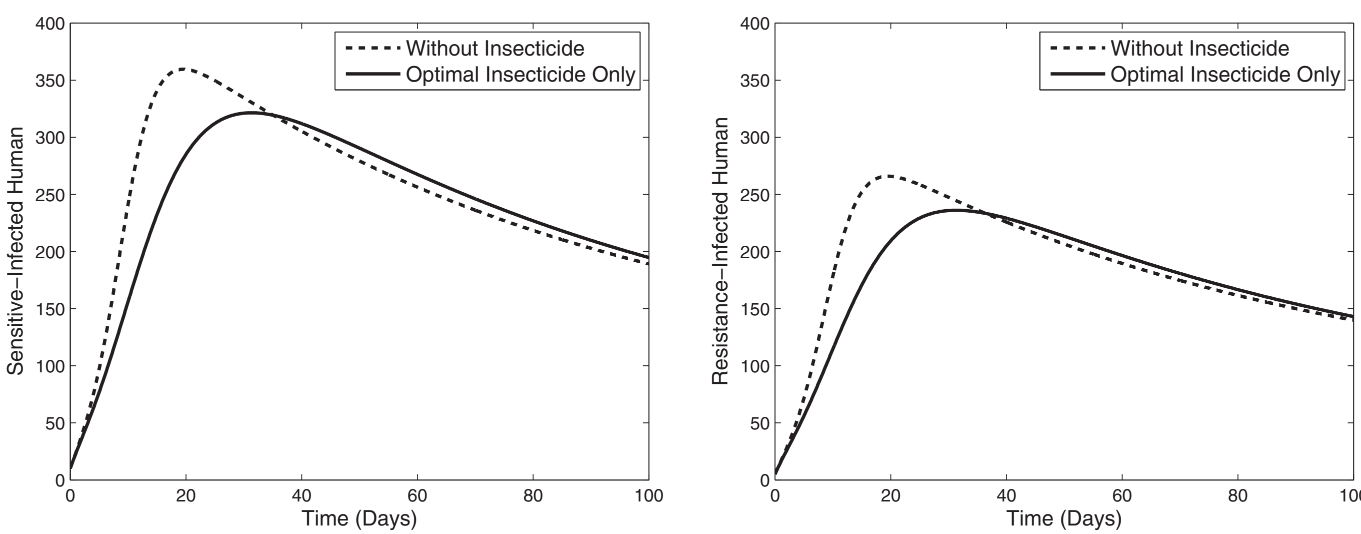

Fig. 7. The dynamics of I_{Hs} and I_{Hr} using control u_2^*.

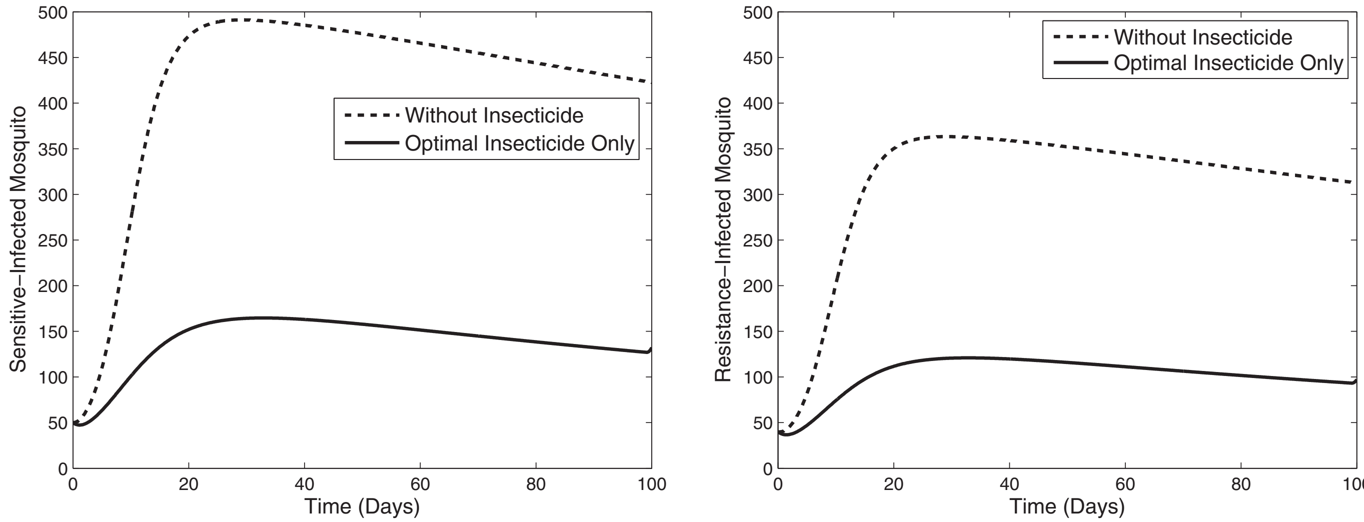

Fig. 8. The dynamics of I_{Vs} and I_{Vr} using control u_2^*.

