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Optimal control analysis of a malaria transmission model with applications to Democratic Republic of Congo

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Abstract. In this paper, a dynamical model of malaria transmission with vector-bias and time-dependent controls is investigated. The controls include the RTS,S malaria vaccine, using insecticide-treated mosquito net, treatment of infectious human, and indoor spraying. For constant controls, the existence and stability of equilibrium, as well as the existence of backward bifurcation, are obtained. The sensitivity analysis quantifies the impact of parameters and controls on the basic reproduction number. For time-dependent controls, by using the Pontryagin's maximum principle the existence and expression of optimal controls are established. As an application of the model and control strategies, the malaria transmission and controls in Democratic Republic of Congo are discussed. To be specific, we simulate the reported cases of Democratic Republic of Congo by World Health Organization and predict the trends. Cost-effectiveness analysis and numerical simulations show that combining all controls can minimize the number of infected humans to the full extent, using insecticide-treated mosquito net is the most cost-effectiveness strategy, combining RTS,S malaria vaccine with using insecticide-treated mosquito net and treatment of infectious human is also cost-effective among all the strategies with good effect.

Keywords: malaria transmission model, stability, bifurcation, optimal control, cost-effectiveness.

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1 Introduction

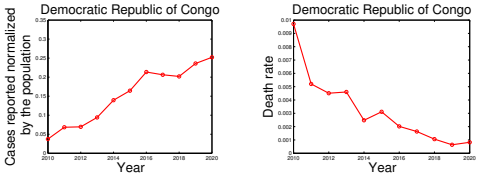
Malaria, caused by protozoan parasites belonging to the genus Plasmodium, is a mosquito-borne disease, which affects health systems and economies significantly. According to the World Health Organization (WHO) 2021 reports, 241 million cases of malaria and 627 thousand malaria deaths occurred globally in 2020, 14 million cases more and 69,000 more deaths compared to 2019 [23]. Humans get infected from the bite of infected female Anopheles mosquitoes, especially, from these infected Plasmodium falciparum and Plasmodium vivax. In the WHO African Region, Plasmodium falciparum accounts for 99.7% of estimated malaria cases, while Plasmodium vivax is responsible for 74.1% of malaria cases in the WHO Region of Americas.

Take Democratic Republic of Congo (Congo, DR), an African country, for example. Based on data in Table 1, we can get Fig. 1, which shows that the death rate keeps decreasing from 1% to 0.1% during 2010–2020 with the advancement of society. However, we can see that in Congo, DR, there are still about 5% people infected with malaria in the year 2010, and that the number of population infected with malaria in Congo, DR keeps increasing surprisingly to about 25% in 2020. Therefore, controlling the transmission of malaria in Congo, DR is desperately in need.

Mathematical models have become vital tools for understanding the dynamics of infectious diseases long time ago. The first mathematical model depicting the transmission process of malaria was introduced by Ross [17] and refined by MacDonald [14] later. From then on, the malaria transmission model was developed extensively [4, 15, 16]. Particularly, the vector-bias effect, namely, the greater attractiveness of infectious humans to mosquitoes than susceptible ones [5, 12], was firstly introduced to a malaria transmission model by Kingsolver [11] in 1987. Subsequently, feeding bias by vectors toward infected hosts and incubation time in mosquitoes included, Hosack et al. [7] found

Table 1. Reported cases (from [23]) and the population (from [20]) of Congo, DR.

Year	Reported cases	Death cases	Population	Year	Reported cases	Death cases	Population
2010	2417780	23476	$6.4564 \cdot 10^7$	2016	16821130	33997	$7.8189 \cdot 10^7$
2011	4561981	23748	$6.6755 \cdot 10^7$	2017	16793002	27456	$8.1399 \cdot 10^7$
2012	4791598	21601	$6.9021 \cdot 10^7$	2018	16972207	18030	$8.4068 \cdot 10^7$
2013	6719887	30918	$7.1359 \cdot 10^7$	2019	20480310	13072	$8.6791 \cdot 10^7$
2014	10288519	25502	$7.3767 \cdot 10^7$	2020	22590646	18636	$8.9561 \cdot 10^7$
2015	12538805	39054	$7.6245 \cdot 10^7$				



(a) (b)

Figure 1. (a) The reported cases of malaria normalized by the population; (b) the death rate during 2010–2020.

parasite modified behavior by a refined malaria model. Further, Chamchod and Britton [3] improved the previous models by defining the attractiveness in a different way. Based on these works, a lot of researchers investigated the malaria models with vector bias [1, 10]. All these results show that the vector bias has an important impact on the epidemiology of malaria.

Furthermore, based on the optimal control theory, malaria transmission models are also used in the decision-making of prevention and control of malaria [8,9,15,16,18]. Kim et al. [10] applied two optimal controls (treatment and media awareness) and indicated that the combination of the two controls was the most effective strategy to monitor the disease. It should be pointed that few researcher focus on controlling the malaria with vaccine since the uncertainty of malaria vaccination. However, recently, the World Health Organization has recommended to use the RTS,S malaria vaccine (a vaccination mainly for children under 5) broadly since if the RTS,S vaccine introduced widely and urgently, tens of thousands of children's lives could be saved every year [23].

In this paper, we developed a malaria transmission model with vector-bias effect and time-dependent controls: RTS,S vaccine, using insecticide-treated mosquito net, treatment of infectious human, indoor spraying simultaneously. We will use our model to simulate the reported cases of Congo, DR and propose several strategies to control the spread of malaria in Congo, DR. The research topic in this paper is novel and characteristic. In fact, few research analyze the control strategies with area-specific parameters.

The paper is arranged as follows. In Section 2, we formulate the nonautonomous malaria model with vector bias. Then we analyze the dynamics of the autonomous version in Section 3. Specifically speaking, the existence and stability of the disease-free and endemic equilibria, the bifurcation analysis, as well as the sensitivity analysis, are given. Furthermore, optimal control analysis of the nonautonomous model is performed in Section 4. In Section 5, we apply the model to the malaria transmission in Congo, DR. To be specific, we simulate the reported cases of Congo, DR by WHO and predict the trends in five years. Numerical simulations are used to observe the outcomes, characterizations as well as the cost of these strategies. Furthermore, cost-effectiveness analysis and numerical simulations show that combining all controls can minimize the number of infected humans to the full extent, using insecticide-treated mosquito net is the most cost-effectiveness strategy, combining RTS,S malaria vaccine with using insecticide-treated mosquito net and treatment of infectious human is also cost-effective among all the strategies with good effect. Finally, conclusions are summarized in Section 6.

2 Model formulation

The human population $N_h(t)$ is divided into three compartments, that is, susceptible $S_h(t)$, infected $I_h(t)$, and recovery $R_h(t)$. The susceptible will be vaccinated RTS,S (a malaria vaccine for children under 5) by rate of $u_1(t) \in [0, 0.4]$, δ is the efficiency of vaccination. Assume that Λ_1 is the birth or immigration rate of human population. They either die naturally or diminished following infection with malaria at a rate (infection rate) $\lambda_h = \sigma\beta_1(1 - u_2(t))I_m/(\nu I_h + S_h + R_h)$, where σ is the biting rate, β_1 is the

transmission probability of per bite, ν is the bias parameter, and $u_2(t) \in [0, 0.89]$ refers to a time-dependent control function representing the decrease of transmission rate by the use of insecticide-treated mosquito nets. Infectious individuals are assumed to recover at a rate $\gamma + \tau u_3(t)$, where γ is the spontaneous rate, $u_3(t) \in [0, 0.88]$ also is a time-dependent control function representing the treatment of infectious human with malaria symptoms, and τ is the efficacy to treatment. Infectious individuals who does not recover die naturally at rate d_1, and die of the disease at rate α.

The female anopheles mosquito population $N_m(t)$ is divided into two compartments, susceptible $S_m(t)$ and infectious $I_m(t)$. For mosquito population, the recruitment rate is Λ_2, the infection rate is $\lambda_m = \sigma\beta_2(1 - u_2(t))I_h/(\nu I_h + S_h + R_h)$, where β_2 is the probability for a vector to get infected by an infectious human. Infectious mosquito die at a rate $d_2 + cu_4(t)$, where d_2 is the natural death rate, and $u_4(t) \in [0, 1]$ is the control function on mosquito population by spraying insecticide.

Based on the above details, the malaria mathematical model is given by the following nonautonomous and nonlinear equations:

$$\begin{aligned}
\frac{dS_h}{\mathrm{d}t} &= \Lambda_1 - \frac{\sigma\beta_1(1-u_2)S_hI_m}{\nu I_h + S_h + R_h} - d_1S_h - \delta u_1 S_h + \rho R_h,\\
\frac{\mathrm{d}I_h}{\mathrm{d}t} &= \frac{\sigma\beta_1(1-u_2)S_hI_m}{\nu I_h + S_h + R_h} - (\gamma + d_1 + \alpha + \tau u_3)I_h,\\
\frac{\mathrm{d}R_h}{\mathrm{d}t} &= (\gamma + \tau u_3)I_h - (\rho + d_1)R_h + \delta u_1 S_h,\\
\frac{\mathrm{d}S_m}{\mathrm{d}t} &= \Lambda_2 - \frac{\sigma\beta_2\nu(1-u_2)S_mI_h}{\nu I_h + S_h + R_h} - (d_2 + cu_4)S_m,\\
\frac{\mathrm{d}I_m}{\mathrm{d}t} &= \frac{\sigma\beta_2\nu(1-u_2)S_mI_h}{\nu I_h + S_h + R_h} - (d_2 + cu_4)I_m,
\end{aligned} \tag{1}$$

where all parameters are positive and described in Table 2.

