การศึกษาการควบคุมการระบาดของโรคไข้เลือดออกโดยการพิจารณาการระบาดระหว่างกลุ่มคนและยุง

Optimal Control Strategy of a Dengue Epidemic Dynamics with Human-Mosquito Transmission

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บทคัดย่อ

ในงานวิจัยนี้ ผู้วิจัยได้สร้างแบบจำลองทางคณิตศาสตร์เพื่อศึกษาความสัมพันธ์ระหว่างกลุ่มประชากรคนและยุงลาย ที่มีผลต่อการแพร่ระบาดของโรคไข้เลือดออก โดยผู้วิจัยได้ทำการวิเคราะห์แบบจำลองทั้งเชิงทฤษฎีและเชิงตัวเลข เพื่อยืนยันความมีเสถียรภาพของจุดสมดุลที่ได้จากแบบจำลองและเพื่อแสดงว่าแบบจำลองสามารถนำไปประยุกต์ใช้ในงานวิจัยที่เกี่ยวข้องได้ อีกทั้งผู้วิจัยยังได้ศึกษาหาแนวทางการป้องกันและควบคุมการแพร่ระบาดของโรคไข้เลือดออกเชิงนโยบายโดยใช้ทฤษฎีการควบคุมที่เหมาะสม ผลจากงานวิจัยพบว่า แบบจำลองที่ได้สามารถใช้วางแผนปฏิบัติการเชิงนโยบายในการป้องกันและควบคุมการแพร่ระบาดของโรคไข้เลือดออกที่มียุงลายเป็นพาหะได้

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Abstract

In this paper, we presented a mathematical model of Dengue disease to understand its dynamics by using a set of differential equations to describe the effects between human and mosquito populations. The epidemic and endemic analyses have also presented along with numerical simulations to verify our model so that it can be further studied for public health interventions. Meanwhile, our optimal control problem has been investigated to explore control strategies to stop the Dengue disease outbreak. Our results show that strategically deployed control measures can reduced the numbers of infectious individuals.

Keywords : Dengue fever, Mathematical model, equilibrium, Optimal control theory

Introduction

Dengue illness has caused from a virus, it is possible to become infected by dengue multiple times because the virus has four different serotypes known as DEN1, DEN2, DEN3 and DEN4. Dengue viruses are transmitted to human by the bite of *Aedes aegypti* female mosquitoes causing Dengue fever (DF). The World Health Organization has reported that there are an estimated 50-100 million of dengue infection and has killed an estimated 22,000 people, mostly with the children (World Health Organization, 2010).

There have been many mathematical models (see, e.g., (Esteya 1998; Bowman, 2005; Rodrigues *et al.,* 2012; Singh *et al.,* 2014) to predict the prevalence and transmission dynamics of dengue disease. . We assume that the human population is constant. The vector population has a constant recruitment rate, which depends upon the fractions of eggs and larvae that mature to the adult stage, and a constant per capita mortality. Therefore, the vector population is asymptotically constant (Esteya 1998). In 2011, Helena Sofia Rodrigues, *et.al.* proposed a model based on two populations, humans and mosquitoes, with insecticide control has been presented. It has been shown that with a steady insecticide campaign, it is possible to reduce the number of infected humans and mosquitoes and can prevent an outbreak that could transform an epidemiological episode to an endemic disease (Bowman, 2005). In 2014, B. Singh, et.al. discussed the effects of vaccination strategies on the dynamic of the dengue disease transmission model with assumption that a random fraction of the recovered host population can loses the immunity and becomes susceptible again (Singh *et al.,* 2014). In 2015, Tarig Mohamed, et.al. studied describing the dynamics of dengue fever. The sensitivity index of the basic reproduction number is carried out in order to establish the relative significance of the model parameters in the disease spread (Ali *et al.,* 2015). The last three research papers we mentioned above have presented general ideas to formulate mathematical models with constant control measures, however, none of above suggested to use optimal control theory to seek cost-effective solutions. In addition, not many studies have conducted combination of control measures such as vaccine, medical treatments and elimination of egg or larvae.