(u_1, u_2), that is

$$H(S_H, I_{Hs}, I_{Hr}, R_H, L_V, S_V, I_{Vs}, I_{Vr}, u_1, u_2, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8)$$
$$= I_{Hs} + I_{Hr} + I_{Vs} + I_{Vr} + \frac{c_1}{2}u_1^2 + \frac{c_2}{2}u_2^2 + \sum_{i=1}^{8}\lambda_i g_i,$$

where g_i denotes the right hand side of model (1) which is the i-th state variable equation. The variables $\lambda_i, i = 1, 2, \dots, 8$, are called adjoint variables satisfying the following co-state equations

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= (1 - u_1p_1)\lambda_{Hs}\frac{I_{Vs}}{N_H}(\lambda_1 - \lambda_2) + \delta_H\lambda_1 \\
&\quad + (1 - u_1p_2)\lambda_{Hr}\frac{I_{Vr}}{N_H}(\lambda_1 - \lambda_3), \\
\frac{d\lambda_2}{dt} &= -1 + \delta_H\lambda_2 + (\gamma_s + \mu_s u_1)(\lambda_2 - \lambda_4) \\
&\quad + (1 - u_1p_1)\lambda_{Vs}\frac{S_V}{N_H}(\lambda_6 - \lambda_7), \\
\frac{d\lambda_3}{dt} &= -1 + \delta_H\lambda_3 + (\gamma_r + \mu_r u_1)(\lambda_3 - \lambda_4) \\
&\quad + (1 - u_1p_2)\lambda_{Vr}\frac{S_V}{N_H}(\lambda_6 - \lambda_8), \\
\frac{d\lambda_4}{dt} &= -\alpha\lambda_1 + (\delta_H + \alpha)\lambda_4, \\
\frac{d\lambda_5}{dt} &= (\eta + \varepsilon_L + \delta_L)\lambda_5 - \eta\lambda_6, \\
\frac{d\lambda_6}{dt} &= (\varepsilon_V u_2 + \delta_V)\lambda_6 + (1 - u_1p_1)\lambda_{Vs}\frac{I_{Hs}}{N_H}(\lambda_6 - \lambda_7) \\
&\quad + (1 - u_1p_2)\lambda_{Vr}\frac{I_{Hr}}{N_H}(\lambda_6 - \lambda_8), \\
\frac{d\lambda_7}{dt} &= -1 + (\varepsilon_V u_2 + \delta_V)\lambda_7 + (1 - u_1p_1)\lambda_{Hs}\frac{S_H}{N_H}(\lambda_1 - \lambda_2), \\
\frac{d\lambda_8}{dt} &= -1 + (\varepsilon_V u_2 + \delta_V)\lambda_8 + (1 - u_1p_2)\lambda_{Hr}\frac{S_H}{N_H}(\lambda_1 - \lambda_3),
\end{aligned} \tag{5}$$

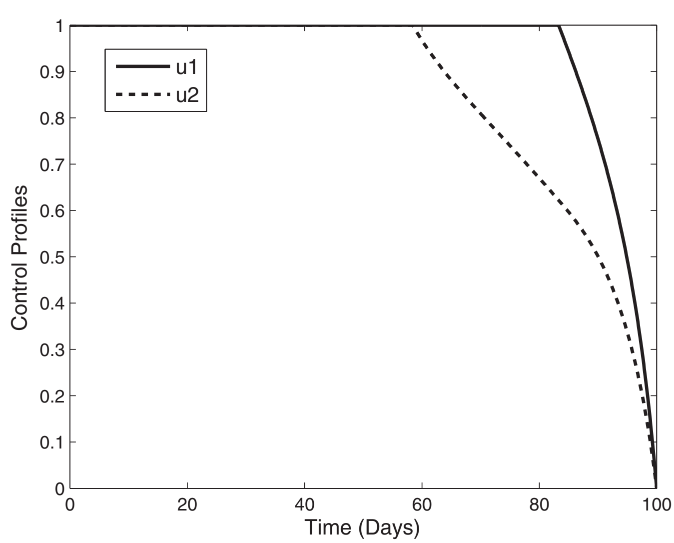

Fig. 9. The profile of the optimal controls u_1^* and u_2^*.

where the terminal conditions $\lambda_i(t_f) = 0, i = 1, \dots, 8$.

