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# The roles of maturation delay and vaccination on the spread of Dengue virus and optimal control

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**Abstract**

A mathematical model of Dengue virus transmission between mosquitoes and humans, incorporating a control strategy of imperfect vaccination and vector maturation delay, is proposed in this paper. By using some analytical skills, we obtain the threshold conditions for the global attractiveness of two disease-free equilibria and prove the existence of a positive equilibrium for this model. Further, we investigate the sensitivity analysis of threshold conditions. Additionally, using the Pontryagin maximum principle, we obtain the optimal control strategy for the disease. Finally, numerical simulations are delivered to verify the correctness of the theoretical results, the feasibility of a vaccination control strategy, and the influences of the controlling parameters on the control and elimination of this disease. Theoretical results and numerical simulations show that the vaccination rate and effectiveness of vaccines are two key factors for the control of Dengue spread, and the manufacture of the Dengue vaccine is also architecturally significant.

**Keywords:** Dengue vaccination; maturation delay; disease-free equilibrium and endemic equilibrium; attractiveness and bifurcation; sensitivity and optimal control

## 1 Introduction

Dengue is a vector-borne disease which transcends international borders as the most important arbovirus disease currently threatening human populations. In the light of evolution, at least approximately 50-100 million people are affected by the Dengue virus each year [1]. The Dengue virus is transmitted to humans by mosquitos, mostly the *Aedes aegypti* and *Aedes albopictus*. As far back as 1981, Jousset [2] published geographic locations of *Aedes aegypti* strains and the Dengue virus. To better describe the influences of the Dengue virus, many scholars have investigated Dengue transmission in mathematical models (see [3–5] and the references therein). Particularly, Esteva *et al.* [6] proposed a Dengue virus transmission model and analyzed the global stability of equilibria, and the control measures of the vector population are also discussed in terms of threshold conditions. Further, Wang *et al.* [7] proposed a nonlocal and time-delayed reaction-diffusion model of the Dengue virus, and established threshold dynamics in terms of the basic reproduction number. In addition, Garba *et al.* [8] proposed a deterministic model for the transmission dynamics of a strain of Dengue, which allows for

transmission by exposed humans and mosquitoes. They proved the existence and local asymptotical stability of the disease-free equilibrium if the basic reproduction number is less than unity. The authors also examined the phenomenon of backward bifurcation.

How to control and eliminate the Dengue virus has always been a hot topic. Until now, the available strategy that controls the spread of Dengue virus only controls the vector. Despite combined community participation and vector control, together with active disease surveillance and insecticides, the examples of successful Dengue prevention and control on a national scale are few [1]. Besides, with the increase of vector resistance, the intervals between treatments are shorter. Moreover, as a result of the high costs of development and registration and low gains, only few insecticide products are offered on the market [9]. Considering these realities, vaccination could be more effective to protect against the Dengue virus [10].

It is a well-known fact that vaccination has already been successfully applied to control and eliminate various infectious diseases. Particularly, in 1760, the Swiss mathematician Daniel Bernoulli published an investigation on the impact of immunization with cowpox. Then, the means of protecting people from infection through immunization began to be widely used. In addition, the method has already successfully decreased both mortality and morbidity [11–13]. In fact, during the 1940s, Dengue vaccines were under development. In recent years, however, with the increase in Dengue infections and a serious need for faster development of a vaccine [14], the progress in Dengue vaccines development has amazingly accelerated. To guide public support for vaccine development in both industrialized and developing countries, economic analysis has been conducted, including previous cost-effectiveness studies of Dengue [15–17]. The cost of the disease burden is compared with the possibility of making a vaccination campaign, by the authors of this analytical work; finally, they consider that Dengue vaccines, as a means of intervention, have a potential economic benefit.

On the other hand, there are three successive aquatic juvenile phases (egg, larva and pupa) and one adult pupa of the life cycle of mosquitoes [18]. The duration of the development from egg to adult (1-2 weeks) is often compared to the average life span of an adult mosquito (about 3 weeks). The size of the mosquito population is strongly affected by temperature, and the number of female mosquitoes changes accordingly due to seasonal variations [19, 20]. Therefore, it is vital to consider the maturation time of mosquitoes [21], the length of the larval phase from egg to adult mosquitoes, and the impact on the spread of the Dengue virus.

Based on the above-mentioned information and the immature Dengue vaccine, a delayed mathematical model of dynamical Dengue transmission between mosquitoes and humans, incorporating a control strategy of imperfect vaccination, is proposed in this paper, aiming to discuss the influences of vaccination and a maturation delay for controlling and eliminating the Dengue virus. The rest of the paper is structured as follows. Section 2 describes an imperfect vaccination model with the maturation time of mosquitoes, and the basic properties of this model are presented in Section 3. In Section 4, the threshold conditions and the existence and attractiveness of equilibria of the model are discussed. In Section 5, we will investigate the sensitivity of our threshold conditions. In Section 6, we discuss the optimal control strategy for the disease. Finally,

we give numerical simulations in Section 7, and present some concluding comments in Section 8.

## 2 Model formulation

In this section, we present a mathematical model to study the transmission dynamics of the Dengue virus. The model is based on a susceptible, infectious, recovered and vaccinated structure and explains the transmission process of humans and mosquitoes. Let $S_h(t)$, $I_h(t)$, $R_h(t)$ and $V_h(t)$ denote the numbers of susceptible (individuals who can contract the disease), infectious (individuals who are capable of transmitting the disease), resistant (individuals who have recovered and acquired immunity) and vaccinated (individuals who were vaccinated and are now immune) individuals at time $t$, respectively. Similarly, $S_m(t)$ and $I_m(t)$ represent the numbers of susceptible (mosquitoes able to contract the disease) and infectious (mosquitoes capable of transmitting the disease to humans) adult female mosquitoes at time $t$. Here the total numbers of humans and mosquitoes are denoted by $N_h(t) = S_h(t) + I_h(t) + V_h(t) + R_h(t)$ and $N_m(t) = S_m(t) + I_m(t)$, respectively.

Since the development of mosquitoes from eggs to adults is density dependent, a Ricker type function is taken to ensure the birth rate into the adult mosquitoes. Additionally, let the positive constant $\tau$ be the maturation time of the mosquito, that is, the average time needed for an egg to develop into an adult mosquito. Therefore, the birth rate function of mosquitoes is taken as $r_m N_m(t-\tau)e^{-d_j\tau}e^{-\alpha N_m(t)}$, where the meanings of the parameters can be found in Table 1. For more biological explanation, we refer to [22].

Additionally, for some potentially human infections (such as measles, hepatitis B, influenza, polio, etc.), there has been considerable focus on vaccinating newborns or infected individuals. Therefore, Dengue can be a serious candidate for this type of vaccination. Further, we suppose that a mass vaccination program may be initiated whenever there is an increase of the risk of an epidemic, and the vaccination may reduce but not completely eliminate susceptibility to infection, or the immunity, which is obtained by the vaccination process, is temporary. The new model for the transmission between humans and mosquitoes is given in the flowchart (Figure 1).

**Table 1 Parameter interpretations, value ranges and sources of model (1)**

| Param. | Description | Value | Source |
|---|---|---|---|
| $b$ | Average number of bites by infectious mosquitoes (day$^{-1}$) | [0, 1] | [10] |
| $\beta_{hm}$ | Transmission probability from infectious individuals to mosquitoes | [0, 1] | [10] |
| $\beta_{mh}$ | Transmission probability from infectious mosquitoes to humans | [0, 1] | [10] |
| $1/\mu_h$ | Average human life expectancy (day) | [18250, 27375] | [23] |
| $\eta_h$ | Dengue recovery rate in humans (day$^{-1}$) | [0.1, 0.6] | [23] |
| $1/\alpha$ | Size of mosquitoes at which egg laying is maximized without delay | - | - |
| $r_m$ | Maximum per capita daily mosquito egg production rate (day$^{-1}$) | [0.036, 42.5] | [22] |
| $\tau$ | Maturation time of the mosquito (day) | [5, 30] | [22] |
| $d_j$ | Death rate of juvenile mosquitoes (day$^{-1}$) | [0.28, 0.46] | [22] |
| $d_m$ | Natural death rate of adult female mosquitoes (day$^{-1}$) | [0.016, 0.25] | [23] |
| $q$ | Vertical transmission probability of virus in mosquitoes | [0, 1] | - |
| $\psi$ | Fraction of susceptible class that has been vaccinated | [0, 1] | - |
| $\theta$ | Waning rate of immunity | [0, 1] | - |
| $\sigma$ | Infection rate of vaccinated members | [0, 1] | - |