In the remainder of this paper, we will first present the dengue fever model with control measures incorporated. We will then conduct an equilibrium analysis for the epidemic and endemic dynamics of the system when the controls are constants. Then, we will turn to time-dependent control system and perform an optimal control study for the dengue fever model. Numerical simulations will also be presented. Finally, we round up the paper by conclusion and discussion.

Methods

In this section, we derive a mathematical model with vaccination and treatment for dengue disease patients. The model is based on monitoring the dynamics of the populations of susceptible humans (S_h), the vaccination (V_h), infected humans (I_h), recovered human (R_h). The total human population (N_h) is constant so, $N_h = S_h + V_h + I_h + R_h$. There are also four other state variables related to female, aquatic stage or larva mosquitoes (A_m), uninfected female mosquitoes (M_s), and infected female mosquitoes (M_i).

Let a portion σ, $0 \le \sigma \le 1$, of newborn host be vaccinated. Assume that the host and vector population has constant with birth and death rate equal to μ_h and μ_v, respectively, c is average daily biting, β_1, β_2 are transmission probability from M_i, I_h respectively. Q_m is number of eggs at each deposit per capita and K is maximal capacity of larvae $(k * m)$. λ_m is maturation rate from larvae to adult and natural mortality of larva at a rate μ_A. The recovery rate of the host population is defined by γ. ϕ_1 is the effectiveness of the vaccine, ϕ_2 is an average treatment, ϕ_3 is an elimination of egg or larvae. k is number of larvae per human and m is female mosquitoes per human. For human population the equations are;

$$\begin{aligned}
\frac{dS_h}{dt} &= \mu_h N_h - \left(c\beta_1 \frac{M_i}{N_h} + \mu_h + \phi_1 \right) S_h, \\
\frac{dV_h}{dt} &= \phi_1 S_h - \left(\sigma c\beta_1 \frac{M_i}{N_h} + \mu_h \right) V_h, \\
\frac{dI_h}{dt} &= c\beta_1 \frac{M_i}{N_h} (S_h + \sigma V_h) - (\gamma + \phi_2 + \mu_h) I_h, \\
\frac{dR_h}{dt} &= (\gamma + \phi_2) I_h - \mu_h R_h,
\end{aligned} \tag{1}$$

and for vector population

$$\begin{aligned}
\frac{dA_m}{dt} &= Q_m \left(1 - \frac{A_m}{K} \right) (M_s + M_i) - (\lambda_{ms} + \phi_3 + \mu_A) A_m, \\
\frac{dM_s}{dt} &= \lambda_{ms} A_m - \left(c\beta_2 \frac{I_h}{N_h} + \mu_v \right) M_s, \\
\frac{dM_i}{dt} &= c\beta_2 \frac{I_h}{N_h} M_s - \mu_v M_i.
\end{aligned} \tag{2}$$

Disease-free equilibrium

With constant controls and setting $I_h = R_h = M_i = 0$, the disease-free equilibrium (DFE) of the system (1) and (2) is given by

$$\varepsilon_0 = (S_0, V_0, 0, 0, A_0, M_{S0}, 0) \tag{3}$$

where $S_0 = \dfrac{\mu_h N_h}{\mu_h + \phi_1}$, $A_0 = \dfrac{\lambda_{ms} Q_m K - \mu_v K (\lambda_{ms} + \mu_A + \phi_3)}{\lambda_{ms} Q_m}$,

$V_0 = \dfrac{\phi_1 N_h}{\mu_h + \phi_1}$, $M_{S0} = \dfrac{\lambda_{ms} Q_m K - \mu_v K (\lambda_{ms} + \mu_A + \phi_3)}{\mu_v Q_m}$.