Steps to obtain the optimal controls $u = (u_1^*, u_2^*)$ are as following [8,11].

1. Minimize the Hamilton function H with respect to u, that is $\frac{\partial H}{\partial u} = 0$ which is the stationary condition. We obtain

$$u_1^* = \begin{cases} 0 & \text{for} \quad u_1 \le 0 \\ \dfrac{\triangle_1 + \triangle_2 + \triangle_3}{c_1 N_H} & \text{for} \quad 0 < u_1 < 1, \\ 1 & \text{for} \quad u_1 \ge 1 \end{cases}$$

$$u_2^* = \begin{cases} 0 & \text{for} \quad u_2 \le 0 \\ \dfrac{\varepsilon_V(\lambda_6 S_V + \lambda_7 I_{Vs} + \lambda_8 I_{Vr})}{c_2} & \text{for} \quad 0 < u_2 < 1, \\ 1 & \text{for} \quad u_2 \ge 1 \end{cases}$$

where

$$\triangle_1 = N_H\,\mu_s\,I_{Hs}(\lambda_2 - 1) + N_H\,\mu_r\,I_{Hr}(\lambda_3 - 1),$$
$$\triangle_2 = p_1\,\lambda_{Hs}\,I_{Vs}\,S_H(\lambda_2 - \lambda_1) + p_1\,\lambda_{Vs}\,I_{Hs}\,S_V(\lambda_7 - \lambda_6) \text{ and}$$
$$\triangle_3 = p_2\,\lambda_{Hr}\,I_{Vr}\,S_H(\lambda_3 - \lambda_1) + p_2\,\lambda_{Vr}\,I_{Hr}\,S_V(\lambda_8 - \lambda_6).$$

2. Solving the state system $\dot{x}(t) = \frac{\partial H}{\partial \lambda}$ which is the model (1), where $x = (S_H, I_{Hs}, I_{Hr}, R_H, L_V, S_V, I_{Vs}, I_{Vr})$, $\lambda = (\lambda_1, \lambda_2, ..., \lambda_8)$ and the initial condition $x(0)$.
3. Solving the co-state system $\dot{\lambda}(t) = -\frac{\partial H}{\partial x}$ which is the system (5) with the end condition $\lambda_i(t_f) = 0, i = 1, \dots, 8$.

Hence, we obtain the following theorem.

