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Within-Host Model of Dengue Viral Infection with Immune Response and Vaccination: Dynamics Analysis and Optimal Control

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ABSTRACT

In this study, we propose a within-host model describing dengue viral infection. The model incorporates immune response and latency stage of cells when getting infected by dengue viruses. We verify that all solutions are nonnegative and bounded. Two equilibrium points (infection-free and infected) are established, and the basic reproduction number is computed. Local stability analysis is performed and each equilibrium point is stable under some conditions. The Lyapunov functional and geometric approaches are implemented to show the global stability of infection-free and infected equilibrium point, respectively. Numerical simulation of the model is carried out to confirm the stability of both equilibrium points i.e., the case when the basic reproduction number is less than and greater than one, respectively. Further, an optimal control problem is applied into the model by adding vaccination as control variable to seek the optimal strategy in preventing dengue viral infection. Our numerical results of optimal control model demonstrate that vaccination not only reduces exposed and infected cells, viruses, B-cells and cytotoxic T lymphocytes (CTLs), but also increases antibody. Our results indicate that vaccination can delay the peak of infection, potentially mitigating disease spread. Although most of the dengue patients are not in severe case, it is still better not to get infected and being risk. Therefore, dengue vaccination measure is highly recommended for public health policy in order to reduce both number of dengue infected patients and cost of treatment.

Keywords: Dengue viral infection; Immune response; Optimal control; Vaccination; Within-host model

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1. Introduction

Dengue fever is one of the world's most threatening mosquito-borne diseases caused by dengue virus [1, 2]. It is transmitted to humans through the bite of infected mosquitoes [3]. Dengue incidence has grown dramatically worldwide in recent decades. According to World Health Organization, there are approximately 100-400 million infections occurring each year, where about 50% of the world's population is now at risk of dengue [3]. Dengue viral infection is often asymptomatic or gives mild symptoms, however, it sometimes causes severe cases and even death. In the case of having symptoms, they will appear about 3-14 days after infection. An infection usually lasts for about 7-14 days and is cleared eventually by immune system. Until the present time, there is no specific medication to directly cure dengue fever, hence prevention is essential. People should try to avoid being bitten by a mosquito and/or for those who are living in the risk or endemic area, ones may take dengue vaccine. Recently, the new dengue vaccine called Qdenga® is available in Thailand, Indonesia, Brazil, Argentina, UK, and European Union and its efficacy is around 80%, which is better than a previous one [4].

The pathogenesis of dengue viral infection is very complex, which interplays among host cells, virus and immune response, and is not completely understood [5-7]. The target cells of dengue virus are monocytes, dendritic cells, macrophages, endothelial and epithelial cells. Immune cells have been shown to play a key role in eliminating dengue viruses. When the pathogen enters the body, an innate immune system (i.e., interferon) will first come to fight against these pathogens. Later, the pathogen will be carried to thymus to activate the adaptive immune response to do its job. Cytotoxic T lymphocytes (CTLs) will kill cells which are infected by dengue virus, and B-cells will be activated and secrete antibodies that neutralizes the antigen-presenting viruses [8-10]. In this study, we therefore would further our understanding of dengue viral infection in pathogenesis level through mathematical model.

Mathematical model has been used to improve understanding of a number of diseases including dengue fever in both population level (human and/or mosquito) and pathogenesis level. For population level, mathematical models can demonstrate and predict disease transmission dynamics based on the serological population profile considering biological parameter values which are estimated from real collected data. On the other hand, at the pathogenesis level (within-host), models could help to better understand the evolution of viro-immunological response during an infection. It could be used to investigate the factors that associated with enhanced infectiousness during infection, progression towards severe disease, and how to prevent it via pharmacological interventions and protection against infection via previous infection or vaccination. Overall, these within-host models can quantify the parameters that determine the kinetics of viral load and its distribution in the population. In the past two decades, there are several models proposed for dengue transmission in population level and some examples are the work by Esteva and Vargas, 2000 [11], Derouich and Boutayeb, 2006 [12], Barbazan et al., 2010 [13], Andraud et al., 2012 [14], Rodrigues et al., 2014 [15], Phaijoo and Gurung, 2015 [16], Sardar et al., 2015 [17], Khan and Fatmawati, 2021 [18], Alharbi and Hasan, 2024 [19] and Gholami et al., 2025 [20]. Some researchers applied optimal control problems into their