Next-generation matrix analysis

We start our analysis by determining the basic reproduction number, R_0. R_0 is mathematically defined as the spectral radius of the next-generation matrix. To compute the basic reproduction number, we use the well-known method of van den Driessche and Watmough (Van den Driessche, P. & Watmough, J., 2002). By system (1), I_h and M_i are directly related to the infection. We have

$$\begin{bmatrix} \dfrac{dI_h}{dt} \\ \dfrac{dM_i}{dt} \end{bmatrix} = \begin{bmatrix} c\beta_1 \dfrac{M_i}{N_h}(S_h + \sigma V_h) \\ c\beta_2 \dfrac{I_h}{N_h} M_s \end{bmatrix} - \begin{bmatrix} (\gamma + \phi_2 + \mu_h) I_h \\ \mu_v M_i \end{bmatrix} = \mathcal{F} - \mathcal{V},$$

where $\mathcal{F}$ denotes the rate of appearance of new infections and $\mathcal{V}$ denotes the rate of transfer of individuals into or out of each population set. The next-generation matrix is defined as FV^{-1}, where F and V are the Jacobian matrices given by

$$F = \mathcal{DF}(\varepsilon_0) = \begin{bmatrix} 0 & \dfrac{c\beta_1 (S_0 + \sigma V_0)}{N_h} \\ \dfrac{c\beta_2 M_{S0}}{N_h} & 0 \end{bmatrix}, \quad V = \mathcal{DV}(\varepsilon_0) = \begin{bmatrix} \mu_h + \gamma + \phi_2 & 0 \\ 0 & \mu_v \end{bmatrix}, \tag{4}$$

where ε_0 is DFE defined in Equation (3). By spectral radius, we have

$$R_0 = \sigma\left(FV^{-1}\right) = \sqrt{\frac{c^2 \beta_1 \beta_2 M_{S0} (S_0 + \sigma V_0)}{N_h^2 \mu_v (\mu_h + \gamma + \phi_2)}}. \tag{5}$$

Consequently, based on the work in the paper proposed by Van Den Driessche and Watmough (Van den Driessche, P. & Watmough, J., 2002), we immediately have the following result:

<u>Theorem1</u> The disease-free equilibrium of the model is locally asymptotically stable *if* $R_0 < 1$, and unstable *if* $R_0 > 1$.

To study the global asymptotic stability of the DFE, we will apply the following result introduced by Castillo-Chavez et al (Chavez *et al.,* 2001).

Lemma1 Consider a model system written in the form

$$\frac{dX_1}{dt} = F(X_1, X_2)$$
$$\frac{dX_2}{dt} = G(X_1, X_2), \qquad G(X_1, 0) = 0$$

where $X_1 \in \mathbf{R}^m$ denotes (its components) the number of uninfected individuals and $X_2 \in \mathbf{R}^m$ denotes (its components) the number of infected individuals including latent, infections, etc.; $X_0 = (X_1^*, 0)$ denotes the disease-free equilibrium of the system. Also assume the conditions (H1) and (H2) below:

(H1) For $dX_1 / dt = F(X_1, 0)$ is globally asymptotically stable;

(H2) $G(X_1, X_2) = AX_2 - \hat{G}(X_1, X_2)$, $\hat{G}(X_1, X_2) \geq 0$ for $(X_1, X_2) \in \Omega$, where the Jacobian $A = (\partial G / \partial X_2) G(X_1^*, 0)$ is an M-matrix (the off diagonal elements of A are nonnegative) and Ω is the region where the model makes biological sense. Then the DFE is globally asymptotically stable.

Theorem2 The DFE of the model (1) is globally asymptotically stable.