Table 2. Parameters for model (1).

Parameter	Description	Value	Ref.
Λ_1	Recruitment rate of the human population	$3.67 \cdot 10^6$	[23]
Λ_2	Recruitment rate of the mosquito population	$8 \cdot 10^8$ year^{-1}	Fitting
σ	Mosquitoes biting rate	$0.3 \cdot 365$ year^{-1}	[4]
β_1	Human transmission rate	0.01	[4]
β_2	Mosquito transmission rate	0.3	[4]
d_1	Natural death rate of human	$\frac{1}{65}$year^{-1}	[4]
d_2	Natural death rate of mosquitoes	$\frac{1}{15} \cdot 365$ year^{-1}	[4]
γ	Recovery rate of infection human	0.2336	Fitting
ρ	Loss of the immunity rate in human	$\frac{1}{2}$ year^{-1}	[4]
α	Disease induced death rate	$3.3 \cdot 10^{-3}$year^{-1}	[23]
ν	Probability that a mosquito picks infected	1.9	Fitting
ν	human randomly		
τ	Proportion of effectively treated individuals	0.8	Assumed
c	Increased death rate of mosquito	0.8	Assumed

Continued on next page

Table 2 (*Continued from previous page*)

Parameter	Description	Value	Ref.
c	by the insecticide		
δ	Effectiveness of RTS,S malaria vaccine	0.4	[23]
u_1	RTS,S malaria vaccination coverage rate	$0-0.4$	Assumed
u_2	Effectiveness Insecticide-treated mosquito nets	$0-0.89$	Assumed
u_3	Effectiveness Treatment of infectious human	$0-0.88$	Assumed
u_4	Effectiveness Spraying of insecticides	$0-1$	Assumed

Firstly, as a basic property of solutions for model (1), we have the following lemma.

Lemma 1. *If the initial value* $(S_h(0), I_h(0), R_h(0), S_m(0), I_m(0))$ *are positive, then solution* $(S_h(t), I_h(t), R_h(t), S_m(t), I_m(t))$ *for all* $t > 0$ *also are positive. Furthermore,*

$$\limsup_{t\to\infty} N_h(t) \leqslant \frac{\Lambda_1}{d_1}, \qquad \limsup_{t\to\infty} N_m(t) \leqslant \frac{\Lambda_2}{d_2}.$$

The proof of this lemma is omitted for simplicity.

3 Analysis of model with constant controls

In this section, we assume that all the controls u_i $(i = 1, 2, 3, 4)$ in model (1) are constants. We will investigate the dynamical behaviors of model (1), including the calculation of basic reproduction number, the existence of equilibria and their stability, the backward bifurcation analysis, and the sensitivity analysis.

3.1 Equilibrium and stability

It is easy to see that model (1) has a unique disease-free equilibrium

$$E_0 = \left(\frac{\Lambda_1(d_1+\rho)}{d_1(d_1+\delta u_1+\rho)}, 0, \frac{\Lambda_1\delta u_1}{d_1(d_1+\delta u_1+\rho)}, \frac{\Lambda_2}{d_2+cu_4}, 0\right).$$

Using the next generation matrix method (see [19]), we can easily obtain the basic reproduction number of model (1)

$$R_0 = \frac{\sigma^2\beta_1\beta_2\Lambda_2 d_1\nu(1-u_2)^2(d_1+\rho)}{\Lambda_1(\gamma+d_1+\alpha+\tau u_3)(d_2+cu_4)^2(d_1+\rho+\delta u_1)}.$$

Based on the result in [19], the following theorem is established immediately.

Theorem 1. *The disease-free equilibrium* E_0 *is locally asymptotically stable if* $R_0 < 1$*, and is unstable if* $R_0 > 1$.

Let $E^* = (S_h^*, I_h^*, R_h^*, S_m^*, I_m^*)$ be the endemic equilibrium of model (1). Denote

$$\lambda_h^* = \frac{\sigma\beta_1(1-u_2)I_m^*}{\nu I_h^* + S_h^* + R_h^*}, \qquad \lambda_m^* = \frac{\sigma\beta_2\nu(1-u_2)I_h^*}{\nu I_h^* + S_h^* + R_h^*}.$$

Then, after some simple computations, we get

$$
\begin{aligned}
S_h^* &= \Lambda_1(\rho+d_1)(\gamma+d_1+\alpha+\tau u_3)\big(\big[\rho(d_1+\alpha)+d_1(\gamma+d_1+\alpha+\tau u_3)\big]\lambda_h^* \\
&\quad + d_1(\rho+d_1+\delta u_1)(\gamma+d_1+\alpha+\tau u_3)\big)^{-1}, \\
I_h^* &= \lambda_h^* S_h^*(\gamma+d_1+\alpha+\tau u_3)^{-1}, \\
R_h^* &= \big((\gamma+\tau u_3)\lambda_h^* + (\gamma+d_1+\alpha+\tau u_3)\delta u_1\big)S_h^*\big((\gamma+d_1+\alpha+\tau u_3)(\rho+d_1)\big)^{-1}, \\
S_m^* &= \Lambda_2(\lambda_m^*+d_2+cu_4)^{-1}, \qquad I_m^* = \lambda_m^* S_m^*(d_2+cu_4)^{-1}, \\
\lambda_h^* &= \big(\sigma\beta_1(1-u_2)\Lambda_2\lambda_m^*\big[\big(\rho(d_1+\alpha)+d_1(\gamma+d_1+\alpha+\tau u_3)\big)\lambda_h^* \\
&\quad + d_1(\rho+d_1+\delta u_1)(\gamma+d_1+\alpha+\tau u_3)\big]\big)\big(\big[(\gamma+\tau u_3+\nu\rho+\nu d_1)\lambda_h^* \\
&\quad + (\rho+d_1)(\gamma+d_1+\alpha+\tau u_3)+\delta u_1(\gamma+d_1+\alpha+\tau u_3)\big]^2 \\
&\quad \times \Lambda_1(d_2+cu_4)(\lambda_m^*+d_2+cu_4)\big)^{-1}, \\
\lambda_m^* &= \sigma\beta_2\nu(1-u_2)(\rho+d_1)\lambda_h^*\big((\gamma+\tau u_3+\nu\rho+\nu d_1)\lambda_h^* \\
&\quad + (\rho+d_1)(\gamma+d_1+\alpha+\tau u_3)+\delta u_1(\gamma+d_1+\alpha+\tau u_3)\big)^{-1}.
\end{aligned}
$$

Therefore, we can get λ_h^* satisfies the quadratic equation

$$
b_0{\lambda_h^*}^2 + b_1\lambda_h^* + b_2 = 0, \tag{2}
$$

where

$$
\begin{aligned}
b_0 &= \Lambda_1(d_2+cu_4)(\gamma+\tau u_3+\nu\rho+\nu d_1)\big(\sigma\beta_2\nu(1-u_2)(\rho+d_1) \\
&\quad + (d_2+cu_4)(\gamma+\tau u_3+\nu\rho+\nu d_1)\big), \\
b_1 &= \sigma\nu\beta_2\Lambda_1(1-u_1)(1-u_2)(d_2+cu_4)(\rho+d_1)(\rho+d_1+\delta u_1)(\gamma+d_1+\alpha+\tau u_3) \\
&\quad + 2\Lambda_1(d_2+cu_4)^2(\rho+d_1+\delta u_1)(\gamma+d_1+\alpha+\tau u_3)(\gamma+\tau u_3+\nu\rho+\nu d_1) \\
&\quad - \sigma^2\beta_1\beta_2\nu(1-u_2)^2(\rho+d_1)\Lambda_2\big(\rho(d_1+\alpha)+d_1(\gamma+d_1+\alpha+\tau u_3)\big), \\
b_2 &= \Lambda_1(d_2+cu_4)^2(\rho+d_1+\delta u_1)^2(\gamma+d_1+\alpha+\tau u_3)^2(1-R_0).
\end{aligned}
$$

Thus, the existence of endemic equilibrium of model (1) is equivalent to the existence of positive roots of equation (2). Based on Vieta's theorem, when either of the following conditions hold, then equation (2) has positive roots

(i) $\Delta = b_1^2 - 4b_0b_2 \geqslant 0,\ b_1 < 0,\ b_2 \geqslant 0;$
(ii) $b_2 < 0.$

It is easily to see that $b_2 > 0\ (=, <)$ is equivalent to $R_0 < 1\ (=, >)$. For the convenience, define the constants:

$$
\begin{aligned}
R_1 &:= 1 - \frac{b_1^2}{4b_0\Lambda_1(d_2+cu_4)^2(\rho+d_1+\delta u_1)^2(\gamma+d_1+\alpha+\tau u_3)^2}, \\
R_2 &:= \frac{d_1[\sigma\nu\beta_2(1-u_2)(\rho+d_1)+2(d_2+cu_4)(\gamma+\tau u_3+\nu\rho+\nu d_1)]}{(d_2+cu_4)[\rho(d_1+\alpha)+d_1(\gamma+d_1+\alpha+\tau u_3)]}, \\
R_c &:= \max\{R_1, R_2\}.
\end{aligned}
$$

Then $\Delta > 0\ (=, <)$ is equivalent to $R_0 > R_1\ (=, <)$, and $b_1 < 0\ (=, >)$ is equivalent to $R_0 > R_2\ (=, <)$. Therefore, we can establish the following conclusion on the existence of endemic equilibrium for model (1).