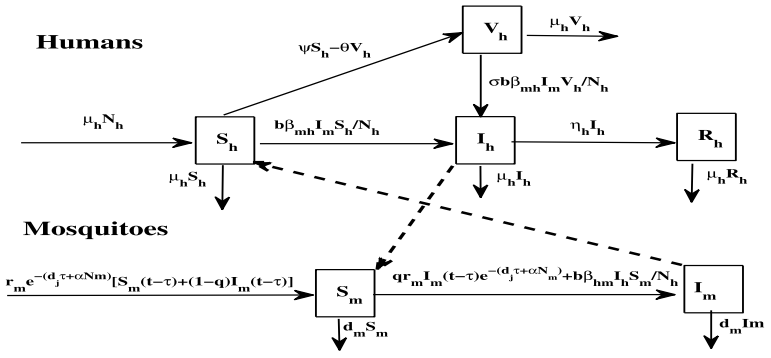


**Figure 1 Flowchart of the transmission of Dengue virus transmission between mosquitoes and humans.**

Based on these considerations, a mathematical model with maturation and imperfect vaccination can be described as

$$\begin{cases} \frac{dS_h(t)}{dt} = \mu_h N_h + \theta V_h(t) - (b\beta_{mh}\frac{I_m(t)}{N_h(t)} + \psi + \mu_h) S_h(t), \\ \frac{dV_h(t)}{dt} = \psi S_h(t) - (\sigma b \beta_{mh}\frac{I_m(t)}{N_h(t)} + \theta + \mu_h) V_h(t), \\ \frac{dI_h(t)}{dt} = b\beta_{mh}\frac{I_m(t)}{N_h(t)}(S_h(t) + \sigma V_h(t)) - (\eta_h + \mu_h) I_h(t), \\ \frac{dR_h(t)}{dt} = \eta_h I_h(t) - \mu_h R_h(t), \\ \frac{dS_m(t)}{dt} = r_m S_m(t-\tau) e^{-d_j \tau} e^{-\alpha N_m(t)} - b\beta_{hm}\frac{I_h(t)}{N_h(t)} S_m(t) - d_m S_m(t) \\ \qquad + (1-q) r_m I_m(t-\tau) e^{-d_j \tau} e^{-\alpha N_m(t)}, \\ \frac{dI_m(t)}{dt} = q r_m I_m(t-\tau) e^{-d_j \tau} e^{-\alpha N_m(t)} + b\beta_{hm}\frac{I_h(t)}{N_h(t)} S_m(t) - d_m I_m(t). \end{cases} \tag{1}$$

The meanings of parameters of model (1) are shown in Table 1. The initial conditions of model (1) are given as

$$\begin{aligned} &S_h(0) > 0, \qquad V_h(0) \geq 0, \qquad I_h(0) \geq 0, \qquad R_h(0) \geq 0, \\ &S_m(\theta) = \phi_s(\theta) > 0, \qquad I_m(\theta) = \phi_i(\theta) > 0, \end{aligned} \tag{2}$$

where $\phi_s(\theta)$ and $\phi_i(\theta)$ are positive continuous functions for $\theta \in [-\tau, 0]$.

## 3 Basic properties

In this section, the basic dynamical features of model (1) will be explored. First, from the first to the fourth equation of this model, we have $dN_h/dt = 0$. Then the total number of humans $N_h(t) := N_h$ is constant. Further, it follows from model (1) that the total number of adult female mosquitoes $N_m(t) = S_m(t) + I_m(t)$ satisfies

$$\frac{dN_m(t)}{dt} = r_m N_m(t-\tau) e^{-d_j \tau} e^{-\alpha N_m(t)} - d_m N_m(t) \tag{3}$$

with the initial condition

$$N_m(\theta) = \phi_s(\theta) + \phi_i(\theta) > 0 \quad \text{for all } \theta \in [-\tau, 0]. \tag{4}$$

Letting

$$N_m^* = \frac{1}{\alpha}\ln\left(\frac{r_m e^{-d_j\tau}}{d_m}\right),$$

it follows that $N_m^*$ is a unique positive equilibrium of equation (3), and it exists if and only if $r_m e^{-d_j\tau} > d_m$.

Now, we define a threshold condition for the mosquito population

$$\mathcal{R}_{01} = \frac{r_m e^{-d_j\tau}}{d_m}.$$

In fact, $\mathcal{R}_{01}$ is the threshold condition of the existence of a positive equilibrium with model (3).

The following theorem describes the global dynamical behavior of model (3).

**Theorem 1** *Solution $N_m(t)$ of model* (3) *with the initial condition* (4) *is positive for any finite time $t \geq 0$. Further,*

(i) *if $\mathcal{R}_{01} \leq 1$, then solution $N_m(t)$ is bounded and the trivial equilibrium $N_m = 0$ is globally asymptotically stable*;

(ii) *if $\mathcal{R}_{01} > 1$, then $h < N_m(t) < H$ for any $t \geq 0$, where*

$$h = \frac{1}{2}\min\left\{\min_{\theta\in[-\tau,0]}\left\{\phi_s(\theta)+\phi_i(\theta)\right\}, N_m^*\right\}, \qquad H = 1+\max\left\{N_m^*, \max_{\theta\in[-\tau,0]}\left\{\phi_s(\theta)+\phi_i(\theta)\right\}\right\}.$$

*Moreover, model* (3) *has a unique positive equilibrium $N_m^*$ which is globally asymptotically stable.*

*Proof* Noting that $N_m(\theta) > 0$ for any $\theta \in [-\tau, 0]$, if there is a $t^* > 0$ such that $N_m(t^*) = 0$ and $N_m(t) > 0$ for all $t < t^*$, then $\mathrm{d}N_m(t^*)/\mathrm{d}t \leq 0$. It follows from (3) that

$$\frac{\mathrm{d}N_m(t^*)}{\mathrm{d}t} = r_m N_m\left(t^*-\tau\right)e^{-d_j\tau} > 0,$$

which leads to a contradiction with $\mathrm{d}N_m(t^*)/\mathrm{d}t \leq 0$. Hence $N_m(t) > 0$ for any finite time $t \geq 0$.

Now we prove (i). Assume that $\mathcal{R}_{01} \leq 1$. We claim that $N_m(t) \leq H$. Otherwise, there is a $t_1 > 0$ such that $N_m(t_1) = H$ and $N_m(t) < H$ for any $t < t_1$. Then we have $\mathrm{d}N_m(t_1)/\mathrm{d}t \geq 0$. From (3), we have

$$\begin{aligned}\frac{\mathrm{d}N_m(t_1)}{\mathrm{d}t} &= r_m N_m(t_1-\tau)e^{-d_j\tau}e^{-\alpha H} - d_m H \leq H\left(r_m e^{-d_j\tau}e^{-\alpha H} - d_m\right)\\ &< H\left(r_m e^{-d_j\tau} - d_m\right) \leq 0,\end{aligned}$$

which leads to a contradiction. Hence $N_m(t) \leq H$ for any $t \geq 0$.

Next we turn to (ii). Assume that $\mathcal{R}_{01} > 1$. We claim that $h < N_m(t) < H$ for any $t \geq 0$. Otherwise, there is a $t_2 > 0$ such that $N_m(t_2) = H$ and $N_m(t) < H$ for any $t < t_2$. From (3), we have

$$\frac{\mathrm{d}N_m(t_2)}{\mathrm{d}t} = r_m N_m(t_2-\tau)e^{-d_j\tau}e^{-\alpha H} - d_m H < H\left(r_m e^{-d_j\tau}e^{-\alpha H} - d_m\right) \leq 0.$$

The last inequality is true since $H > N_m^*$. But the definition of $t_2$ implies that $\mathrm{d}N_m(t_2)/\mathrm{d}t \geq 0$, a contradiction. Hence $N_m(t) < H$ for any $t \geq 0$. Similarly, we assume there is a $\tilde{t} > 0$ such that $N_m(\tilde{t}) = h$ and $N_m(t) > h$ for any $t < \tilde{t}$, and $\mathrm{d}N_m(\tilde{t})/\mathrm{d}t \leq 0$. Again from (3), since $h \leq N_m^*$, we have

$$\frac{\mathrm{d}N_m(\tilde{t})}{\mathrm{d}t} = r_m N_m(\tilde{t}-\tau)e^{-d_j\tau}e^{-\alpha h} - d_m h > h\left(r_m e^{-d_j\tau}e^{-\alpha h} - d_m\right) \geq 0,$$

which leads to a contradiction. Therefore, $h < N_m(t) < H$ for any $t \geq 0$.

In order to prove that the global stability of equilibria $N_m = 0$ and $N_m^*$, we denote the right hand side of (3) as functions $f(N_m(t)$ and $N_m(t-\tau))$. Since $\partial f(x,y)/\partial y > 0$, it follows that (3) generates an eventually strongly monotone semiflow on the space $\mathcal{C}$ of a continuous function on $[-\tau, 0]$ with the usual pointwise ordering (see Smith [24]). If $\mathcal{R}_{01} \leq 1$, there is only a single trivial equilibrium $N_m = 0$. By Theorem 2.3.1 in [24], the equilibrium $N_m = 0$ is globally asymptotically stable. If $\mathcal{R}_{01} > 1$, there are two equilibria $N_m = 0$ and $N_m^*$. By Theorem 2.3.2 in [24], solutions of (3) converge to one of two equilibria. To eliminate the possibility of $N_m = 0$ as an attractor, we linearize the system about $N_m = 0$ and use Theorem A2 in [25] to conclude that it is unstable when $\mathcal{R}_{01} > 1$. Hence $N_m(t) \to N_m^*$ as $t \to \infty$. □

## 4 Existence and attractiveness of equilibria

We define, firstly, a threshold condition for the full model (1) as follows:

$$\mathcal{R}_{02} = \frac{(\theta + \sigma\psi + \mu_h)b^2\beta_{mh}\beta_{hm}N_m^*}{d_m(1-q)(\mu_h + \eta_h)(\theta + \psi + \mu_h)N_h}.$$

In fact, the value of $\mathcal{R}_{02}$ determines the existence of a positive equilibrium of model (1).