Proof. We adopt the notations in Lemma1 and verify the conditions (H1) and (H2). In our model, $X_1 = (S_h, V_h, R_h, A_m, M_s)$, $X_2 = (M_s, M_i)$ and $X_1^* = (S_0, V_0, R_0, A_0, M_0)$. We note that the system is linear and its solution can be easily found as:

$$\frac{dX_1}{dt} = F(X_1, X_2) = \begin{bmatrix} \mu_h N_h - \left(c\beta_1 \dfrac{M_i}{N_h} + \mu_h + \phi_1 \right) S_h \\ \phi_1 S_h - \left(\sigma c \beta_1 \dfrac{M_i}{N_h} + \mu_h \right) V_h \\ (\gamma + \phi_2) I_h - \mu_h R_h \\ Q_m \left(1 - \dfrac{A_m}{K} \right) (M_s + M_i) - (\lambda_{ms} + \phi_3 + \mu_A) A_m \\ \lambda_{ms} A_m - \left(c\beta_2 \dfrac{I_h}{N_h} + \mu_v \right) M_s \end{bmatrix}. \tag{6}$$

We have

$$\frac{dX_1}{dt} = F(X_1, 0) = \begin{bmatrix} \mu_h N_h - (\mu_h + \phi_1) S_h \\ \phi_1 S_h - \mu_h V_h \\ -\mu_h R_h \\ Q_m \left(1 - \dfrac{A_m}{K} \right) M_s - (\lambda_{ms} + \phi_3 + \mu_A) A_m \\ \lambda_{ms} A_m - \mu_v M_s \end{bmatrix}.$$

Thus, $R(t) \to 0$, $S(t) \to S_o$, $V(t) \to V_o$, $A_m(t) \to A_o$, and $M_s(t) \to M_{So}$ as $t \to \infty$. Hence, $X_1^* = (S_0, V_0, R_0, A_0, M_{S0})$ is globally asymptotically stable for the subsystem (6).

Now, note that

$$G(X_1, X_2) = AX_2 - \hat{G}(X_1, X_2) \tag{7}$$

where $A = \frac{\partial G}{\partial X_2}(X_1^*, 0)$. Substituting into (7) gives, $\hat{G}(X_1, X_2) = (0,0)^T \geq 0$. We complete the proof.

Endemic equilibrium

When the disease is presence in the population, $I_h \neq 0$ and $M_i \neq 0$, there may be several critical points where $I_h \neq 0$ and $M_i \neq 0$, which are the endemic equilibrium points of the model. These points will be denoted as $\varepsilon_1^* = (S_h^*, V_h^*, I_h^*, R_h^*) \neq 0$ and $\varepsilon_2^* = (A_m^*, M_s^*, M_i^*) \neq 0$

Local stability

Next, we proceed to analyze the stability properties of the endemic equilibrium. First we prove the following result regarding the local stability.

Theorem3 The positive endemic equilibrium ε_1^* is locally asymptotically stable.

Proof. The jacobian matrix of the system (1) at $x = \varepsilon_1^*$ is given by

$$J(S_h^*, V_h^*, I_h^*) = \begin{bmatrix} -(\alpha_1 M_i^* + \mu_h + \phi_1) & 0 & 0 \\ \phi_1 & -(\sigma\alpha_1 M_i^* + \mu_h) & 0 \\ \alpha_1 M_i^* & \sigma\alpha_1 M_i^* & -(\gamma + \phi_2 + \mu_h) \end{bmatrix}$$

where $\alpha_1 = \frac{c\beta_1}{N_h}$ and $W = (\gamma + \phi_2 + \mu_h)$. The characteristic polynomial of $J(\varepsilon_1^*)$ is

$$\begin{aligned} 0 &= \det\left[J(\varepsilon_1^*) - \lambda I^*\right] \\ &= \left(-\lambda - (\alpha_1 M_i^* + \mu_h + \phi)_1\right)\left(-\lambda - (\sigma\alpha_1 M_i^* + \mu_h)\right)\left(-\lambda - (\gamma + \phi_2 + \mu_h)\right) = 0 \end{aligned}$$

Thus $\lambda_1 = -(\alpha_1 M_i^* + \mu_h + \phi)$, $\lambda_2 = -(\sigma\alpha_1 M_i^* + \mu_h)$, $\lambda_3 = -(\gamma + \phi_2 + \mu_h)$, which all of the eigenvalues are negative numbers. Thus, ε_1^* is locally asymptotically stable. We complete the proof.