Theorem 2. *Model* (1) *always has a unique disease-free equilibrium* E_0.

(i) *If* $R_c < R_0 < 1$, *then model* (1) *has two endemic equilibria*;
(ii) *If* $R_2 < R_0 = R_1 < 1$, *then model* (1) *has a unique endemic equilibrium* E^* *of multiplicity two*;
(iii) *If* $R_2 < R_0 = 1$, *then model* (1) *has a unique endemic equilibrium* E^*;
(iv) *If* $R_0 > 1$, *then model* (1) *has a unique endemic equilibrium* E^*;
(v) *Otherwise, model* (1) *has no endemic equilibrium.*

Remark 1. Theorem 2 shows that model (1) can generate a backward bifurcation under the condition $R_c < R_0 < 1$. The analysis will be given in Section 3.2 in detail.

Moreover, when $R_0 > 1$, the local stability of endemic equilibrium E^* can be obtained by the linearization method. The characteristic equation of linearized system at equilibrium E^* and the corresponding coefficients c_i $(i = 1, 2, 3, 4, 5)$ in characteristic equation are presented in Appendix. We have the following conclusion.

Theorem 3. *When* $R_0 > 1$, *then endemic equilibrium* E^* *is locally asymptotically stable if the following conditions corresponding to Hurwitz criterion hold*:

$$c_3 > 0, \qquad c_2c_3 - c_1c_4 > 0, \qquad c_1c_2c_3 - c_3^2 - c_4c_1^2 > 0. \tag{3}$$

Remark 2. By parameter values in Table 2 and letting $u_i = 0$, we can get the values of c_i in Appendix, i.e., $c_1 = 26.6808$, $c_2 = 16.4375$, $c_3 = 1.8222$, $c_4 = 0.0254$, and then $c_2c_3 - c_1c_4 = 29.2739 > 0$, $c_1c_2c_3 - c_3^2 - c_4c_1^2 = 777.7324 > 0$. Therefore, we checked equation (3) numerically.

3.2 Bifurcation analysis

In this subsection, the forward and backward bifurcations are investigated for model (1). The main method on the bifurcation analysis is presented in [2] based on the centre manifold theory in [2]. We can establish the following result.

Theorem 4. *Let constant* $\mathcal{A}$ *is defined below. If* $\mathcal{A} > 0$, *then model* (1) *exhibits a backward bifurcation at* $R_0 = 1$. *If* $\mathcal{A} < 0$, *then model* (1) *exhibits a forward bifurcation at* $R_0 = 1$.

Proof. We choose the transmission rate β_1 as a bifurcation parameter. Clearly, $R_0 = 1$ is equivalent to

$$\beta_1 = \beta_1^* = \frac{\Lambda_1(d_2 + cu_4)^2(\gamma + d_1 + \alpha + \tau u_3)(\rho + d_1 + \delta u_1)}{\sigma^2\nu\beta_2(1 - u_2)^2\Lambda_2 d_1(\rho + d_1)}.$$

According to Theorem 1, equilibrium E_0 is locally stable if $\beta_1 < \beta_1^*$, and unstable if $\beta_1 > \beta_1^*$. Hence, $\beta_1 = \beta_1^*$ is a bifurcation value. Let $x_1 = S_h$, $x_2 = I_h$, $x_3 = R_h$, $x_4 = S_m$, $x_5 = I_m$, and $x = (x_1, x_2, x_3, x_4, x_5)^{\mathrm{T}}$. Then model (1) can be written in the form $\mathrm{d}x/\mathrm{d}t = f(x)$ with $f = (f_1, f_2, f_3, f_4, f_5)$, that is,

$$\begin{aligned}
\frac{\mathrm{d}x_1}{\mathrm{d}t} &= \Lambda_1 - \frac{\sigma\beta_1(1-u_2)x_1x_5}{\nu x_2 + x_1 + x_3} - d_1x_1 - \delta u_1 x_1 + \rho x_3 := f_1,\\
\frac{\mathrm{d}x_2}{\mathrm{d}t} &= \frac{\sigma\beta_1(1-u_2)x_1x_5}{\nu x_2 + x_1 + x_3} - (\gamma + d_1 + \alpha + \tau u_3)x_2 := f_2,\\
\frac{\mathrm{d}x_3}{\mathrm{d}t} &= (\gamma + \tau u_3)x_2 - (\rho + d_1)x_3 + \delta u_1 x_1 := f_3,\\
\frac{\mathrm{d}x_4}{\mathrm{d}t} &= \Lambda_2 - \frac{\sigma\beta_2\nu(1-u_2)x_4x_2}{\nu x_2 + x_1 + x_3} - (d_2 + cu_4)x_4 := f_4,\\
\frac{\mathrm{d}x_5}{\mathrm{d}t} &= \frac{\sigma\beta_2\nu(1-u_2)x_4x_2}{\nu x_2 + x_1 + x_3} - (d_2 + cu_4)x_5 := f_5.
\end{aligned} \tag{4}$$

It is not difficult to obtain that the Jacobian matrix of system (4) at E_0 with $\beta_1 = \beta_1^*$ is

$$J_0 = \begin{bmatrix}
-(d_1+\delta u_1) & 0 & \rho & 0 & -\sigma\beta_1^*(1-u_2)\frac{(\rho+d_1)}{(\rho+d_1+\delta u_1)}\\
0 & -(\gamma+d_1+\alpha+\tau u_3) & 0 & 0 & \sigma\beta_1^*(1-u_2)\frac{(\rho+d_1)}{(\rho+d_1+\delta u_1)}\\
\delta u_1 & \gamma+\tau u_3 & -(\rho+d_1) & 0 & 0\\
0 & -\frac{\sigma\beta_2\nu\Lambda_2 d_1(1-u_2)}{(d_2+cu_4)\Lambda_1} & 0 & -(d_2+cu_4) & 0\\
0 & \frac{\sigma\beta_2\nu\Lambda_2 d_1(1-u_2)}{(d_2+cu_4)\Lambda_1} & 0 & 0 & -(d_2+cu_4)
\end{bmatrix}$$

and the corresponding characteristic equation is

$$\begin{aligned}
\det(\lambda E - J_0) = {}& \lambda(\lambda + d_1)(\lambda + \rho + d_1 + \delta u_1)(\lambda + d_2 + cu_4)\\
& \times (\lambda + \gamma + d_1 + \alpha + \tau u_3 + d_2 + cu_4).
\end{aligned} \tag{5}$$

It is clear that equation (5) admits a simple zero eigenvalue and all other eigenvalues are negative.

In the following, we calculate the right eigenvector $\mathbf{w} = (w_1, w_2, w_3, w_4, w_5)^{\mathrm{T}}$ and the left eigenvector $\mathbf{v} = (v_1, v_2, v_3, v_4, v_5)$ with respect to the zero eigenvalue of J_0. From $J_0\mathbf{w} = 0$ we can get

$$\begin{aligned}
&w_1 = -\frac{q_1d_1 + q_2(d_1+\alpha)}{qd_1(\rho + d_1 + \delta u_1)}pw_5, \qquad w_2 = \frac{p}{q}w_5,\\
&w_3 = \frac{q_1d_1 - \delta u_1(d_1+\alpha)}{d_1q(\rho + d_1 + \delta u_1)}w_5, \qquad w_4 = -w_5, \qquad w_5 > 0
\end{aligned}$$

with $q = \gamma + d_1 + \alpha + \tau u_3$, $q_1 = \gamma + \tau u_3$, $q_2 = \rho + d_1$, $q_3 = d_2 + cu_4$, $n = \sigma\beta_2\nu\Lambda_2 d_1(1-u_2)/((d_2+cu_4)\Lambda_1)$, $p = \sigma\beta_1^*(1-u_2)(\rho+d_1)/(\rho+d_1+\delta u_1)$. Then from $\mathbf{v}J_0 = 0$ we can get

$$v_1 = 0, \qquad v_2 = \frac{q_3}{p}v_5, \qquad v_3 = 0, \qquad v_4 = 0, \qquad v_5 > 0.$$

Calculate the constants a and b as follows:

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k(E_0)}{\partial x_i \partial x_j} \\ &= \frac{\partial^2 f_2(E_0)}{\partial x_2 \partial x_5} v_2 w_2 w_5 + \frac{\partial^2 f_2(E_0)}{\partial x_3 \partial x_5} v_2 w_3 w_5 + \frac{\partial^2 f_5(E_0)}{\partial x_1 \partial x_2} v_5 w_1 w_2 \\ &\quad + \frac{\partial^2 f_5(E_0)}{\partial x_2^2} v_5 w_2^2 + \frac{\partial^2 f_5(E_0)}{\partial x_2 \partial x_3} v_5 w_2 w_3 + \frac{\partial^2 f_5(E_0)}{\partial x_2 \partial x_4} v_5 w_2 w_4, \\ b &= \sum_{k,i=1}^{5} v_k w_i \frac{\partial^2 f_k(E_0)}{\partial x_i \partial \beta_1^*} = \frac{\partial^2 f_2(E_0)}{\partial x_5 \partial \beta_1^*} v_2 w_5. \end{aligned}$$

From system (4) we can obtain

$$\begin{aligned} &\frac{\partial^2 f_2(E_0)}{\partial x_2 \partial x_5} = -\sigma\nu\beta_1(1-u_2)\frac{d_1(\rho+d_1)}{\Lambda_1(\rho+d_1+\delta u_1)}, \\ &\frac{\partial^2 f_2(E_0)}{\partial x_3 \partial x_5} = -\sigma\beta_1(1-u_2)\frac{d_1(\rho+d_1)}{\Lambda_1(\rho+d_1+\delta u_1)}, \\ &\frac{\partial^2 f_5(E_0)}{\partial x_1 \partial x_2} = -\sigma\beta_2\nu(1-u_2)\frac{\Lambda_2 d_1^2}{q_3\Lambda_1^2}, \qquad \frac{\partial^2 f_5(E_0)}{\partial^2 x_2} = -2\nu\sigma\beta_2(1-u_2)\frac{\Lambda_2 d_1^2}{q_3\Lambda_1^2}, \\ &\frac{\partial^2 f_5(E_0)}{\partial x_2 \partial x_3} = -\sigma\beta_2\nu(1-u_2)\frac{\Lambda_2 d_1^2}{q_3\Lambda_1^2}, \qquad \frac{\partial^2 f_5(E_0)}{\partial x_2 \partial x_4} = \sigma\beta_2\nu(1-u_2)\frac{d_1}{\Lambda_1}, \\ &\frac{\partial^2 f_2(E_0)}{\partial x_5 \partial \beta_1} = \sigma(1-u_2)\frac{\rho+d_1}{\rho+d_1+\delta u_1}. \end{aligned}$$

Therefore, we have

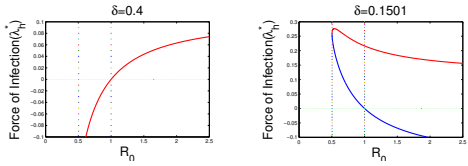
$$a = \frac{\sigma(1-u_2)\mathcal{A}}{\Lambda_1^2 q^2 q_2 q_3(d_1+\rho+\delta u_1)}, \qquad b = \frac{\nu(d_1+\rho)(d_2+cu_4)}{\beta_1^*(d_1+\rho+\delta u_1)} v_5 w_5$$

with

$$\begin{aligned} \mathcal{A} &= \beta_1^* q q_2^2 q_3 \Lambda_1 \delta u_1 (d_1+\alpha) + \nu\beta_2 p^2 \Lambda_2 d_1 q_2 (d_1+\alpha)(\rho+d_1+\delta u_1)^2 \\ &\quad - \beta_1^* d_1 q q_2^2 q_3 \Lambda_1 \big[\nu(\rho+d_1+\delta u_1)+q_1\big] \\ &\quad - \nu\beta_2 p q_2 (\rho+d_1+\delta u_1)^2 \big(2\Lambda_2 d_1^2 p + \Lambda_1 d_1 q q_3\big). \end{aligned}$$

Clearly, $b > 0$ and $a > 0$ (< 0) if and only if $\mathcal{A} > 0$ (< 0). Thus, from the results in [2] we can obtain that the conclusions in Theorem 6 hold. This completes the proof. □

Remark 3. Figure 2 gives the numerical examples of forward and backward bifurcations. From Fig. 2 we know that the efficiency rate of RTS,S vaccine δ has great impact on the dynamical behaviors of model (1). Besides, for Fig. 2(a) with $\alpha = 2.9227$, we can get $\mathcal{A} = -5.7645 < 0$, and for Fig. 2(b) with $\alpha = 4.8561$, we can get $\mathcal{A} = 5.1993 > 0$. This checks Theorem 4 numerically.



(a) (b)

Figure 2. Bifurcation diagrams of model (1) for the force of infection at steady state λ_h^* versus R_0 when take $\sigma = 14$, $\beta_1 = 0.03$, $\beta_2 = 0.38$, $\Lambda_2 = 1.1563 \cdot 10^5$, $d_1 = 0.01$, $\nu = 3$, $\rho = 0.075$, $\Lambda_1 = 6 \cdot 10^5$, $d_2 = 0.008$, $\gamma = 0.05$, $\tau = 0.6$, $u_1 = 0.31$, $u_2 = 0.3002$, $u_3 = 0.5$, $u_4 = 0.2$, $c = 0.1$, $\alpha = 0.02,\ 0.01,\ 10$: (a) forward bifurcation, (b) backward bifurcation.

3.3 Sensitivity of basic reproduction number to parameters and controls

Sensitivity analysis is a technique that permits exploration of complex models by evaluating how the quantities of interest (QOI) change with the variation of parameters of interest (POI). Generally, the growth of an epidemic is partly characterized by the basic reproduction number R_0. For this, we analytically calculate the sensitivity indices of R_0 to parameter p as follows: [4]:

$$\Upsilon_p^{R_0} = \frac{\partial R_0}{\partial p} \cdot \frac{p}{R_0}.$$

In addition, the sign of the sensitivity index suggests whether the quantities of interest, R_0 increases (> 0) or decreases (< 0) with the parameter of interest p.

The sensitivity index of R_0 with respect to parameters Λ_1, Λ_2, σ, β_1, β_2, and ν are constant as shown in Table 3. For others, we get

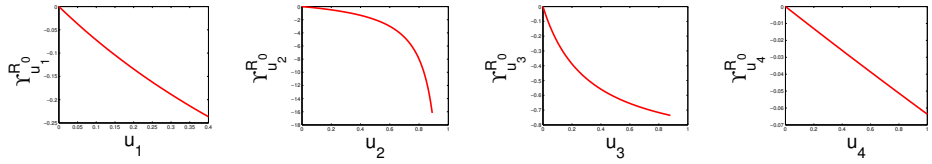
$$\Upsilon_{d_1}^{R_0} = \frac{d_1 \delta u_1}{(d_1+\rho)(d_1+\rho+\delta u_1)} + \frac{\gamma+\alpha+\tau u_3}{A_2},$$

$$\Upsilon_{\gamma}^{R_0} = -\frac{\gamma}{A_2}, \qquad \Upsilon_{\alpha}^{R_0} = -\frac{\alpha}{A_2}, \qquad \Upsilon_{d_2}^{R_0} = -\frac{d_2}{d_2+cu_4},$$

where $A_2 = \gamma + d_1 + \alpha + \tau u_3$, which are related to controls. The ranges of these indices are summarized in Table 3, which shows the most sensitive parameter is the average number of times one mosquito would bite a human per year, σ, while the least sensitive parameter is the disease induced death rate of human, α. In general, R_0 decreases with the increase of parameters γ, d_2, and Λ_1. Besides, R_0 increases with the increase of parameters d_1, Λ_2, β_1, β_2, and ν.

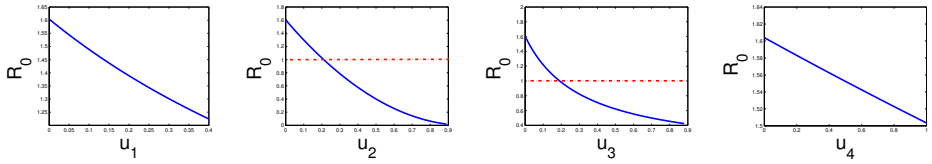
Table 3. Sensitivity indices of basic reproduction number, R_0, for model (1) at the baseline parameter values in Table 2.

Parameter	Sensitivity indices value	Parameter	Sensitivity indices range
Λ_1	-0.5000	d_1	$[+0.9363, +0.9800]$
Λ_2	$+0.5000$	d_2	$[-1.0000, -0.9682]$
σ	$+1.000$	γ	$[-0.9232, -0.2218]$
β_1	$+0.5000$	α	$[-0.0013, -0.0031]$
β_2	$+0.5000$	ν	$+0.5000$



(a) (b) (c) (d)

Figure 3. Sensitivity indices of R_0 with respect to the controls.



(a) (b) (c) (d)

Figure 4. Vary of R_0 with respect to the controls.