For model (1), we get two nontrivial disease-free equilibria, that is, the disease-free equilibrium without mosquitoes $E_{01}$ for $\mathcal{R}_{01} \leq 1$, and the disease-free equilibrium with mosquitoes $E_{02}$ for $\mathcal{R}_{01} > 1$ and $\mathcal{R}_{02} < 1$, where $E_{01}$ and $E_{02}$ are given by

$$E_{01} = \left(\frac{(\theta + \mu_h)N_h}{\psi + \theta + \mu_h}, \frac{\psi N_h}{\psi + \theta + \mu_h}, 0, 0, 0, 0\right),$$
$$E_{02} = \left(\frac{(\theta + \mu_h)N_h}{\psi + \theta + \mu_h}, \frac{\psi N_h}{\psi + \theta + \mu_h}, 0, 0, N_m^*, 0\right).$$

Further, model (1) admits endemic equilibria $E^*(S_{h(1,2)}^*, V_{h(1,2)}^*, I_{h(1,2)}^*, R_{h(1,2)}^*, S_{m(1,2)}^*, I_{m(1,2)}^*)$ for $\mathcal{R}_{01} > 1$ and $\mathcal{R}_{02} > 1$, where

$$S_{h(1,2)}^* = \left(\frac{\sigma b^2\beta_{mh}\beta_{hm}N_m^*I_{h(1,2)}^*}{\psi N_h[d_m(1-q)N_h + b\beta_{hm}I_{h(1,2)}^*]} + \frac{\mu_h + \theta}{\psi}\right)V_{h(1,2)}^*, \qquad R_{h(1,2)}^* = \frac{\eta_h}{\mu_h}I_{h(1,2)}^*,$$
$$I_{m(1,2)}^* = \frac{b\beta_{hm}N_m^*I_{h(1,2)}^*}{d_m(1-q)N_h + b\beta_{hm}I_{h(1,2)}^*}, \qquad S_{m(1,2)}^* = N_m^* - I_{m(1,2)}^*,$$
$$V_{h(1,2)}^* = \frac{(\eta_h + \mu_h)\psi I_{h(1,2)}^*}{(\sigma M + \theta + \mu_h + \sigma\psi)M}, \qquad M = \frac{b^2\beta_{mh}\beta_{hm}N_m^*I_{h(1,2)}^*}{N_h[d_m(1-q)N_h + b\beta_{hm}I_{h(1,2)}^*]},$$

and $I^*_{h(1,2)}$ is obtained by the solutions $I_h$ of the following equation:

$$AI_h^2 + BI_h + C = 0 \tag{5}$$

with

$$\begin{aligned}
A &= b^2\beta_{hm}^2(\mu_h+\eta_h)\big[\big(\sigma b\beta_{mh}N_m^* + (\theta+\mu_h)N_h\big)\big(b\beta_{mh}N_m^* + (\psi+\mu_h)N_h\big) + \theta\psi N_h^2\big],\\
B &= b\beta_{hm}N_h\big\{-\sigma\mu_h b^3\beta_{mh}^2\beta_{hm}N_m^{*2} + 2d_m(1-q)\mu_h(\mu_h+\eta_h)(\psi+\theta+\mu_h)N_h^2\\
&\quad + b\beta_{mh}N_m^*N_h\big[d_m(1-q)(\mu_h+\eta_h)\big(\theta+\mu_h+\sigma(\psi+\mu_h)\big) - \mu_h b\beta_{hm}(\theta+\sigma\psi+\mu_h)\big]\big\},\\
C &= \mu_h d_m(1-q)N_h^3\big[d_m(1-q)(\mu_h+\eta_h)(\psi+\theta+\mu_h)N_h - (\theta+\sigma\psi+\mu_h)b^2\beta_{mh}\beta_{hm}N_m^*\big]\\
&= \mu_h d_m(1-q)N_h^3\frac{1}{d_m(1-q)(\mu_h+\eta_h)(\psi+\theta+\mu_h)N_h}(1-\mathcal{R}_{02}).
\end{aligned}$$

It is obvious that $A>0$ for positive parameters, and $\mathcal{R}_{02}\geq 1$ if and only if $C\leq 0$. Further, if $B>0$ and $C>0$, there is no positive root of equation (5); if $B<0$ and $B^2-4AC>0$, there are two positive roots of equation (5); if $C<0$, there is a unique positive root of equation (5). According to the above-mentioned discussion, we have a conclusion as follows.

**Theorem 2** *If $\mathcal{R}_{01}\leq 1$, then model* (1) *has a unique disease-free equilibrium without mosquitoes $E_{01}$; if $\mathcal{R}_{01}>1$ and $\mathcal{R}_{02}<1$, then model* (1) *has a unique disease-free equilibrium with mosquitoes $E_{02}$. Furthermore, if $\mathcal{R}_{01}>1$, the following statements are valid*:

(i) *if $C\leq 0$, then model* (1) *has a unique endemic equilibrium*;

(ii) *if $B<0$ and $B^2-4AC>0$, then model* (1) *has two endemic equilibria*;

(iii) *if $B>0$ and $C\geq 0$, then model* (1) *has no endemic equilibrium*.

Noting that $C\leq 0$ if and only if $\mathcal{R}_{02}\geq 1$. It is clear from Theorem 2 (Case (i)) that the model has a unique endemic equilibrium if $\mathcal{R}_{01}\geq 1$ and $\mathcal{R}_{02}>1$. Further, Case (ii) indicates the possibility of backward bifurcation (where a local asymptotically stable disease-free equilibrium co-exists with a locally asymptotically stable endemic equilibrium) in model (1) for $\mathcal{R}_{01}\geq 1$ and $\mathcal{R}_{02}<1$. To check for this, the discriminant $B^2-4AC$ is set to zero and solved for the critical value of $\mathcal{R}_{02}$, denoted by $\mathcal{R}_{02}^c$. Thus, backward bifurcation would occur for values of $\mathcal{R}_{02}$ such that $\mathcal{R}_{01}\geq 1$ and $\mathcal{R}_{02}^c<\mathcal{R}_{02}<1$.

To obtain the stability of the equilibria of model (1), we take out the variate of $R_h(t)$ and linearize model (1) about equilibria $(S_h^*, V_h^*, I_h^*, S_m^*, I_m^*)$ and we get the following Jacobian matrix:

$$J=\begin{pmatrix}
a_{11}-\lambda & \theta & 0 & 0 & -b\beta_{mh}\frac{S_h^*}{N_h}\\
\psi & a_{22}-\lambda & 0 & 0 & -\sigma b\beta_{mh}\frac{V_h^*}{N_h}\\
b\beta_{mh}\frac{I_m^*}{N_h} & \sigma b\beta_{mh}\frac{I_m^*}{N_h} & -(\eta_h+\mu_h)-\lambda & 0 & b\beta_{mh}\frac{S_h^*+\sigma V_h^*}{N_h}\\
0 & 0 & -b\beta_{hm}\frac{S_m^*}{N_h} & a_{44}-\lambda & a_{45}\\
0 & 0 & b\beta_{hm}\frac{S_m^*}{N_h} & a_{54} & a_{55}-\lambda
\end{pmatrix},$$

where

$$a_{11} = -\left(b\beta_{mh}\frac{I_m^*}{N_h} + \psi + \mu_h\right), \qquad a_{22} = -\left(\sigma b\beta_{mh}\frac{I_m^*}{N_h} + \theta + \mu_h\right),$$
$$a_{45} = r_m e^{-(d_j\tau+\alpha N_m^*)}\left[(1-q)e^{-\lambda\tau} - \alpha N_m^* + \alpha q I_m^*\right],$$
$$a_{54} = b\beta_{hm}\frac{I_h(t)}{N_h} - \alpha q I_m^*(t-\tau)e^{-(d_j\tau+\alpha N_m^*)},$$
$$a_{44} = r_m e^{-(d_j\tau+\alpha N_m^*)}\left(e^{-\lambda\tau} - \alpha N_m^* + \alpha q I_m^*\right) - d_m,$$
$$a_{55} = q r_m e^{-(d_j\tau+\alpha N_m^*)}\left(e^{-\lambda\tau} - \alpha I_m^*\right) - d_m,$$

and $\lambda$ is an eigenvalue. We obtain the characteristic equation about $E_{01}$ according to the Jacobian matrix of model (1)

$$F(\lambda) = (\lambda + \eta_h + \mu_h)\left[\lambda^2 + (\theta + \psi + 2\mu_h)\lambda + (\theta + \psi + \mu_h)\mu_h\right] \times \left(\lambda + d_m - q r_m e^{-(d_j+\lambda)\tau}\right)\left(\lambda + d_m - r_m e^{-(d_j+\lambda)\tau}\right).$$

To continue, we recall Theorem 4.7 in [26], which states that $\lambda = A + Be^{-\lambda\tau}$ has a root with positive real part if $A + B > 0$, and has no roots with nonnegative real parts if $A + B < 0$ and $B \geq A$. By this theorem, we see that all roots of the above characteristic equation have negative real parts for $\mathcal{R}_{01} < 1$. Therefore, $E_{01}$ is asymptotically stable.

Now, on the globally asymptotically stable disease-free equilibrium without mosquitoes $E_{01}$ of model (1), we have Theorem 3.

**Theorem 3** *If $\mathcal{R}_{01} < 1$, then model* (1) *has a unique disease-free equilibrium without mosquitoes $E_{01}$, which is globally asymptotically stable.*

*Proof* It obvious that $\lim_{t\to\infty} S_m(t) = \lim_{t\to\infty} I_m(t) = 0$ for $\mathcal{R}_{01} < 1$ depending on Theorem 1. So we merely prove that

$$\lim_{t\to\infty} S_h(t) = \frac{(\theta + \mu_h)N_h}{(\psi + \theta + \mu_h)}, \qquad \lim_{t\to\infty} V_h(t) = \frac{\psi N_h}{(\psi + \theta + \mu_h)}, \tag{6}$$

and

$$\lim_{t\to\infty} I_h(t) = \lim_{t\to\infty} R_h(t) = 0.$$

Due to $\lim_{t\to\infty} I_m(t) = 0$, for a small enough positive constant $\epsilon$, there is a constant $T > 0$ such that $I_m(t) < \epsilon$, for all $t > T$. Then, from the third equation of model (1), we have

$$\frac{\mathrm{d}I_h(t)}{\mathrm{d}t} < b\beta_{mh}\epsilon - (\mu_h + \eta_h)I_h(t), \quad \text{for all } t > T.$$

By the comparison theorem and the arbitrariness of $\epsilon$, we have $\lim_{t\to\infty} I_h(t) = 0$. Further, it follows that $\lim_{t\to\infty} R_h(t) = 0$.