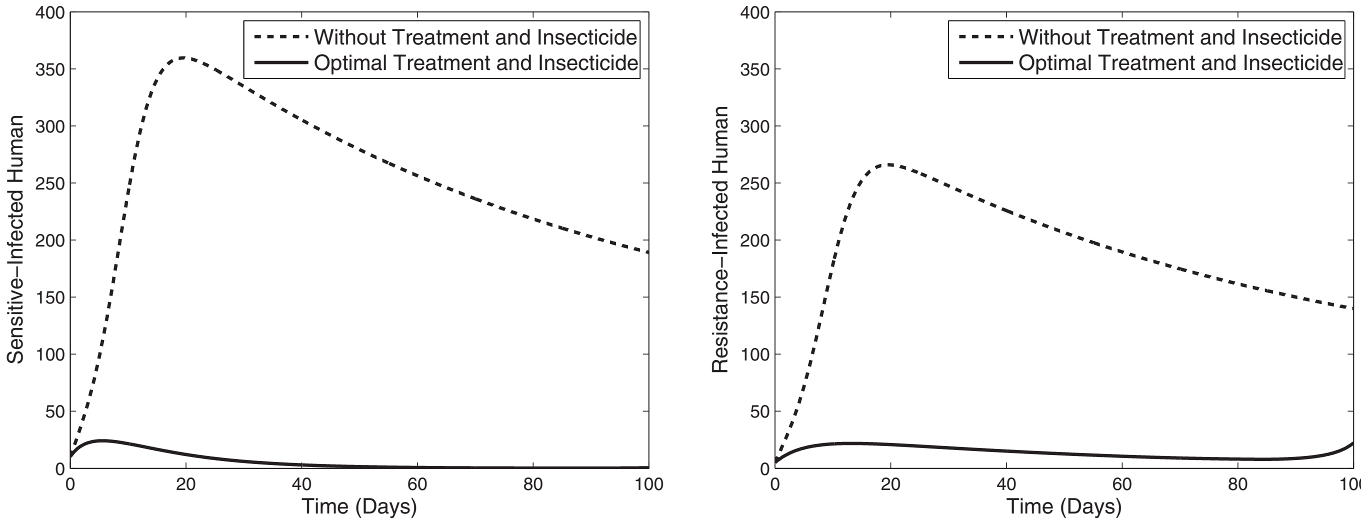

Fig. 10. The dynamics of I_{Hs} and I_{Hr} using controls u_1^* and u_2^*.

Theorem 3. *The optimal controls* (u_1^*, u_2^*) *minimizing the objective function* $J(u_1, u_2)$ *on* Γ *are*

$$u_1^* = \max\left\{0, \min\left(1, \frac{\triangle_1 + \triangle_2 + \triangle_3}{c_1 N_H}\right)\right\},$$

$$u_2^* = \max\left\{0, \min\left(1, \frac{\varepsilon_V(\lambda_6 S_V + \lambda_7 I_{Vs} + \lambda_8 I_{Vr})}{c_2}\right)\right\},$$

where

$$\triangle_1 = N_H \mu_s I_{Hs}(\lambda_2 - 1) + N_H \mu_r I_{Hr}(\lambda_3 - 1),$$
$$\triangle_2 = p_1 \lambda_{Hs} I_{Vs} S_H(\lambda_2 - \lambda_1) + p_1 \lambda_{Vs} I_{Hs} S_V(\lambda_7 - \lambda_6),$$
$$\triangle_3 = p_2 \lambda_{Hr} I_{Vr} S_H(\lambda_3 - \lambda_1) + p_2 \lambda_{Vr} I_{Hr} S_V(\lambda_8 - \lambda_6),$$

and λ_i, $i = 1, \ldots, 8$, *are the solutions of the co-state system (5).*

Substituting the optimal control (u_1^*, u_2^*) which is obtained from the state system (1) and the co-state system (5), we obtain the optimal system.

4. Numerical simulation

In this section we give some numerical simulations of model (1) with and without optimal control. The optimal control strategy is obtained by the iterative method of Runge–Kutta method of order 4 [8]. We start to solve the state equations by the forward Runge–Kutta method of order 4. Then we use the backward Runge–Kutta method of order 4 to solve the co-state equations with the transversality conditions.

We consider three scenarios. In the first scenario, we consider only the optimal treatment control. In the second scenario, we consider only the optimal insecticide control. In the last one, we use the optimal treatment and insecticide controls. Parameters used in these simulations could be seen in Table 2. In these simulations, we use initial condition $x(0) = (700, 10, 5, 7, 1000, 950, 50, 40)$, weighting constants $c_1 = 50$, $c_2 = 20$ and proportions $p_1 = 0.3$ and $p_2 = 0.6$.

4.1. First scenario

In this scenario, only the treatment control is considered. The profile of the optimal treatment control u_1^* for this scenario could be seen in Fig. 3. To reduce malaria cases in 100 days, the treatment should be given in maximum control over 93 days before dropping to the lower bound in the 100-th day.

The dynamics of the infected populations of this scenario are given in Figs. 4 and 5. We observe in Fig. 4 that the control strategy decreases the number of the infected host population significantly. Specifically, using the control strategy, the sensitive infected host population start to decrease from the 20-th day and the resistant infected host population start to decrease from the 30-th day. Similar conditions also hold in the vector population. We see in Fig. 5 that the control strategy resulted in a decrease in the number of the infected vector population as against an increase in the uncontrolled case.

4.2. Second scenario

In the second scenario, we consider only the insecticide control. The profile of the optimal insecticide control u_2^* is in Fig. 6. To decrease malaria cases in 100 days, the insecticide should be given intensively in almost 100 days.

The dynamics of the infected host and vector populations are given in Figs. 7 and 8 respectively. In this scenario, the dynamics of the infected host population with and without control do not different significantly. Contrary, the dynamics of the infected vector population with and without control give a significant difference. So, the insecticide control gives a significant effect in controlling infected vectors.