The sensitivity indices of R_0 with respect to the constant controls are given by

$$\Upsilon^{R_0}_{u_1} = -\frac{\delta u_1}{\rho + d_1 + \delta u_1}, \qquad \Upsilon^{R_0}_{u_2} = -\frac{2u_2}{1 - u_2},$$
$$\Upsilon^{R_0}_{u_3} = -\frac{\tau u_3}{\gamma + d_1 + \alpha + \tau u_3}, \qquad \Upsilon^{R_0}_{u_4} = -\frac{2cu_4}{d_2 + cu_4}.$$

Applying parameter values from Table 2, we get Fig. 3, which shows that the effect of the four controls are closely related to the control levels. To be specific, using of bednets u_2 affects transmission mostly, followed by u_3, u_4. Besides, from Fig. 4 we know that using of insecticide-treated bednets and treatment of infectious can reduce the value of basic reproduction number under 1.

Remark 4. It should be emphasized that to eliminate the disease, we must adjust some constant controls u_i large enough to make sure $R_0 < R_c$ (but $R_0 < 1$) since the backward bifurcation may happen when $R_c < R_0 < 1$. Furthermore, in the reality, it is not easy to keep the controls constant all the time. We know the fact that constant controls can be regarded as an approximation of time-dependent ones. Therefore, in the next section, we consider the model with time dependent controls and investigate the optimal controls according to optimal control theory.

4 Optimal control

The purpose of this section is to achieve the optimal control of model (1) with time dependent controls. We introduce the feasible control set as follows:

$$\Delta = \big\{\boldsymbol{u} = \big(u_1(t), u_2(t), u_3(t), u_4(t)\big)\colon\ u_i \text{ is measurable},\ i = 1, 2, 3, 4,\ \text{and}$$
$$0 \leqslant u_1(t) \leqslant 0.4,\ 0 \leqslant u_2(t) \leqslant 0.89,\ 0 \leqslant u_3(t) \leqslant 0.88,\ 0 \leqslant u_4(t) \leqslant 1\ \ \forall t \in [0, T]\big\}.$$

The optimal control for model (1) aims at minimizing the number of malaria-infected humans I_h and mosquito I_m and the cost needed during the intervention period. Therefore, the objective functional is defined by

$$J(\boldsymbol{u}) := \int_0^T g(t,\phi,\boldsymbol{u})\,\mathrm{d}t = \int_0^T \left(A_1 I_h + A_2 I_m + \sum_{i=1}^{4} \frac{\xi_i}{2} u_i^2 \right) \mathrm{d}t,$$

where $\phi = (S_h, I_h, R_h, S_m, I_m)$ is the solution of model (1), A_1, A_2 are the weight constants with respect to the number of infected humans and infected mosquitoes; $\xi_i \geqslant 0$ $(i = 1,2,3,4)$ are the weight constants on the benefit and cost; $\xi_i u_i^2/2$ $(i = 1,2,3,4)$ is the cost of corresponding control.

In the following, we need to solve the optimal control problem: find a control $\boldsymbol{u}^* \in \Delta$ such that $\min J(\boldsymbol{u}) = J(\boldsymbol{u}^*)$. Firstly, the existence of an optimal control is settled by the following theorem.

Theorem 5. *There exists an optimal control $\boldsymbol{u}^* \in \Delta$ for the objective functional $J(\boldsymbol{u})$ subject to model* (1) *with positive initial conditions such that $J(\boldsymbol{u}^*)$ is minimal.*

Theorem 5 can be proved by using the similar arguments as in [6, 16]. Hence, we here omit the proof for simplicity.

In fact, the characterization of optimal control is often deduced by Pontryagin's maximum principle [8]. This idea is to convert the optimal control problem into a type of problem of minimizing point wise Hamiltonian H with respect to $\boldsymbol{u}$. The Hamiltonian associated to our problem is

$$H\big(t,\phi,\boldsymbol{u},\lambda(t)\big) = g(t,\phi,\boldsymbol{u}) + \sum_{i=1}^{5} \lambda_i(t) f_i(t,\phi,\boldsymbol{u})$$

with $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t))$ representing the adjoint variables and $f_i(t,\phi,\boldsymbol{u})$ $(i = 1,2,3,4,5)$ denoting the right-hand side of model (1). Let $q = \gamma + d_1 + \alpha + \tau u_3$.

Theorem 6. *Given an optimal control $\boldsymbol{u}^* = (u_1^*, u_2^*, u_3^*, u_4^*)$, there exists a nontrivial adjoint vector function $\lambda(t)$ satisfying*

$$\begin{aligned}
\frac{\mathrm{d}\lambda_1}{\mathrm{d}t} &= (d_1 + \delta u_1)\lambda_1 - \delta u_1 \lambda_3 \\
&\quad + \frac{(1-u_2)[\sigma\beta_1 I_m(\nu I_h + R_h)(\lambda_1 - \lambda_2) + \nu\sigma\beta_2 S_m I_h(\lambda_5 - \lambda_4)]}{(\nu I_h + S_h + R_h)^2}, \\
\frac{\mathrm{d}\lambda_2}{\mathrm{d}t} &= q\lambda_2 - A_1 - (\gamma + \tau u_3)\lambda_3 \\
&\quad + \frac{(1-u_2)[\sigma\nu\beta_1 S_h I_m(\lambda_2 - \lambda_1) + \nu\sigma\beta_2 S_m(S_h + R_h)(\lambda_4 - \lambda_5)]}{(\nu I_h + S_h + R_h)^2}, \\
\frac{\mathrm{d}\lambda_3}{\mathrm{d}t} &= -\rho\lambda_1 + (\rho + d_1)\lambda_3 \\
&\quad + \frac{\sigma(1-u_2)[\beta_1 S_h I_m(\lambda_2 - \lambda_1) + \nu\beta_2 S_m I_h(\lambda_5 - \lambda_4)]}{(\nu I_h + S_h + R_h)^2},
\end{aligned} \tag{6}$$

$$\begin{aligned}
\frac{\mathrm{d}\lambda_4}{\mathrm{d}t} &= \frac{\nu\sigma\beta_2(1-u_2)I_h}{\nu I_h + S_h + R_h}(\lambda_4-\lambda_5) + (d_2+cu_4)\lambda_4,\\
\frac{\mathrm{d}\lambda_5}{\mathrm{d}t} &= -A_2 + \frac{\sigma\beta_1(1-u_2)S_h}{\nu I_h + S_h + R_h}(\lambda_1-\lambda_2) + (d_2+cu_4)\lambda_5,\\
\lambda_i(T) &= 0 \quad \textit{for } i = 1,2,3,4,5.
\end{aligned} \tag{7}$$

The controls u_i^* $(i=1,2,3,4)$ *satisfy the optimality condition*

$$\begin{aligned}
u_1^* &= \min\left\{0.4,\ \max\left\{0,\ \frac{\delta S_h(\lambda_1-\lambda_3)}{\xi_1}\right\}\right\},\\
u_2^* &= \min\left\{0.89,\ \max\left\{0,\ \frac{\sigma[\beta_1 S_h I_m(\lambda_2-\lambda_1)+\nu\beta_2 S_m I_h(\lambda_5-\lambda_4)]}{\xi_2(\nu I_h + S_h + R_h)}\right\}\right\},\\
u_3^* &= \min\left\{0.88,\ \max\left\{0,\ \frac{\tau I_h(\lambda_2-\lambda_3)}{\xi_3}\right\}\right\},\\
u_4^* &= \min\left\{1,\ \max\left\{0,\ \frac{c(S_m\lambda_4 + I_m\lambda_5)}{\xi_4}\right\}\right\}.
\end{aligned} \tag{8}$$

Proof. The differential equations (6), (7) that governs the adjoint variables are obtained by the following differentiation of the Hamiltonian function:

$$\frac{\mathrm{d}\lambda_1}{\mathrm{d}t} = -\frac{\partial H}{\partial S_h},\quad \frac{\mathrm{d}\lambda_2}{\mathrm{d}t} = -\frac{\partial H}{\partial I_h},\quad \frac{\mathrm{d}\lambda_3}{\mathrm{d}t} = -\frac{\partial H}{\partial R_h},\quad \frac{\mathrm{d}\lambda_4}{\mathrm{d}t} = -\frac{\partial H}{\partial S_m},\quad \frac{\mathrm{d}\lambda_5}{\mathrm{d}t} = -\frac{\partial H}{\partial I_m}.$$

Moreover, the optimality conditions $\partial H/\partial u_i = 0$ $(i=1,2,3,4,5)$ yield

$$\begin{aligned}
\frac{\partial H}{\partial u_1} &= \xi_1 u_1 - \lambda_1\delta S_h + \lambda_3\delta S_h = 0,\\
\frac{\partial H}{\partial u_2} &= \xi_2 u_2 + \frac{\sigma\beta_1 S_h I_m}{\nu I_h + S_h + R_h}(\lambda_1-\lambda_2) + \frac{\sigma\nu\beta_2 S_m I_h}{\nu I_h + S_h + R_h}(\lambda_4-\lambda_5) = 0,\\
\frac{\partial H}{\partial u_3} &= \xi_3 u_3 - \tau I_h\lambda_2 + \tau I_h\lambda_3 = 0, \qquad \frac{\partial H}{\partial u_4} = \xi_4 u_4 - cS_m\lambda_4 - cI_m\lambda_5 = 0.
\end{aligned}$$