Results : Optimal control

Now we turn to the more general model with time-dependent controls $\phi_1(t), \phi_2(t)$, and $\phi_3(t)$. We consider the system on a time interval [0,T]. The function $\phi_1(t)$, $\phi_2(t)$, and $\phi_3(t)$ are assumed to be at least Lebesgue measurable on [0,T]. The control set is defined as

$\Omega = \{\phi_1(t), \phi_2(t), \phi_3(t) \mid 0 < \phi_1(t) < \phi_{1\max}, \ 0 < \phi_2(t) < \phi_{2\max}, \ 0 < \phi_3(t) < \phi_{3\max}\}$ where $\phi_{1\max}$, $\phi_{2\max}$, and $\phi_{3\max}$ denote the upper bounds for the effort of vaccination, treatment, and elimination rate of egg or larvae, respectively. The bounds reflect practical limitation on the maximum rate of control in given time period. The presence of time-dependent controls makes the analysis of our system difficult. In fact, the disease dynamics

now depend on the evolution of control. In what follows we perform an optimal control study on this problem. We aim to minimize the total number of infections and the costs of control over the time interval $[0,\ T]$; i.e.,

$$\min_{\phi_{1,2,3,4}\in\Omega}\int_0^T \left[\begin{array}{l} I(t)+c_{21}\phi_1(t)S_h(t)+c_{22}\phi_1^{\ 2}(t)+c_{31}\phi_2(t)I_h(t)+c_{32}\phi_2^{\ 2}(t) \\ \quad +c_{41}\phi_3(t)A_m(t)+c_{42}\phi_3^{\ 2}(t) \end{array}\right] dt \tag{8}$$

Here, the parameters c_{21}, c_{22}, c_{31}, c_{32}, c_{41}, and c_{42} with appropriate units, define the appropriate costs associated with these controls. Quadratic terms are introduced to indicate nonlinear costs potentially arising at high intervention level. The minimization process is subject to the differential equation of our system, which are now referred to as the state equations. Correspondingly, the unknows I_h and M_i are now called the state variables, in contrast to the control variables $\phi_1(t),\ \phi_2(t),$ and $\phi_3(t)$. Our goal is to determine the optimal controls $\phi_1^*(t),\ \phi_2^*(t),$ and $\phi_3^*(t),$ so as to minimize the objective functional in (8).

Let us first define the adjoint functions $\lambda_{S_h}, \lambda_{V_h}, \lambda_{I_h}, \lambda_{A_m}, \lambda_{M_s}$ and λ_{M_i} associated with the state equations for S_h, V_h, I_h, A_m, M_s and M_i respectively. We then form the Hamitonian, H, by multiplying state equation, and adding each of these products to the integrand of the objective functional. As a result, we obtain

$$\begin{aligned} H &= I(t)+c_{21}\phi_1(t)S_h(t)+c_{22}\phi_1^{\ 2}(t)+c_{31}\phi_2(t)I(t)+c_{32}\phi_2^{\ 2}(t)+c_{41}\phi_3(t)A_m(t)+c_{42}\phi_3^{\ 2}(t) \\ &+\lambda_{S_h}\left(\mu_h N_h-\left(c\beta_1\frac{M_i}{N_h}+\mu_h+\phi_1\right)S_h\right)+\lambda_{V_h}\left(\phi_1 S_h-\left(\sigma c\beta_1\frac{M_i}{N_h}+\mu_{h1}\right)V_h\right) \\ &+\lambda_{I_h}\left(c\beta_1\frac{M_i}{N_h}(S_h+\sigma V_h)-(\gamma+\phi_2+\mu_h)I_h\right)+\lambda_{A_m}\left(Q_m\left(1-\frac{A_m}{K}\right)(M_s+M_i)-(\lambda_{ms}+\phi_3+\mu_A)A_m\right) \\ &+\lambda_{M_s}\left(\lambda_{ms}A_m-\left(c\beta_2\frac{I_h}{N_h}+\mu_v\right)M_s\right)+\lambda_{M_i}\left(c\beta_2\frac{I_h}{N_h}M_s-\mu_v M_i\right) \end{aligned}$$