4.3. Third scenario

In this scenario, we consider the treatment and insecticide controls simultaneously. The profile of the optimal treatment control u_1^* and insecticide control u_2^* of this scenario is in Fig. 9. To reduce malaria cases in 100 days, the treatment control should be given intensively in 83 days and kept close to zero on the 100-th day. While the insecticide control is given intensively in 58 days and then reduced to near zero at the end of the 100-th day.

Using the optimal controls in Fig. 9, the dynamics of the infected host and vector populations are given in Figs. 10 and 11 respectively. It is seen that both of the infected host and vector populations decrease significantly with the existing controls.

Based on the simulation results, we conclude that the combination of treatment and insecticide is more effective to reduce the infected host and vector populations. To obtain optimal results, treatment and insecticide should be given intensively since the beginning and during the outbreak of malaria in the population.

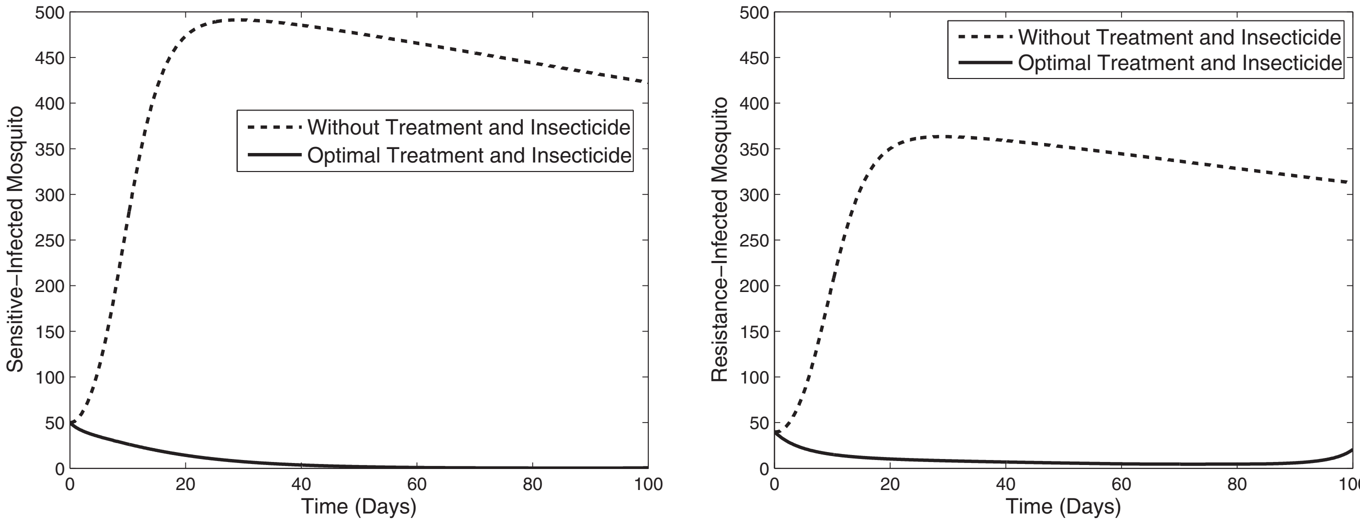

Fig. 11. The dynamics of I_{Vs} and I_{Vr} using controls u_1^* and u_2^*.

5. Conclusion

In this paper, we formulate a deterministic model of malaria transmission considering the resistance of malaria parasite to the antimalarial drugs. The model incorporates mass treatment and insecticide as optimal control strategies. Here, we consider the sensitive and resistant strains of malaria parasites in human and mosquito populations. For the model without control, we obtain two basic reproduction ratios, R_{0s} and R_{0r}, corresponding to the sensitive and resistant strains respectively. These ratios determine the existence and stability of the equilibrium of the model. The disease-free equilibrium is locally asymptotically stable if $R_{0s}, R_{0r} < 1$. These results are summarized in the bifurcation diagram. Finally, the optimal control theory is derived analytically by applying the Pontryagin Maximum Principle for the above malaria transmission model. We have carried out numerical simulations to perform the optimal mass treatment and insecticide control. The combination of the mass treatment and insecticide gave a better and efficient results for reducing malaria prevalence. However, we found that the mass treatment is very important rather than the insecticide during the outbreak of malaria in the population although the implementation cost of the mass treatment is more expensive than the insecticide.

Acknowledgments

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