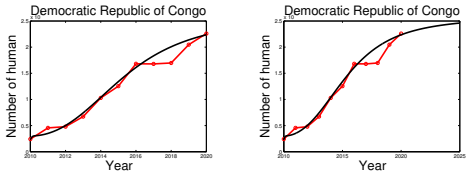
Then we get

$$\begin{aligned}
u_1^o &= \frac{\delta S_h(\lambda_1-\lambda_3)}{\xi_1}, \qquad u_2^o = \frac{\sigma[\beta_1 S_h I_m(\lambda_2-\lambda_1)+\nu\beta_2 S_m I_h(\lambda_5-\lambda_4)]}{\xi_2(\nu I_h + S_h + R_h)},\\
u_3^o &= \frac{\tau I_h(\lambda_2-\lambda_3)}{\xi_3}, \qquad u_4^o = \frac{c(S_m\lambda_4 + I_m\lambda_5)}{\xi_4}.
\end{aligned}$$

Combining with the upper bounds on u_1^*, u_2^*, u_3^*, and u_4^*, we get the characterizations in (8). □

5 Applications to malaria transmission in Congo, DR

As shown in Fig. 1 and Table 1, the situation of malaria spread in Congo, DR is quite serious. To make suitable control strategies, we will first simulate the reported cases



(a) (b)

Figure 5. Comparisons of the reported malaria cases in WHO (black curve) and the solution of infectious human I_h for model (1): (a) simulation of the reported malaria cases in Congo, DR from 2010 to 2020; (b) prediction of human malaria for Congo, DR in five years.

with model (1). Then we can get that the basic reproduction number of Congo, DR is estimated to be $R_0 \doteq 1.6038$ with parameter values in Table 2. According to Theorem 2, the disease in Congo, DR will be endemic, and Fig. 5(b) further verifies it. Therefore, it is necessary to carry out research on optimal control strategies, so that reasonable responses can be made from prevention and treatment to eradicate the disease as soon as possible and minimize the loss as much as possible.

5.1 Data and parameters estimation

In this subsection, model (1) is used to simulate the reported annual malaria human cases in WHO [23]. Here we use parameter values in Table 2. Some parameters values are chosen based on references, and some are to match the data. We explain part of them in the following.

1. The Birth rate of Congo, DR is 4.103% [21], and the total population of Congo, DR in 2020 is $8.9561 \cdot 10^7$, so that the recruitment is $3.67 \cdot 10^6$.
2. The number of mosquito biting per day is 0.25–0.4 [4]. To fit the model better, we take biting $0.3 \cdot 365$ per year.
3. The life span of human in Congo, DR is 62 [22]. So the corresponding death rate is $1/62$.
4. The average life expectancy of adult mosquito is about 15 to 20 days. Here we take $1/d_2$ to be $15/365$ year.
5. The recovery rate γ is 3 months to 50 years assumed by [4]. Here we take the immunity period to malaria of humans $1/\gamma$ to be 2 years.
6. The average disease induced death rate is $3.3 \cdot 10^{-3}$ by data in Table 1.

Based on these parameter values, we carry out the numerical simulations of our model and obtain a reasonable match between the infected human of model (1) and the malaria data of Congo, DR from 2010 to 2020 in Fig. 5. It indicates that the transmission of malaria in Congo, DR has not arrived at a stable period yet and the disease will become more serious without further control measures.

Moreover, on the basis of parameter values in Table 2, the basic reproduction number of Congo, DR are estimated to be 1.6038. Therefore, according to Theorem 2, the disease in Congo, DR will be endemic and Fig. 5(b) further verifies it. Thus, it is necessary to

carry out research on optimal control strategies, so that reasonable responses can be made from prevention and treatment to eradicate the disease as soon as possible and minimize the loss as much as possible.

5.2 Effect of some control strategies

To eradicate the spread of malaria in Congo, DR as soon as possible and to minimize the corresponding loss as much as possible, we carry out research on optimal control, so the reasonable responses can be made by the government of Congo, DR. In this section, we propose the following strategies to control the spread of malaria in Congo, DR.

- Scenario I: Only one control strategy
  Strategy A: RTS,S malaria vaccine u_1.
  Strategy B: Insecticide-treated mosquito net u_2.
  Strategy C: Treatment of infectious human u_3.
  Strategy D: Insecticide spraying u_4.
- Scenario II: Coupled control strategies
  Strategy E: RTS,S malaria vaccine u_1 and insecticide-treated mosquito net u_2.
  Strategy F: RTS,S malaria vaccine u_1 and treatment of infectious human u_3.
  Strategy G: RTS,S malaria vaccine u_1 and insecticide spraying u_4.
  Strategy H: Insecticide-treated mosquito net u_2 and treatment of infectious human u_3.
  Strategy I: Insecticide-treated mosquito net u_2 and insecticide spraying u_4.
  Strategy J: Treatment of infectious human u_3 and insecticide spraying u_4
- Scenario III: Threefold control strategies
  Strategy K: RTS,S malaria vaccine u_1, insecticide-treated mosquito net u_2, and treatment of infectious human u_3.
  Strategy L: RTS,S malaria vaccine u_1, insecticide-treated mosquito net u_2, and insecticide spraying u_4.
  Strategy M: RTS,S malaria vaccine u_1, treatment of infectious human u_3, and insecticide spraying u_4.
  Strategy N: Insecticide-treated mosquito net u_2, treatment of infectious human u_3, and insecticide spraying u_4.
- Scenario IV: Fourfold control strategies
  Strategy O: RTS,S malaria vaccine u_1, using insecticide-treated mosquito net u_2, treatment of infectious human u_3, and insecticide spraying u_4.

In the following, we obtain the optimal controls numerically by solving model (1), adjoint system (6), (7) and using the characterization of optimal controls (8) by the forward-backward sweep method [13]. In detail, the forward fourth-order Runge–Kutta method is used to solve the state system, and backward fourth-order Runge–Kutta method is used for solving the adjoint system. The adjoint system is solved under the initial assumption of zero controls and obtained solutions of the state system. The controls are updated by taking average of the previous result and the characterizations in (8). This condition continues repeatedly up to the consecutive iteration are negligibly close.

Choose weight constants $\xi_1 = 100$, $\xi_2 = 80$, $\xi_3 = 240$, $\xi_4 = 70$, $A_1 = A_2 = 100$ and use parameter values in Table 2. Additionally, the initial condition values for the state system are taken $S_h(0) = 3\cdot 10^7$, $I_h(0) = 22590646$, $R_h(0) = 3.4\cdot 10^7$, $S_m(0) = 5\cdot 10^6$, $I_m(0) = 3\cdot 10^5$.

Remark 5. It needs to point out that the parameter values used above are in Table 2, which are closely related to the situation in Congo, DR, and the initial values of human population above are taken based on real data in Table 1.

For all the scenarios, we can see from Figs. 6, 7, 9, 10 that the magnitudes of infected humans reduce to lower levels in a way. The control profiles of u_1^*, u_2^*, u_3^*, and u_4^* are also depicted in Fig. 6 and Figs. 8–10.

Moreover, from Fig. 11 and Table 4 we can get the following result: using RTS,S only is the cheapest but the effect is poor; combining all the controls could reduce the infected population to the full extent but is the most expensive; the longer these controls go on the more effective they are.

Remark 6. Actually, for strategy A, that is, using the RTS,S vaccine u_1 only, the effect is poor; see Figs. 6(a), 6(b). This implies that using RTS,S vaccine only is not good enough, people need to change their way of life and apply other interventions such as using insecticide-treated mosquito net in the daily life.

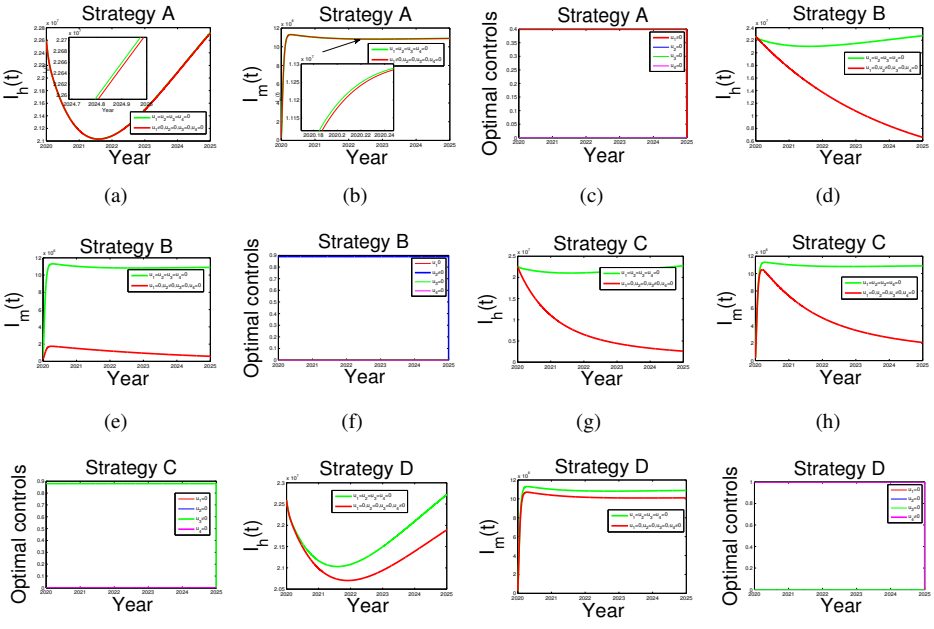


Figure 6. Simulations depicting optimal use of scenario I.