From the first and second equations of model (1), we have

$$\begin{aligned}&\mu_h N_h + \theta V_h(t) - \left(b\beta_{mh}\frac{\epsilon}{N_h} + \psi + \mu_h\right)S_h(t)\\ &\quad\le \frac{\mathrm{d}S_h(t)}{\mathrm{d}t} \le \mu_h N_h + \theta V_h(t) - (\psi + \mu_h)S_h(t)\end{aligned}$$

and

$$\psi S_h(t) - \left(\sigma b\beta_{mh}\frac{\epsilon}{N_h} + \theta + \mu_h\right)V_h(t) \le \frac{\mathrm{d}V_h(t)}{\mathrm{d}t} \le \psi S_h(t) - (\theta + \mu_h)V_h(t).$$

Then it is easy to see that (6) is valid, that is, $E_{01}$ is globally attractive. This completes the proof. □

Finally, we give a conclusion on the global attractiveness of the disease-free equilibrium with mosquitoes $E_{02}$ of model (1).

**Theorem 4** *Supposing that* $\mathcal{R}_{01} > 1$. *If*

$$\mathcal{R}^*_{02} := \frac{b^2\beta_{mh}\beta_{hm}N^*_m}{d_m(1 - qe^{d_m\tau})(\mu_h + \eta_h)N_h} < 1,$$

*then model* (1) *has a unique disease-free equilibrium with mosquitoes* $E_{02}$, *which is globally attractive*.

*Proof* From the expressions of $\mathcal{R}_{02}$ and $\mathcal{R}^*_{02}$, we get $\mathcal{R}_{02} < 1$ for $\mathcal{R}^*_{02} < 1$. Therefore, model (1) has a unique disease-free equilibrium with mosquitoes $E_{02}$ for $\mathcal{R}^*_{02} < 1$ and $\mathcal{R}_{01} > 1$. From the sixth equation of model (1) we get

$$\frac{\mathrm{d}I_m(t)}{\mathrm{d}t} \ge -d_m I_m(t).$$

By integrating the above inequality from $t - \tau$ to $t$, we obtain $I_m(t - \tau) \le e^{d_m\tau}I_m(t)$. Then

$$\begin{cases}\frac{\mathrm{d}I_m(t)}{\mathrm{d}t} \le d_m(qe^{d_m\tau} - 1)I_m(t) + b\beta_{hm}\frac{N^*_m}{N_h}I_h(t),\\ \frac{\mathrm{d}I_h(t)}{\mathrm{d}t} \le b\beta_{mh}I_m(t) - (\eta_h + \mu_h)I_h(t).\end{cases}$$

Consider the following auxiliary system:

$$\begin{cases}\frac{\mathrm{d}u(t)}{\mathrm{d}t} = d_m(qe^{d_m\tau} - 1)u(t) + b\beta_{hm}\frac{N^*_m}{N_h}v(t),\\ \frac{\mathrm{d}v(t)}{\mathrm{d}t} = b\beta_{mh}u(t) - (\eta_h + \mu_h)v(t).\end{cases} \tag{7}$$

It is obvious that the equilibrium $(0, 0)$ always exists. The characteristic equation of model (7) about $(0, 0)$ is

$$I(\lambda) = \lambda^2 + (b_2 - a_1)\lambda - (b_2a_1 + a_2b_1) = 0, \tag{8}$$

where $a_1 = d_m(qe^{d_m\tau} - 1)$, $a_2 = b\beta_{hm}N_m^*/N_h$, $b_1 = b\beta_{mh}$ and $b_2 = \eta_h + \mu_h$. To obtain two negative solutions about (8), it is required that

$$\lambda_1 + \lambda_2 = a_1 - b_2 < 0, \qquad \lambda_1 \cdot \lambda_2 = -(b_2a_1 + a_2b_1) > 0.$$

So we see that the equilibrium $(0,0)$ of model (7) is globally asymptotically stable for $\mathcal{R}_{02}^* < 1$.

According to the above discussion and the comparison theorem of differential equations, we know that $\lim_{t\to\infty} I_m(t) = 0$ and $\lim_{t\to\infty} I_h(t) = 0$ for $\mathcal{R}_{01} > 1$ and $\mathcal{R}_{02}^* < 1$. Finally, in the light of Theorem 1, we get $\lim_{t\to\infty}(S_h(t), I_h(t), V_h(t), R_h(t), S_m(t), I_m(t)) = E_{02}$. This completes the proof. □

**Remark 1** Obviously, $qe^{d_m\tau} \approx q$ due to the small vertical transmission probability $q$ according to existing literature, therefore $\mathcal{R}_{02} \approx \mathcal{R}_{02}^*$.

To discuss the stability of the endemic equilibrium $E^*$, we write the corresponding characteristic equation for $E^*$ as follows:

$$\begin{aligned}
H(\lambda) = {} & \left[\lambda + d_m\left(1 + \alpha N_m^* - e^{-\lambda\tau}\right)\right]\Bigg\{(\lambda + \mu_h)\Bigg\{\Bigg[(\lambda + \mu_h + \eta_h)\Bigg(\lambda + d_m\left(1 - qe^{-\lambda\tau}\right) \\
& + b\beta_{hm}\frac{I_{h(1,2)}^*}{N_h}\Bigg) - b^2\beta_{mh}\beta_{hm}\frac{S_{m(1,2)}^*(S_{h(1,2)}^* + \sigma V_{h(1,2)}^*)}{N_h^2}\Bigg]\Bigg[\lambda^2 + \Bigg((1+\sigma)b\beta_{mh}\frac{I_{m(1,2)}^*}{N_h} \\
& + \psi + \theta + \mu_h\Bigg)\lambda + b\beta_{mh}\frac{I_{m(1,2)}^*}{N_h}\left(\sigma b\beta_{mh}\frac{I_{m(1,2)}^*}{N_h} + \theta + \sigma\psi + \mu_h\right)\Bigg] \\
& + \sigma b^3\beta_{mh}^2\beta_{hm}\frac{V_{h(1,2)}^*I_{m(1,2)}^*S_{m(1,2)}^*}{N_h^3}\left[\sigma\left(\lambda + b\beta_{mh}\frac{I_{m(1,2)}^*}{N_h} + \psi\right) + \theta + \mu_h\right]\Bigg\} \\
& - \mu_h b\beta_{mh}\frac{I_{m(1,2)}^*}{N_h}(\lambda + \mu_h + \eta_h)\left[\lambda + d_m\left(1 - qe^{-\lambda\tau}\right) + b\beta_{hm}\frac{I_{h(1,2)}^*}{N_h}\right] \\
& \times\left[\lambda + \sigma b\beta_{mh}\frac{I_{m(1,2)}^*}{N_h} + \theta + \sigma\psi + \mu_h\right]\Bigg\} = 0. \qquad (9)
\end{aligned}$$

Nevertheless, the study of solving this transcendental equation (9) is very difficult. And though we get the conditions by math software, it is not difficult to imagine that the conditions are very complex. Of course, it is very difficult to make a rational interpretation on biology. So the solving of (9) is insignificant, and we omit it.

## 5 Description of sensitivity analysis

Sensitivity indices enable us to measure the relative change in a state variable when a model parameter changes. The normalized forward sensitivity index of a variable to a model parameter is the ratio of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

**Definition 1** (Sensitivity index [27]) The normalized forward sensitivity index of a variable, $u$, that depends differentiably on a parameter, $p$, is defined as

$$\gamma_p^u := \frac{\partial u}{\partial p} \times \frac{p}{u}. \qquad (10)$$

**Table 2 Sensitivity indices of $\mathcal{R}_{02}$ and $\mathcal{R}^*_{02}$ to the parameter values for model (1)**

| Variable | Parameter | Sensitivity index | Variable | Parameter | Sensitivity index |
|---|---|---|---|---|---|
| $\mathcal{R}_{02}$ | $\theta$ | 0.06051 | $\mathcal{R}^*_{02}$ | $\theta$ | - |
| | $\sigma$ | 0.92280 | | $\sigma$ | - |
| | $\psi$ | −0.06075 | | $\psi$ | - |
| | $q$ | 0.01010 | | $q$ | 0.01237 |
| | $\tau$ | - | | $\tau$ | 0.0025 |
| | $b$ | 2 | | $b$ | 2 |
| | $\beta_{mh}$ | 1 | | $\beta_{mh}$ | 1 |
| | $\beta_{hm}$ | 1 | | $\beta_{hm}$ | 1 |

Table 2 represents sensitivity indices of model parameters to $\mathcal{R}_{02}$ and $\mathcal{R}^*_{02}$, as the values of parameters for model (1) are fixed as: $b = 0.8$, $\beta_{mh} = \beta_{hm} = 0.375$, $\mu_h = 0.00004$, $\eta_h = 0.2$, $\tau = 10$, $d_m = 0.02$, $q = 0.01$, $\sigma = 0.2$, $\theta = 0.01$ and $\psi = 0.6$.