To achieve the optimal control, the adjoint functions must satisfy $\frac{d\lambda_{S_h}}{dt}=-\frac{\partial H}{\partial S_h}$, $\frac{d\lambda_{V_h}}{dt}=-\frac{\partial H}{\partial V_h}$, $\frac{d\lambda_{I_h}}{dt}=-\frac{\partial H}{\partial I_h}$, $\frac{d\lambda_{A_m}}{dt}=-\frac{\partial H}{\partial A_m}$, $\frac{d\lambda_{M_s}}{dt}=-\frac{\partial H}{\partial M_s}$ and $\frac{d\lambda_{M_i}}{dt}=-\frac{\partial H}{\partial M_i}$ with transversality conditions (or final time conditions): $\lambda_{S_h}(T)=0,\ \lambda_{V_h}(T)=0,\ \lambda_{I_h}(T)=0,\ \lambda_{A_m}(T)=0,\ \lambda_{M_s}(T)=0$ and $\lambda_{M_i}(T)=0.$

The characterization of the optimal control $\phi_1^*(t),\ \phi_2^*(t)$ and $\phi_3^*(t)$ are based on the conditions $\frac{\partial H}{\partial \phi_1}=0,$ $\frac{\partial H}{\partial \phi_2}=0,$ $\frac{\partial H}{\partial \phi_3}=0,$ respectively, subject to the constraints $0\le\phi_1\le\phi_{1\max},\ 0\le\phi_2\le\phi_{2\max},$ and $0\le\phi_3\le\phi_{3\max}.$

Specifically, we have $\phi_1^*(t)=\max\left(0,\min\left(\phi_1(t),\ \phi_{1\max}\right)\right),\quad \phi_2^*(t)=\max\left(0,\min\left(\phi_2(t),\ \phi_{2\max}\right)\right)$

and $\phi_3^*(t)=\max\left(0,\min\left(\phi_3(t),\ \phi_{3\max}\right)\right)$

where $\phi_1(t)=\left(\left(\lambda_{s_h}-\lambda_{V_h}\right)S_h(t)-c_{21}S_h(t)\right)/2c_{22},\qquad \phi_2(t)=\left(\lambda_{I_h}I_h(t)-c_{31}I_h(t)\right)/2c_{32},$

and $\phi_3(t)=\left(\lambda_{A_m}A_m(t)-c_{41}A_m(t)\right)/2c_{42}.$

Due to the presence of both initial conditions (for the state equations) and final time conditions (for the adjoint equations), and the fact that most models of our interest are nonlinear, the optimal control system has to be solved numerically. We will use the Forward-Backward Sweep Method to conduct the numerical simulation.

The initial conditions for the problem were:

$S_{h0} = N_h - E_{h0} - I_{h0}$, $E_{h0} = 216$, $I_{h0} = 434$, $R_{h0} = 0$, $A_{m0} = kN_h$, $K = kN_h$, $S_{m0} = mN_h$. The simulations were carried out using the following values:

Table 1 Dengue fever model parameters.