Although the interventions raised above all have good outcomes to some extent, due to limited resources in a country or a city, we need to evaluate which intervention is more economical. Cost-effectiveness analysis is widely used to do this evaluation [15, 16, 18].

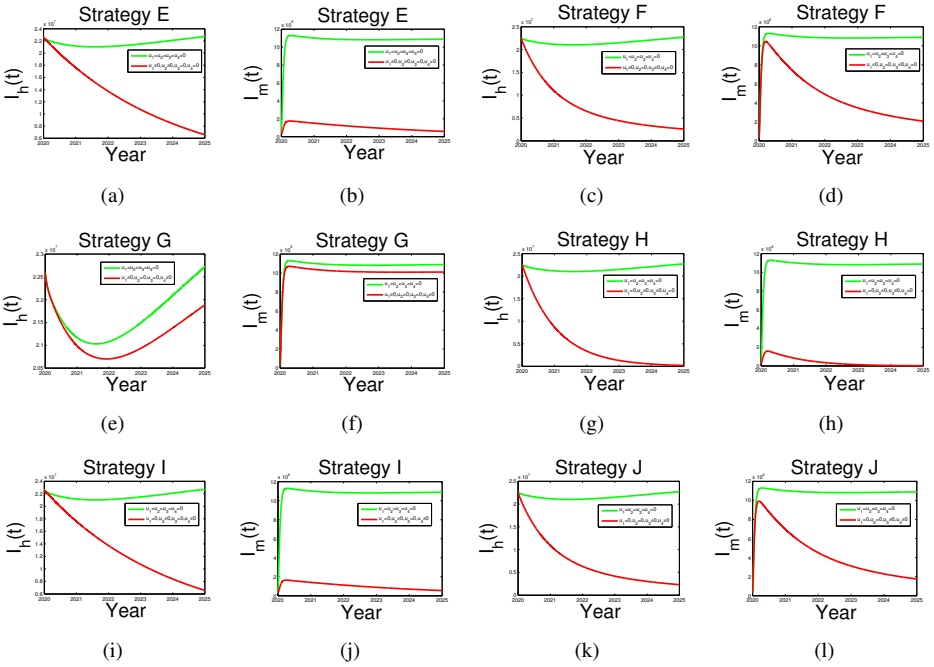


Figure 7. Simulations depicting optimal use of scenario II.

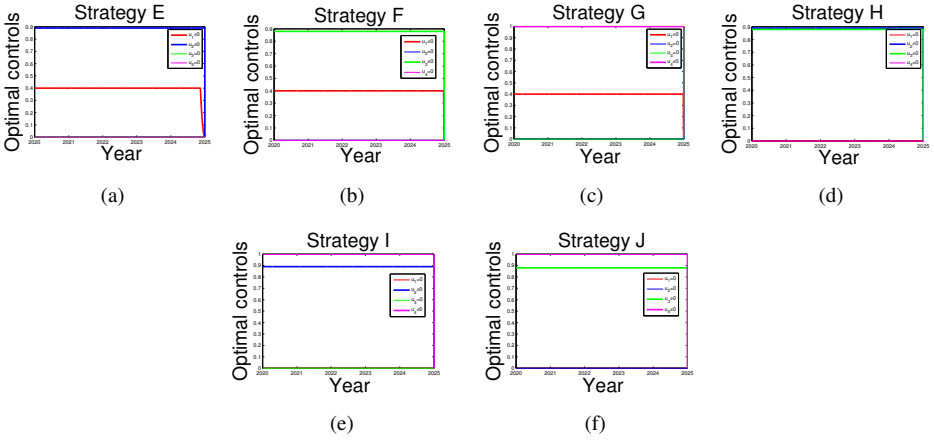


Figure 8. The characterizations of optimal control for scenario II.

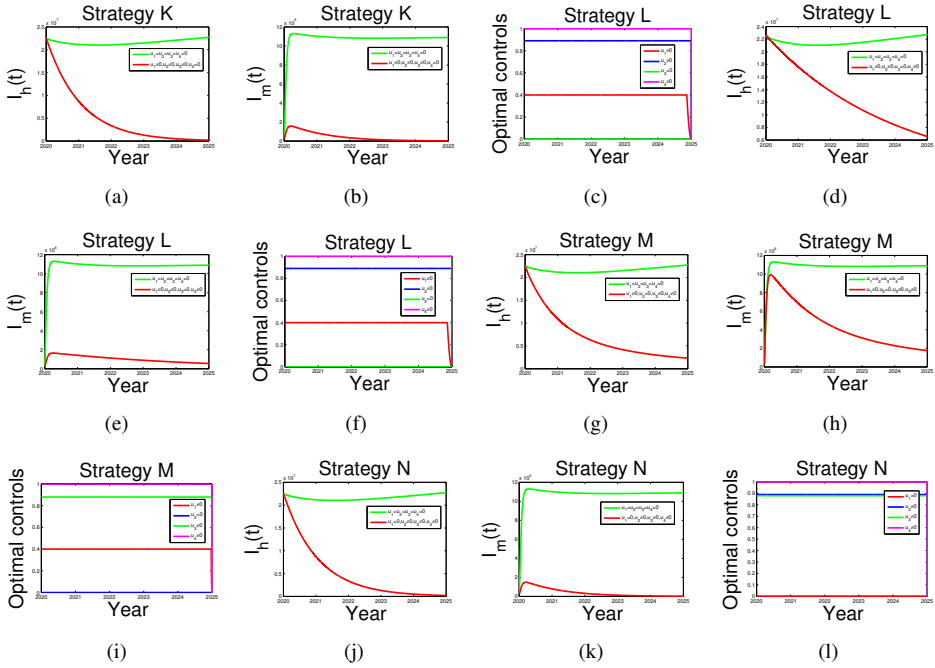


Figure 9. Simulations depicting optimal use of scenarios III.

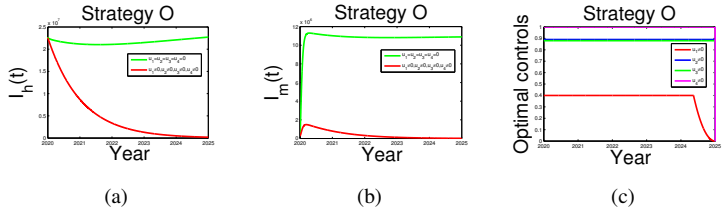


Figure 10. Simulations depicting optimal use of strategy O.

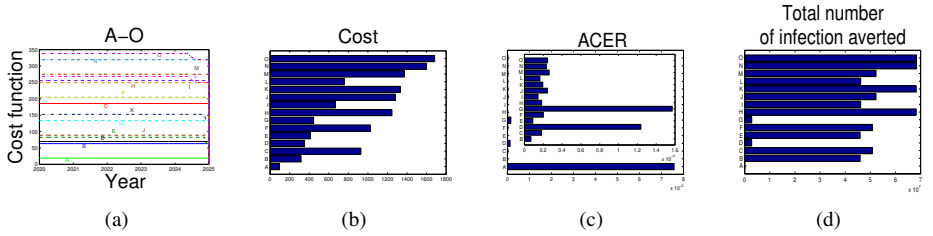


Figure 11. (a) Cost function for strategy A–O; (b) total cost for strategy A–O; (c) average cost-effectiveness ratio; (d) total number of infection averted.

5.3 Cost-effectiveness analysis

In this subsection, two approaches are applied to evaluate which intervention is more economical, that is, the average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER). Cost-effectiveness analysis is widely used to do this evaluation [15, 16, 18].

5.3.1 Average cost-effectiveness ratio (ACER)

The average cost-effectiveness ratio (ACER) deals with a single intervention and evaluates that intervention against its baseline option, namely, no intervention.

$$\mathrm{ACER} = \frac{\text{Total cost produced of scenarios } i}{\text{Total number of infection averted of scenarios } i}.$$

From Table 4 we can see the ACER of each scenarios, and Fig. 11(c) shows more clearly that the most cost-effective strategy is strategy B, and strategy A is the least cost-effective one. To further investigate the cost-effectiveness of the various control strategies, we evaluated the incremental cost-effectiveness ratio (ICER).