Note from Table 2 that $\mathcal{R}_{02}$ and $\mathcal{R}^*_{02}$ all show the greatest sensitivities to the biting rate $b$, followed by the transmission probabilities $\beta_{mh}$ and $\beta_{hm}$. Accordingly, a reduction of 1% in the biting rate $b$ decreases $\mathcal{R}_{02}$ by 2%, which equals the decrease in $\mathcal{R}^*_{02}$ when identically varying the biting rate parameter $b$; further, a reduction of 1% in the transmitting rate $\beta_{mh}$ or $\beta_{hm}$ decreases $\mathcal{R}_{02}$ and $\mathcal{R}^*_{02}$ both by 1%. Next, a reduction of 1% in the waning rate $\theta$ decreases $\mathcal{R}_{02}$ by 0.06051%, a reduction of 1% in the infection rate of vaccinated members $\sigma$ decreases $\mathcal{R}_{02}$ by 0.92280%, and a reduction of 1% of the vaccinated fraction of the susceptible class $\psi$ increases $\mathcal{R}_{02}$ by 0.06075%. Lastly, a reduction of 1% in the vertical transmission probability $q$ decreases $\mathcal{R}_{02}$ and $\mathcal{R}^*_{02}$ by 0.01010% and 0.01237%, respectively; a reduction of 1% in the maturation time of the mosquito $\tau$ decreases $\mathcal{R}^*_{02}$ by 0.0025%.

Obviously, the sensitivity index of the infection rate of vaccinated members $\sigma$ exceeds that of the fraction $\psi$ of the susceptible class that was vaccinated, though the value of $\sigma$ ($\sigma = 0.2$) is smaller than the value of $\psi$ ($\psi = 0.6$). The sensitivity index of the fraction $\psi$ of the susceptible class that was vaccinated is substantial near the sensitivity index of the waning rate $\theta$ for the values above. Then the sensitivity index of the vertical transmission probability $q$ is very small. This is perhaps related to the small value of $q$ ($q = 0.01$). The sensitivity level of $\tau$ is the smallest, that is, the maturation time of the mosquito has less effect on the variation of $\mathcal{R}^*_{02}$.

## 6 Analysis of optimal vaccination

Optimal control techniques are of great use in developing the optimal strategies to prevent the spread of the Dengue virus. To face the challenges of obtaining an optimal control strategy, we make the following notational conventions. Suppose $t_f$ and $\triangle$ are given constants and define an admissible control set $U = \{\psi(t) \text{ is measurable}, 0 \le \psi(t) \le \triangle, t \in [0, t_f]\}$. Here $\psi(t)$ is called a control variable, to reduce or even eradicate the disease, and to find a suitable compromise between minimal number of the infected individuals and the costs of the campaign. The objective function is given by

$$\min J[\psi] = \int_0^{t_f} \left[\gamma_D I_h(t)^2 + \gamma_V \psi(t)^2\right] \mathrm{d}t, \tag{11}$$

subject to

$$\begin{cases} \frac{\mathrm{d}S_h(t)}{\mathrm{d}t} = \mu_h N_h + \theta V_h(t) - (b\beta_{mh}\frac{I_m(t)}{N_h(t)} + \psi(t) + \mu_h)S_h(t), \\ \frac{\mathrm{d}V_h(t)}{\mathrm{d}t} = \psi(t)S_h(t) - (\sigma b\beta_{mh}\frac{I_m(t)}{N_h(t)} + \theta + \mu_h)V_h(t), \\ \frac{\mathrm{d}I_h(t)}{\mathrm{d}t} = b\beta_{mh}\frac{I_m(t)}{N_h(t)}(S_h(t) + \sigma V_h(t)) - (\eta_h + \mu_h)I_h(t), \\ \frac{\mathrm{d}R_h(t)}{\mathrm{d}t} = \eta_h I_h(t) - \mu_h R_h(t), \\ \frac{\mathrm{d}S_m(t)}{\mathrm{d}t} = r_m S_m(t-\tau)e^{-d_j\tau}e^{-\alpha N_m(t)} - b\beta_{hm}\frac{I_h(t)}{N_h(t)}S_m(t) - d_m S_m(t) \\ \qquad\quad + (1-q)r_m I_m(t-\tau)e^{-d_j\tau}e^{-\alpha N_m(t)}, \\ \frac{\mathrm{d}I_m(t)}{\mathrm{d}t} = qr_m I_m(t-\tau)e^{-d_j\tau}e^{-\alpha N_m(t)} + b\beta_{hm}\frac{I_h(t)}{N_h(t)}S_m(t) - d_m I_m(t), \end{cases} \tag{12}$$

with the initial condition (2). Here, positive constants $\gamma_D$ and $\gamma_V$ represent the weights of the costs of treatment of infected individuals and vaccination, respectively. Since the state variables are continuous, the solutions of the control system are bounded. Also, the objective function is convex in the control $\psi(t)$. Hence, the existence of the optimal control comes as a direct result from the Filippove-Cesari theorem [28–31]. We, therefore, have the following result.

**Theorem 5** *There is an optimal control $\psi^*(t)$ such that $J(\psi^*(t)) = \min J(\psi(t))$, subject to the control system* (12) *with the initial condition* (2).

In order to find the optimal solution, we find that the Lagrangian and Hamiltonian methods serve for the optimal control problem (11) with (12). In fact, the Lagrangian of the optimal problem is given by

$$\widetilde{L}(I_h, \psi) = \gamma_D I_h(t)^2 + \gamma_V \psi(t)^2.$$

To find the optimal control function for the optimal control problem, we define the corresponding Hamiltonian as

$$\begin{aligned} &H(S_h, V_h, I_h, R_h, S_m, I_m, \lambda, \psi) \\ &\quad = \gamma_D I_h^2 + \gamma_V \psi^2 + \lambda_1\left[\mu_h N_h + \theta V_h(t) - \left(b\beta_{mh}\frac{I_m(t)}{N_h} + \psi + \mu_h\right)S_h(t)\right] \\ &\qquad + \lambda_2\left[\psi S_h(t) - \left(\sigma b\beta_{mh}\frac{I_m(t)}{N_h} + \theta + \mu_h\right)V_h(t)\right] \\ &\qquad + \lambda_3\left[b\beta_{mh}\frac{I_m(t)}{N_h}\big(S_h(t) + \sigma V_h(t)\big) - (\eta_h + \mu_h)I_h(t)\right] \\ &\qquad + \lambda_4\big(\eta_h I_h(t) - \mu_h R_h(t)\big) + \lambda_5\left[r_m S_m(t-\tau)e^{-d_j\tau}e^{-\alpha N_m(t)}\right. \\ &\qquad \left. - b\beta_{hm}\frac{I_h(t)}{N_h}S_m(t) - d_m S_m(t) + (1-q)r_m I_m(t-\tau)e^{-d_j\tau}e^{-\alpha N_m(t)}\right] \\ &\qquad + \lambda_6\left[qr_m I_m(t-\tau)e^{-d_j\tau}e^{-\alpha N_m(t)} + b\beta_{hm}\frac{I_h(t)}{N_h}S_m(t) - d_m I_m(t)\right], \end{aligned} \tag{13}$$

where $\lambda_i(\cdot)$, $i = 1, \ldots, 6$, are the adjoint functions to be determined suitably.

Now, let us derive a necessary condition for the optimal control strategy by means of the Pontryagin maximum principle [32]. Similar proof methods can also be found in [33–35] and the references therein.

**Theorem 6** *Given an optimal control variable* $\psi^*(t)$ *and the corresponding solution* $(\widetilde{S}_h(\cdot), \widetilde{V}_h(\cdot), \widetilde{I}_h(\cdot), \widetilde{R}_h(\cdot), \widetilde{S}_m(\cdot), \widetilde{I}_m(\cdot))$ *of state system* (12), *there are adjoint functions* $\lambda_i(\cdot)$, $i = 1, \dots, 6$, *satisfying*

$$
\begin{cases}
\frac{\mathrm{d}\lambda_1(t)}{\mathrm{d}t} = (\lambda_1 - \lambda_3) b\beta_{mh} \frac{\widetilde{I}_m(t)}{N_h} + (\lambda_1 - \lambda_2)\psi^* + \lambda_1 \mu_h, \\
\frac{\mathrm{d}\lambda_2(t)}{\mathrm{d}t} = (\lambda_2 - \lambda_1)\theta + (\lambda_2 - \lambda_3)\sigma b\beta_{mh} \frac{\widetilde{I}_m(t)}{N_h} + \lambda_2 \mu_h, \\
\frac{\mathrm{d}\lambda_3(t)}{\mathrm{d}t} = -2\gamma_D \widetilde{I}_h(t) + (\lambda_3 - \lambda_4)\eta_h + \lambda_3 \mu_h + (\lambda_5 - \lambda_6) b\beta_{hm} \frac{\widetilde{S}_m(t)}{N_h}, \\
\frac{\mathrm{d}\lambda_4(t)}{\mathrm{d}t} = \lambda_4 \mu_h, \\
\frac{\mathrm{d}\lambda_5(t)}{\mathrm{d}t} = (\lambda_5 - \lambda_6)\big(b\beta_{hm} \frac{\widetilde{I}_h(t)}{N_h} - \alpha q r_m \widetilde{I}_m(t-\tau) e^{-d_j \tau} e^{-\alpha \widetilde{N}_m(t)}\big) \\
\qquad + \lambda_5 [r_m e^{-d_j \tau} e^{-\alpha \widetilde{N}_m(t)} (\alpha \widetilde{N}_m(t-\tau) - 1) + d_m] \\
\qquad - \Phi_{[0, t_f - \tau]}(t) r_m e^{-(d_j \tau + \alpha \widetilde{N}_m(t))} \lambda_5(t+\tau), \\
\frac{\mathrm{d}\lambda_6(t)}{\mathrm{d}t} = (\lambda_1 - \lambda_3) b\beta_{mh} \frac{\widetilde{S}_h(t)}{N_h} + (\lambda_2 - \lambda_3)\sigma b\beta_{mh} \frac{\widetilde{V}_h(t)}{N_h} + \lambda_5 r_m e^{-d_j \tau} e^{-\alpha \widetilde{N}_m(t)} [\alpha \widetilde{S}_m(t-\tau) \\
\qquad + (1-q)(\alpha \widetilde{I}_m(t-\tau) - 1)] + \lambda_6 [q r_m e^{-d_j \tau} e^{-\alpha \widetilde{N}_m(t)} (\alpha \widetilde{I}_m(t-\tau) - 1) + d_m] \\
\qquad - \Phi_{[0, t_f - \tau]}(t) r_m e^{-(d_j \tau + \alpha \widetilde{N}_m(t))} [(1-q)\lambda_5(t+\tau) + q\lambda_6(t+\tau)],
\end{cases}
\tag{14}
$$