Parameter	Value	Reference	Parameter	Value	Reference
N_h	480×10^3	(Rodrigues et al., 2012)	$1/\mu_v$	10	(Rodrigues *et al.*, 2012)
C	0.8	(Rodrigues et al., 2012)	$1/\mu_L$	4	(Rodrigues *et al.*, 2012)
β_1	0.375	(Rodrigues et al., 2012)	λ_{ms}	0.08	(Rodrigues *et al.*, 2012)
β_2	0.375	(Rodrigues et al., 2012)	γ	$1/4$	(Rodrigues *et al.*, 2012)
$1/\lambda_h$	3	(Rodrigues et al., 2012)	Q_m	400	(Rodrigues *et al.*, 2012)
$1/\mu_A$	$71*365$	(Bowman et al., 2005)	μ_h	0.00003	(Bowman *et al.*, 2005)
k	3	(Bowman et al., 2005)	m	6	(Bowman *et al.*, 2005)

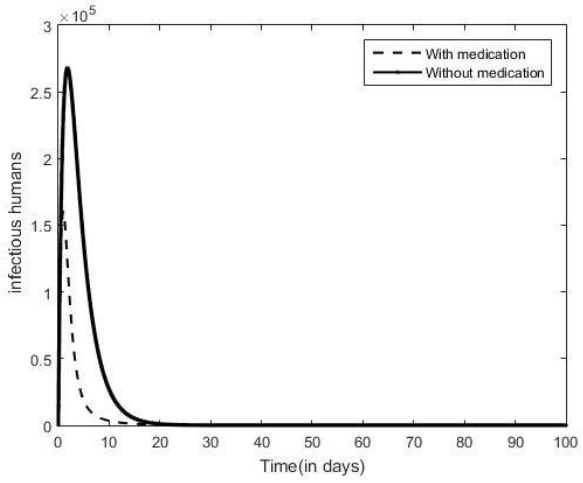

Figure1 Dengue infectious population.

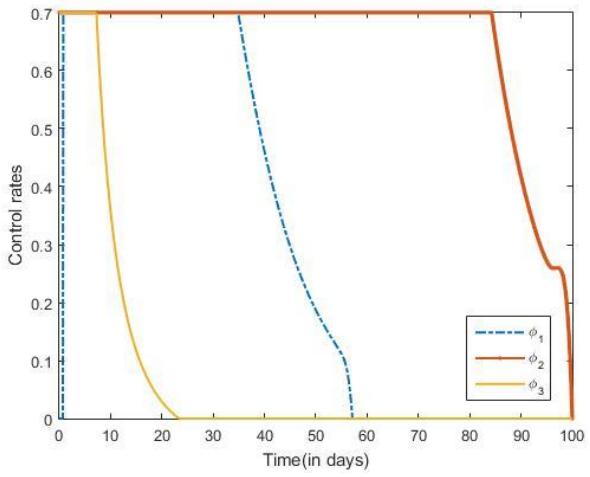

Figure2 Rate of controls (ϕ_1, ϕ_2, ϕ_3).

First set of parameters, let $c_{21} = 0.03$, $c_{22} = 0.5$, $c_{31} = 0.01$, $c_{32} = 0.5$, $c_{41} = 0.000000002$, $c_{42} = 0.05$ and $\phi_{\max} = 0.7$. Figure1 shows the infection curves for the model with controls (dashed line) and that without the optimal controls (solid line). It is clearly seen the infection level has been reduced due to the incorporation of vaccine and other controls.

Discussion

We have presented a mathematical model of dengue fever with controls. The equilibrium analysis has been conducted. The stability of epidemic and endemic points are controlled by the threshold number. If R_0 is less than one, then the disease dies out and the disease-free equilibrium is stable. If R_0 is greater than one, then the disease persists and the disease-free equilibrium is unstable. We have deployed vaccine, medical treatments and elimination of egg or larvae to investigate strategies to reduce numbers of infectious people by using optimal control theory. In conclusion, numerical simulations along with theories have provided and shown that with strategically deployed vaccination, medical treatment and elimination of egg or larvae of mosquitoes can reduce the number of infectious dengue fever people significantly.

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