5.3.2 Incremental cost-effectiveness ratio (ICER)

The incremental cost effectiveness ratio (ICER)

$$\mathrm{ICER} = \frac{\text{Difference in infection averted costs in scenarios } i \text{ and } j}{\text{Difference in total number of infection averted in scenarios } i \text{ and } j}$$

is used to measure up the changes between costs and benefits of two alternative control strategies and is generally described as the additional cost per additional health outcome. The numerator describe the difference of costs[4] of interventions i and j, while the denominator is the difference of health outcomes. To calculate ICER, we rank the control strategies in increasing order effectiveness according to the total infection averted (see Table 4). Firstly, compare the cost effectiveness of strategy A and strategy G. We have

$$\begin{aligned}\mathrm{ICER(A)} &= \frac{96}{1.2621 \cdot 10^4} = 0.0076,\\ \mathrm{ICER(G)} &= \frac{96 - 445}{1.2621 \cdot 10^4 - 2.8326 \cdot 10^6} = 1.2387 \cdot 10^{-4}.\end{aligned}$$

From ICER(A) and ICER(G) we can see that strategy A is strongly dominated[5] and strategy G saves $1.2387 \cdot 10^{-4}$ than strategy A. Therefore, it is better to exclude strategy A from the set of control strategies and alternative interventions to implement to keep the limited resources. Then we compute the ICER between strategy G and strategy D and get

[4] $\int_0^{\mathrm{T}} (1/2)\Sigma_{i=1}^{4} \xi_i u_i^2 \, \mathrm{d}t$ is the total cost.

[5] The lower ICER for strategy G indicates that strategy A is strongly dominated, that is to say, strategy A is more costly but less effective than strategy G.

Table 4. Total infected averted, total cost, and average cost-effectiveness ratio (ACER).

Strategy	Averted	Total cost	ACER
A	$1.2621 \cdot 10^4$	96	$7.6 \cdot 10^{-3}$
G	$2.8326 \cdot 10^6$	445	$1.5708 \cdot 10^{-4}$
D	$2.8224 \cdot 10^6$	349	$1.2377 \cdot 10^{-4}$
B	$4.5973 \cdot 10^7$	317	$6.8914 \cdot 10^{-6}$
E	$4.5973 \cdot 10^7$	411	$8.9356 \cdot 10^{-6}$
I	$4.61619 \cdot 10^7$	667	$1.4445 \cdot 10^{-5}$
L	$4.61620 \cdot 10^7$	761	$1.6479 \cdot 10^{-5}$
C	$5.0780 \cdot 10^7$	928	$1.8282 \cdot 10^{-5}$
F	$5.0786 \cdot 10^{-7}$	1024	$2.0163 \cdot 10^{-5}$
J	$5.2265 \cdot 10^7$	1279	$2.4466 \cdot 10^{-5}$
M	$5.2269 \cdot 10^7$	1374	$2.6293 \cdot 10^{-5}$
H	$6.827344 \cdot 10^7$	1246	$1.8250 \cdot 10^{-5}$
K	$6.827346 \cdot 10^7$	1333	$1.9519 \cdot 10^{-5}$
N	$6.8341149 \cdot 10^7$	1596	$2.3353 \cdot 10^{-5}$
O	$6.8341167 \cdot 10^7$	1682	$2.4615 \cdot 10^{-5}$

$\mathrm{ICER(G)} = 1.5708 \cdot 10^{-4}$, $\mathrm{ICER(D)} = 0.0094$, so we exclude strategy D. Repeating this process up to the final strategy, we obtain that strategy B is the most cost-effectiveness strategy, which is consistent with the result by ACER.

However, from Fig. 9(b) we can see directly that strategy B reduce 32.73% less infected population than strategy H, K, N, O. In other words, from Fig. 11 we can see that strategy H, K, N, O cause reduction of infected population to the most extent, which is what Congo, DR needs at present. Besides, Fig. 9(b) and Table 4 indicate that strategy O cause reduction of infected population mostly. So we compare the incremental cost-effectiveness ratio between these four strategies and found that strategy K is the most cost-effectiveness. Therefore, if the government see reducing the number infected population as the primary goal, then strategy K is a good choice. Now the policy maker must decide which strategy to use.

6 Conclusions and discussions

As we all know, various control measures are applied to wipe out or control malaria since the great loss caused by malaria for the world. Recently, there are some good news on malaria vaccine, that is, WHO recommend to use the RTS,S malaria vaccine broadly [23]. In this paper, controls of RTS,S vaccine, using insecticide-treated mosquito net, treatment of infectious humans, indoor spraying are incorporated to a malaria transmission model with vector-bias effect.

Our model is used to simulate the reported human malaria cases of Congo, DR. Fifteen strategies are proposed to control the spread of malaria in Congo, DR. In addition, cost-effectiveness analysis suggests that the use of insecticide-treated mosquito net minimizes malaria infection and costs needed for implementation. In summary, based on our analysis, we have some suggestions on the control for malaria in Congo, DR.

1. Using RTS,S vaccine only is not effective to control malaria in Congo, DR at present, and people need to combine it with other interventions such as using insecticide-treated mosquito net to block the transmission.
2. The use of insecticide-treated mosquito net is economy, the government should keep everyone have access to it, especially, for children and people in remote regions.
3. To reduce the number of malaria as many as possible, we suggest combine RTS,S malaria vaccine u_1 with insecticide-treated mosquito net u_2 and treatment of infectious human u_3, and carry out these strategies for sufficiently long time.
4. Persistent financial support is also essential to control malaria in Congo, DR.

Of course, this paper could be extended in some ways. For example, one can study the effect of vaccine as well as the waning of vaccine by adding another compartment in the model.

Appendix

The Jacobian matrix of model (1) at endemic equilibrium $E^*(S_h^*, I_h^*, R_h^*, S_m^*, I_m^*)$ is

$$J^* = \begin{bmatrix} -d_1 - \delta u_1 - A_1 & A_3 & A_5 + \rho & 0 & -A_7 \\ A_1 & -A_3 - q & -A_5 & 0 & A_7 \\ \delta u_1 & \gamma + \tau u_3 & -(\rho + d_1) & 0 & 0 \\ A_2 & -A_4 & A_2 & -A_6 - (d_2 + cu_4) & 0 \\ -A_2 & A_4 & -A_2 & A_6 & -(d_2 + cu_4) \end{bmatrix},$$

where

$$A_1 = \frac{\beta_1 a_1 (\nu I_h^* + R_h^*) I_m^*}{a^2}, \quad A_2 = \frac{\nu a_1 \beta_2 S_m^* I_h^*}{a^2}, \quad A_3 = \frac{\nu \beta_1 a_1 S_h^* I_m^*}{a^2},$$
$$A_4 = \frac{\nu \beta_2 a_1 (S_h^* + R_h^*) S_m^*}{a^2}, \quad A_5 = \frac{\beta_1 a_1 S_h^* I_m^*}{a^2}, \quad A_6 = \frac{\nu \beta_2 a_1 I_h^*}{a}, \quad A_7 = \frac{\beta_1 a_1 S_h^*}{a},$$
$$a = \nu I_h^* + S_h^* + R_h^*, \qquad a_1 = \sigma(1 - u_2), \qquad q = \gamma + d_1 + \alpha + \tau u_3.$$

Then we have the characteristic polynomial of J^*

$$\mathcal{F}(\lambda) := (\lambda + d_2 + cu_4)\big(\lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4\big) = 0,$$

where

$$\begin{aligned} c_1 &= d_2 + cu_4 + \rho + 2d_1 + \delta u_1 + A_1 + A_3 + A_6 + q, \\ c_2 &= A_1(A_6 + d_2 + cu_4 + q + \rho + d_1) + d_1 m + (A_3 + q)(A_6 + d_2 + cu_4) \\ &\quad + A_5(\gamma + \tau u_3 - \delta u_1) - A_2 A_4 - A_4 A_7 \\ &\quad + (A_6 + d_2 + cu_4 + A_3 + q)(d_1 + \delta u_1 + \rho + d_1) \end{aligned}$$

$$
\begin{aligned}
c_3 &= (q+\rho+d_1)\big(A_1(A_6+d_2+cu_4)-A_2A_7\big)\\
&\quad + d_1m(A_3+A_6+q+d_2+cu_4)\\
&\quad + (d_1+m)\big((A_3+q)(A_6+d_2+cu_4)-A_4A_7\big)\\
&\quad - \delta u_1\big(A_5(A_6+d_2+cu_4+q)+A_2A_4\big)-A_1\rho(\gamma+\tau u_3)\\
&\quad + A_1q(\rho+d_1)+(\gamma+\tau u_3)\big(A_5(A_6+d_2+cu_4+d_1+\delta u_1)+A_2A_7\big)\\
c_4 &= \big(A_1(A_6+d_2+cu_4)-A_2A_7\big)\big(q(\rho+d_1)-\rho(\gamma+\tau u_3)\big)\\
&\quad + d_1\big((A_3+q)(A_6+d_2+cu_4)-A_4A_7\big)m\\
&\quad + \big(A_5(A_6+d_2+cu_4)+A_2A_7\big)\big((d_1+\delta u_1)(\gamma+\tau u_3)-\delta u_1q\big)
\end{aligned}
$$

with $m=\rho+d_1+\delta u_1$. Thus, by the Hurwitz principle we have Theorem 3 on the local stability of the endemic equilibrium.

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