*and the transversality conditions* $\lambda_i(t_f) = 0$, $i = 1, \dots, 6$. *Here* $\Phi_{[0, t_f - \tau]}(t) = 1$ *if* $t \in [0, t_f - \tau]$. *Otherwise* $\Phi_{[0, t_f - \tau]}(t) = 0$. *Furthermore*,

$$
\psi^*(t) = \min\left\{ \triangle, \max\left\{ 0, \frac{(\lambda_1 - \lambda_2)\widetilde{S}_h(t)}{2\gamma_V} \right\} \right\}. \tag{15}
$$

*Proof* To determine the adjoint equations and transversality conditions, we use the Hamiltonian (13). We obtain the adjoint system as follows:

$$
\begin{aligned}
\frac{\mathrm{d}\lambda_1(t)}{\mathrm{d}t} &= \frac{\partial H}{\partial S_h} - \Phi_{[0, t_f - \tau]}(t) \frac{\partial H}{\partial S_h(t-\tau)}(t+\tau), \\
\frac{\mathrm{d}\lambda_2(t)}{\mathrm{d}t} &= \frac{\partial H}{\partial V_h} - \Phi_{[0, t_f - \tau]}(t) \frac{\partial H}{\partial V_h(t-\tau)}(t+\tau), \\
\frac{\mathrm{d}\lambda_3(t)}{\mathrm{d}t} &= \frac{\partial H}{\partial I_h} - \Phi_{[0, t_f - \tau]}(t) \frac{\partial H}{\partial I_h(t-\tau)}(t+\tau), \\
\frac{\mathrm{d}\lambda_4(t)}{\mathrm{d}t} &= \frac{\partial H}{\partial R_h} - \Phi_{[0, t_f - \tau]}(t) \frac{\partial H}{\partial R_h(t-\tau)}(t+\tau), \\
\frac{\mathrm{d}\lambda_5(t)}{\mathrm{d}t} &= \frac{\partial H}{\partial S_m} - \Phi_{[0, t_f - \tau]}(t) \frac{\partial H}{\partial S_m(t-\tau)}(t+\tau), \\
\frac{\mathrm{d}\lambda_6(t)}{\mathrm{d}t} &= \frac{\partial H}{\partial I_m} - \Phi_{[0, t_f - \tau]}(t) \frac{\partial H}{\partial I_m(t-\tau)}(t+\tau).
\end{aligned}
$$

Thus, the adjoint system can be rewritten as system (14). By the optimal conditions, we have

$$
\left. \frac{\partial H}{\partial \psi} \right|_{\psi = \psi^*(t)} = 2\gamma_V \psi^*(t) - (\lambda_1 - \lambda_2)\widetilde{S}_h(t) = 0.
$$

It follows that

$$\psi^*(t) = \min\left\{\triangle, \max\left\{0, \frac{(\lambda_1 - \lambda_2)\widetilde{S}_h(t)}{2\gamma_V}\right\}\right\}.$$

Considering the feature of the admissible control set $U$, we obtain (15). Thus we complete the proof. □

## 7 Numerical simulation and discussion

We perform some numerical simulations to illustrate the main theoretical results above for stability of equilibria using the Runge-Kutta method with the software MATLAB. According to the possible values of model (1) from Table 1, the values of the model parameters are listed in Table 3. We choose the parameters $N_m^* \approx 1452300$ and $N_h \approx 480000$.

First, from the values of the parameters in Table 3, it is easy to see that $\mathcal{R}_{01} \approx 0.9330 < 1$. Thus from the theoretical conclusion of Theorem 3, we know that the disease-free equilibrium without mosquito $E_{01}$ of model (1) is globally attractive. That is, infectious individuals and the total number of mosquitoes are all decreasing to zero eventually for any initial value. The plots in Figures 2(a) and 2(b) coincide with the theoretical result. We choose, however, model parameters $\tau = 10$, $b = 0.5$, $\beta_{mh} = 0.1$ and $\beta_{hm} = 0.1$, and other parameters are fixed as in Table 3. It is easy to calculate $\mathcal{R}_{01} \approx 5.9336 > 1$ and $\mathcal{R}_{02}^* \approx 0.4591 < 1$. Then the conditions of Theorem 4 are valid. Therefore, the disease-free equilibrium with mosquitoes $E_{02}$ is globally attractive. Theoretical result and numerical simulations in Figures 3(a) and 3(b) imply that infectious individuals and infectious mosquitoes are decreasing to zero eventually, whereas the number of susceptible mosquitoes are not decreasing to zero.

Further, letting $\tau = 5$, $b = 1$ and $\theta = 0.375$, while other parameters are fixed as in Table 3, we get $\mathcal{R}_{01} \approx 37.7369 > 1$ and $\mathcal{R}_{02} \approx 1.3698 > 1$ by direct calculation. The plots in Fig-

**Table 3 The parameter values for model (1)**

| Parameter | $b$ | $\beta_{mh}$ | $\beta_{hm}$ | $\psi$ | $\sigma$ | $\theta$ | $\tau$ |
|---|---|---|---|---|---|---|---|
| Value | 0.8 | 0.375 | 0.375 | 0.6 | 0.05 | 1/365 | 12 |
| Parameter | $q$ | $\eta_h$ | $\mu_h$ | $\alpha$ | $r_m$ | $d_j$ | $d_m$ |
| Value | 0.007 | 1/3 | 1/(71 × 365) | 0.0000025 | 15 | 0.37 | 0.05 |

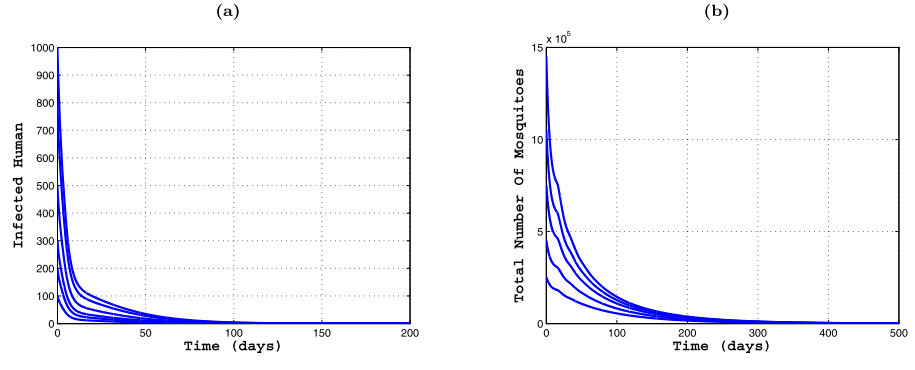


**Figure 2 The global attractiveness of the disease-free equilibrium without mosquitoes $E_{01}$ of model (1), where $\mathcal{R}_{01} \approx 0.9330 < 1$.**

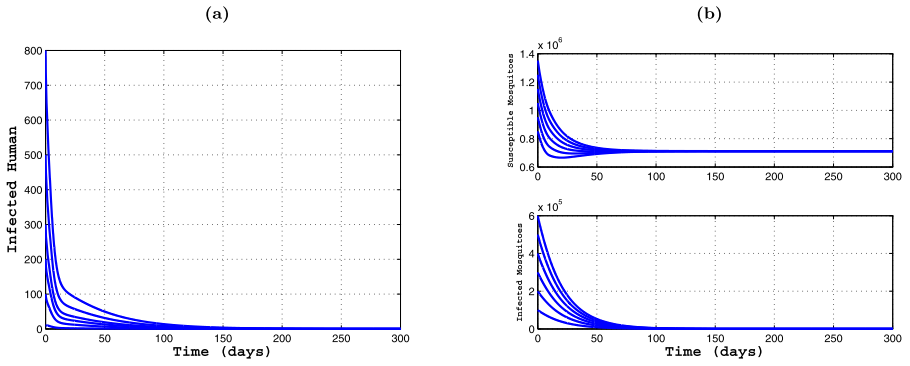


**Figure 3 The global attractiveness of the disease-free equilibrium without mosquitoes $E_{01}$ of model (1), where $\mathcal{R}_{01} \approx 0.9330 < 1$.**

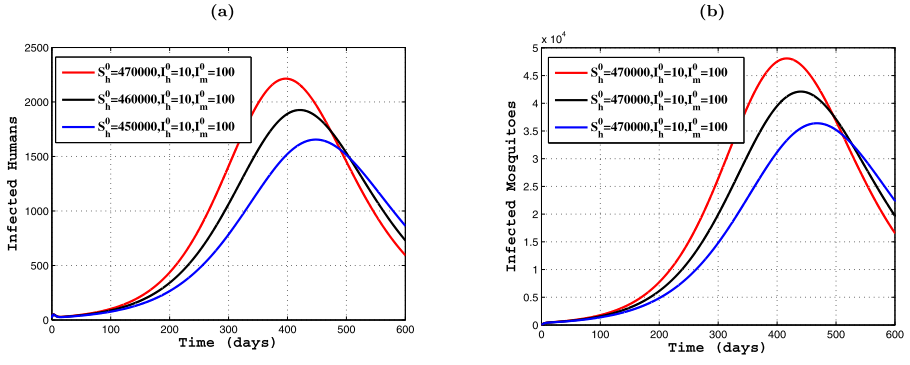


**Figure 4 The global attractiveness of the disease-free equilibrium with mosquitoes $E_{02}$ of model (1), where $\mathcal{R}_{01} \approx 5.9336 > 1$ and $\mathcal{R}_{02}^* \approx 0.4591 < 1$.**

ures 4(a) and 4(b) show that the infected classes (including individuals and mosquitoes) have an obvious explosion in the early phase. Additionally, from Figure 4(a), we also notice the fact that the number of susceptible individuals directly determines the strength and time of Dengue outbreaks, as more susceptible individuals correspond to more violent and earlier outbreaks. Similar results also can be found in Figure 4(b). It really shows that immunization of susceptible individuals is an effective strategy to control outbreaks of the Dengue virus.

Next, we consider how the maturation delay $\tau$ and vaccinated fraction $\psi$ affect the prevention and control of the Dengue virus. We fix $b = 1$ and $\tau$ to be 25, 20, 15, 12 and 10, and other parameters are fixed as in Table 3. Obviously, the plots in Figure 5(a) show that the maturation time directly determines the scale of the mosquito population. This confirms that the change of weather plays an important role in the spread of mosquito-transmitted infectious diseases. Further, to study the effects of the vaccinated fraction of $\psi$, we fix $\tau = 5$, $b = 1$, and $\psi$ to be 0.1, 0.2, 0.3, 0.4, 0.5 and 0.6, and other parameters are fixed as in Table 3. Figure 5(b) indicates that the number of infected individuals is falling fast with the increase of the vaccinated fraction $\psi$. These facts imply that we can prevent the spread of the Dengue virus by adjusting the vaccination rate $\psi$.

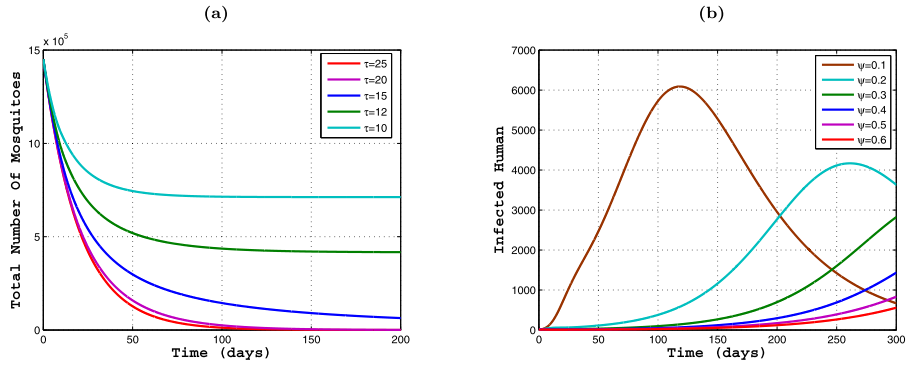


**Figure 5 The influences of the maturation delay and the vaccinated fraction to eliminate Dengue: (a) $b = 1$, $\tau = 25$, 20, 15, 12, and 10; (b) $\tau = 5$, $b = 1$, $\psi = 0.1$, 0.2, 0.3, 0.4, 0.5, and 0.6.**

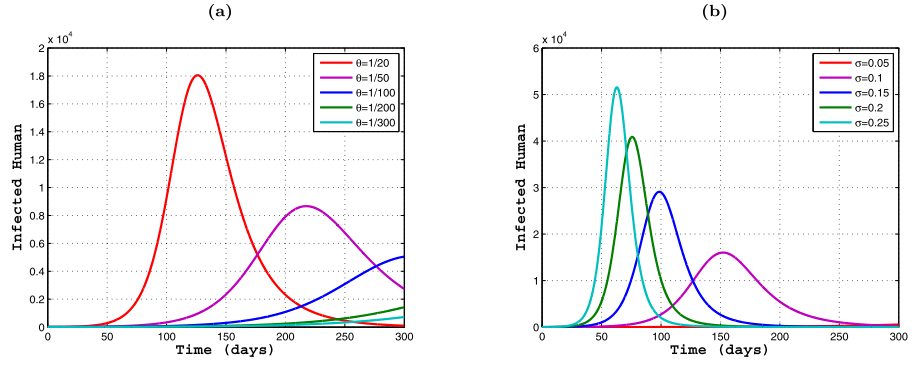


**Figure 6 The influences of the waning rate $\theta$ and the infection rate of vaccinated members $\sigma$ on the elimination of Dengue, where $\tau = 5$, $b = 1$, and other parameters are fixed as in Table 3: (a) $\theta = 1/20$, 1/50, 1/100, 1/200, and 1/300; (b) $\sigma = 0.05$, 0.1, 0.15, 0.2, and 0.25.**

Next, we simulate the effects of the waning rate $\theta$ and the infection rate of vaccinated members $\sigma$ for eliminating Dengue. We choose $\tau = 5$, $b = 1$, and other parameters are fixed as in Table 3. From the plots in Figure 6(a), we clearly see that the number of infected humans reaches a peak at day $\approx 126$, and the amplitude of the peak is large. Further, both the amplitude and the peaking time vary with the waning rate of immunity $\theta$. That is, the peaking time decreases and the amplitude of the peak decreases as $\theta$ reduces. In addition, as the infection rate of vaccinated members $\sigma$ increases, the peaking time decreases and the amplitude of the peak decreases. This is shown in Figure 6(b). Numerical simulations demonstrate that the validity period and the effectiveness of vaccination are two key factors to control the spread of the Dengue virus.

Finally, we also simulate the relationships of $\psi$ and $\sigma$, and $\psi$ and $\theta$. The plots in Figure 7(a) show that, due to the high rate of vaccines losing effect, though the vaccinated rate is high, the Dengue virus can outbreak in a short span of time. Further, we notice that, as the rate of loss of vaccine effectiveness decreases, though the vaccination rate decreases, the number of infected humans is kept in a lower range. Numerical simulations indicate that the improvement of the rate of loss of vaccine effectiveness is more effective than the improvement of the vaccination rate for controlling Dengue. Meanwhile, Figure 7(b) also

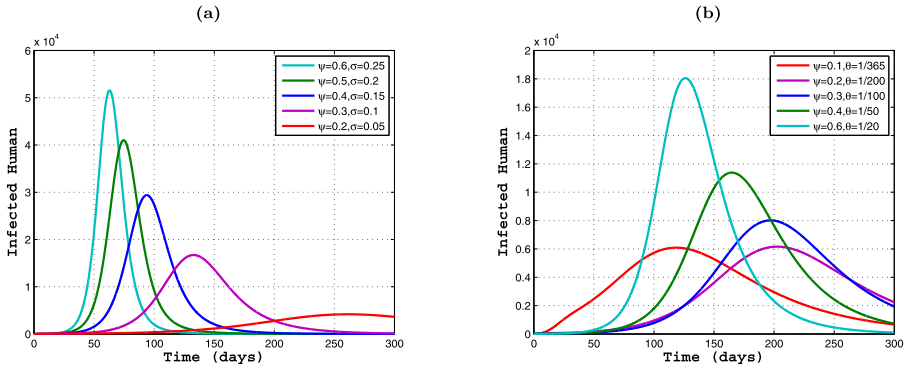


**Figure 7 The relationships of $\psi$ and $\sigma$, and $\psi$ and $\theta$: (a) $\psi = 0.6$ and $\sigma = 0.25$, $\psi = 0.5$ and $\sigma = 0.2$, $\psi = 0.4$ and $\sigma = 0.15$, $\psi = 0.3$ and $\sigma = 0.1$, $\psi = 0.2$ and $\sigma = 0.05$; (b) $\psi = 0.1$ and $\theta = 1/365$, $\psi = 0.2$ and $\theta = 1/200$, $\psi = 0.3$ and $\theta = 1/100$, $\psi = 0.4$ and $\theta = 1/50$, $\psi = 0.5$ and $\theta = 1/20$.**

implicates that the improvement of the period of validity of the vaccine is more effective than the improvement of the vaccination rate for controlling Dengue. Theoretical results and numerical simulations show that the development of highly effective vaccines is the most effective method to control the spread of the disease.

## 8 Concluding remarks

In this paper, we propose a mathematical model to describe Dengue virus transmission between mosquitoes and humans, where imperfect vaccination and vector maturation delay are introduced. The notation used in our mathematical model includes the compartment $V_h$, which represents the group of human population that is vaccinated, in order to distinguish the resistance obtained through vaccination and the one achieved by disease recovery. By using some analytical skills, the dynamical behavior of this model is discussed. This includes the global attractiveness of two disease-free equilibria, the existence of a positive equilibrium, the sensitivity analysis of threshold conditions, and the optimal control strategy for the disease. In addition, numerical simulations are also carried out to verify the correctness of the theoretical results and the feasibility of the vaccination control strategy. Theoretical results and numerical simulations show that the vaccination rate and effectiveness of the vaccine are two key factors for control of the spread of Dengue.

It is well known that there are four distinct serotypes of Dengue virus (DEN1, DEN2, DEN3 and DEN4), according to clinical data collected during the past years. Therefore, one person in an endemic area can suffer from four Dengue infections during his lifetime, one with each serotype. Epidemiological studies [36] support the hypothesis that recovered0 people can be re-infected with a different serotype, and face an increased risk of developing Dengue hemorrhagic fever and Dengue shock syndrome. In recent publications, some multi-strain Dengue fever transmission models have been discussed (see [37–40] and the references therein). However, all individuals who are capable of transmitting the disease are in one class in our model for the purpose of mathematical analysis. Therefore, for a more detailed understanding of the transmission of four Dengue virus strains between mosquitoes and humans, we intend to study the influences of vaccination and maturation delay for a multi-strain Dengue model in the future.

Dengue is a tropical vector-borne disease, difficult to prevent and manage. Researchers agree that the development of a vaccine for Dengue is a question of high priority. Recently,

a novel method to fight mosquitoes is using a bacterium called *Wolbachia*, which exists in spiders and up to 75% of the insects, including ticks and mites. Stable *Wolbachia* strains in *Aedes aegypti* have also been established. And subsequent studies have shown that, very importantly, *Wolbachia* blocks the replication of Dengue viruses in mosquitoes. Thence, an increasing number of people realize that replacing the wild mosquitoes with *Wolbachia* infected mosquitoes is safer, and more feasible than vaccination to some extent. Based on this, there are many mathematical models (including discrete-time and continuous-time models) that are used to investigated the spread of *Wolbachia* infection (see [41–46] and the references therein). As future work we intend to compare the advantages and disadvantages of the two control strategies (*Wolbachia* and vaccination). It would also be interesting to investigate what happens if two control strategies are taken at the same time.

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**Competing interests**
The authors declare that they have no competing interests.

**Authors' contributions**
The authors declare that the study was realized in collaboration with the same responsibility. All authors read and approved the manuscript.

## Publisher's Note



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**References**

1. *Dengue and dengue haemorrhagic fever*. WHO factsheets No. 117 (2009)
2. Jousset, FX: Geographic *Aedes aegypti* strains and dengue-2 virus: susceptibility, ability to transmit to vertebrate and transovarial transmission. Ann. Inst. Pasteur., Virol. **132**, 357-370 (1981)
3. Aldila, D, Götz, T, Soewono, E: An optimal control problem arising from a dengue disease transmission model. Math. Biosci. **242**, 9-16 (2013)
4. Kooi, BW, Maira, A, Nico, S: Analysis of an asymmetric two-strain dengue model. Math. Biosci. **248**, 128-139 (2014)
5. Coutinho, FAB, Burattini, MN, Lopez, LF, Massad, E: Threshold conditions for a non-autonomous epidemic system describing the population dynamics of dengue. Bull. Math. Biol. **68**, 2263-2282 (2006)
6. Esteva, L, Vargas, C: Analysis of a dengue disease transmission model. Math. Biosci. **150**, 131-151 (1998)
7. Wang, WD, Zhao, XQ: A nonlocal and time-delayed reaction-diffusion model of dengue transmission. SIAM J. Appl. Math. **71**, 147-168 (2011)
8. Garba, SM, Gumel, AB, Bakar, MRA: Backward bifurcations in dengue transmission dynamics. Math. Biosci. **215**, 11-25 (2008)
9. Keeling, MJ, Rohani, P: Modeling Infectious Diseases in Humans and Animals p. 415. Princeton University Press, Princeton (2008)
10. Rodrigues, HS, Monteiro, MTT, Torres, DFM: Vaccination models and optimal control strategies to dengue. Math. Biosci. **247**, 1-12 (2014)
11. Scherer, A, McLean, A: Mathematical models of vaccination. Br. Med. Bull. **62**, 187-199 (2002)
12. Kar, TK, Jana, S: Application of three controls optimally in a vector-borne disease: a mathematical study. Commun. Nonlinear Sci. Numer. Simul. **18**, 2868-2884 (2013)
13. Nelson, OO: Determination of optimal vaccination strategies using an orbital stability threshold from periodically driven systems. J. Math. Biol. **68**, 763-784 (2014)
14. Murrel, S, Butler, SCW: Review of dengue virus and the development of a vaccine. Biotechnol. Adv. **29**, 239-247 (2011)
15. Clark, DV, Mammen, MPJ, Nisalak, A, Puthimethee, V, Endy, TP: Economic impact of dengue fever/dengue hemorrhagic fever in Thailand at the family and population levels. Am. J. Trop. Med. Hyg. **72**, 786-791 (2005)
16. Shepard, DS, et al.: Cost-effectiveness of a pediatric dengue vaccine. Vaccine **22**, 1275-1280 (2004)
17. Suaya, JA, et al.: Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. Am. J. Trop. Med. Hyg. **80**, 846-855 (2009)
18. http://www.cdc.gov/ncidod/dvbid/westnile/
19. Bayoh, MN, Lindsay, SW: Effect of temperature on the development of the aquatic stages of *Anopheles gambiae* sensu stricto (Diptera: Culicidae). Bull. Entomol. Res. **93**, 375-381 (2003)
20. Shaman, J, Spiegelman, M, Cane, M, Stieglitz, M: A hydrologically driven model of swamp water mosquito population dynamics. Ecol. Model. **194**, 395-404 (2006)
21. Zhao, XQ, Zou, XF: Threshold dynamics in a delayed SIS epidemic model. J. Math. Anal. Appl. **257**, 282-291 (2001)
22. Fan, GH, Wu, JH, Zhu, HP: The impact of maturation delay of mosquitoes on the transmission of West Nile virus. Math. Biosci. **228**, 119-126 (2010)

23. Tridip, S, Sourav, R, Joydev, C: A mathematical model of dengue transmission with memory. Commun. Nonlinear Sci. Numer. Simul. **22**, 511-525 (2015)
24. Smith, HJ: Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems. Mathematical Surveys and Monographs, vol. 41. Am. Math. Soc., Providence (1995)
25. Cooke, KL, Driessche, P: Analysis of an SEIRS epidemic model with two delays. J. Math. Biol. **32**, 240-260 (1996)
26. Smith, HL: An Introduction to Delay Differential Equations with Applications to the Life Sciences, vol. 57. Springer, New York (2011)
27. Nakul, C, James, MH, Jim, MC: Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model. Bull. Math. Biol. **70**, 1272-1296 (2008)
28. Cesari, L: Optimization-Theory and Applications, Problems with Ordinary Differential Equations. Applications and Mathematics, vol. 17. Springer, New York (1983)
29. Kamien, MI, Schwartz, NL: Dynamics Optimization: The Calculus of Variations and Optimal Control in Economics and Management. Elsevier, Amsterdam (2000)
30. Nababan, S: A Filippov-type lemma for functions involving delays and its application to time-delayed optimal control problems. J. Optim. Theory Appl. **27**(3), 357-376 (1979)
31. Seierstad, A, Sydsaeter, K: Optimal Control Theory with Economic Applications. Elsevier, Amsterdam (1975)
32. Fleming, WH, Rishel, RW: Deterministic and Stochastic Optimal Control. Springer, New York (1975)
33. Bashier, EBM, Patidar, KC: Optimal control of an epidemiological model with multiple time delays. Appl. Math. Comput. **292**, 47-56 (2017)
34. Chen, LJ, Hattaf, K, Sun, JT: Optimal control of a delayed SLBS computer virus model. Physica A **427**, 244-250 (2015)
35. Zhu, QY, Yang, XF, Yang, LX, Zhang, CM: Optimal control of computer virus under a delayed model. Appl. Math. Comput. **218**, 11613-11619 (2012)
36. Stech, H, Williams, M: Alternate hypothesis on the pathogenesis of dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) in dengue virus infection. Exp. Biol. Med. **233**(4), 401-408 (2008)
37. Chung, KW, Lui, R: Dynamics of two-strain influenza model with cross-immunity and no quarantine class. J. Math. Biol. **73**(6), 1-23 (2016)
38. Esteva, L, Vargas, C: Coexistence of different serotypes of dengue virus. J. Math. Biol. **46**(1), 31-47 (2003)
39. Feng, Z, Velasco-Hernández, JX: Competitive exclusion in a vector-host model for the dengue fever. J. Math. Biol. **35**(5), 523-544 (1997)
40. Hartley, LM, Donnelly, CA, Garnett, GP: The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. Trans. R. Soc. Trop. Med. Hyg. **96**, 387-397 (2002)
41. Zheng, B, Tang, MX, Yu, JS: Modeling Wolbachia spread in mosquitoes through delay differential equations. SIAM J. Appl. Math. **74**(3), 743-770 (2014)
42. Zheng, B, Tang, MX, Yu, JS, Qiu, JX: Wolbachia spreading dynamics in mosquitoes with imperfect maternal transmission. J. Math. Biol. **2017** (2017, in press). doi:10.1007/s00285-017-1142-5
43. Huang, MG, Tang, MX, Yu, JS: Wolbachia infection dynamics by reaction-diffusion equations. Sci. China Math. **58**(1), 77-96 (2015)
44. Huang, MG, Yu, JS, Hu, LC, Zhang, B: Qualitative analysis for a Wolbachia infection model with diffusion. Sci. China Math. **59**(7), 1249-1266 (2016)
45. Hu, LC, Huang, MG, Tang, MX, Yu, JS, Zheng, B: Wolbachia spread dynamics in stochastic environments. Theor. Popul. Biol. **106**, 32-34 (2015)
46. Turelli, M, Bartom, NH: Deploying dengue-suppressing Wolbachia: robust models predict slow but effective spatial spread in *Aedes aegypti*. Theor. Popul. Biol. **115**, 45-60 (2017)