models to seek the optimal strategies in preventing infection, e.g., Rodrigues et al., 2014 [15], Khan and Fatmawati, 2021 [18], Pongsumpun et al., 2023 [21], Abidemi et al., 2024 [22], Kugelmann and Oulch, 2024 [23], and Yoda et al., 2024 [24]. On the other hand, relatively few works related to within-host dynamics of dengue viral infection have been studied. Here are the works of within-host model. In 2009, Nuraini et al. [25] proposed four classes model to study the kinetic of dengue virus. They are susceptible monocytes, infected monocytes, free virus particles and immune cells. Their results show that the growth and invasion rate of immune cells is crucial in identifying the infection intensity. In 2012, Ansari and Hesaaraki [26] modified the work of Nuraini et al., 2009 [25] by considering an incidence rate of susceptible monocytes and free viruses as Beddington-DeAngelis functional response. In 2017, Mishra and Gakkhar [27] added two more classes from previous works, and they were B-cells and antibodies. A year later, Perera and Perera [28] modified the model of Mishra and Gakkhar, 2017 [27] by taking a role of innate immune response into account, i.e., the interferons (IFN) as another variable, however, they omit the role of CTLs in this model. In 2020, Thibodeaux et al. [29] modified Nuraini et al., 2009 [25] model under an assumption that target cells are produced at a nonconstant rate. A year later, Kanumoori et al. [30] modified the work of Mishra and Gakkhar, 2017 [27] by adding the interferons (IFN) as another variable making the total population up to seven classes. In this model, CTLs are included. In 2022, Perera and Perera, modified the work of Perera and Perera, 2018 [28] by considering the role of CTLs, this model therefore is similar to the model of Kanumoori et al., 2021 [30]. However, in Perera and Perera, 2022 [31] model, they had some extra terms basing on the assumption or concept that CTLs kill infected cells and viruses kill antibodies. In 2024, Xu and the team [32] proposed a model by considering two types of antibodies i.e., IgM and IgG, macrophage cells, and antigen-presenting cells. However, with a large system of equations, they mainly focused on quantitative study. Further, an optimal control problem has also been applied into the within-host model of dengue infection. However, with authors' knowledge, at the present time there is only one optimal control model by Muthu and Modak, 2023 [33]. Here, they introduced two optimal control variables which are antibiotics to kill viruses and control that simulates the effect of the host's internal immune response.

Due to the fact that there is an incubation period after getting dengue viruses, therefore, in this study we better our understanding by constructing and analyzing within-host model for dengue viral infection which includes the exposed cells. Our model is modified from the work of Kanumoori et al., 2021 [30] and Perera and Perera, 2022 [31]. Latency stage of cells from getting dengue virus to being infected cells is considered. To make the model less complex for analysis, an innate immune response i.e., interferon is omitted, rather we focus on adaptive immune response which is more powerful and more specific to the invading pathogen. And, for the very first time we apply optimal control problem into our model by taking dengue vaccine as our control variable, bringing a novelty for within-host model of dengue infection that included the role of vaccine in pathogenesis level.

The structure of this paper is as follows. We explain how model is formulated in section 2. Section 3 presents all

model properties including nonnegativity and boundedness of solution, equilibrium points, the basic reproduction number and stability analysis. Numerical simulation of the model to confirm equilibrium points stability is shown in section 4. Section 5 presents sensitivity analysis of basic reproduction number. The optimal control model is demonstrated in section 6 with its numerical results in section 7. Finally, we make some concluding remarks in section 8.

2. Formulation of Our Proposed Model

Our proposed model describes the dengue viral infection kinetic for cells e.g., monocytes, macrophages, dendritic cells or hepatocytes etc. It also incorporates immune response including antibodies and cytotoxic T lymphocytes (CTLs). The model is modified from the proposed model of Kanumoori et al., 2021 [30] and Perera and Perera, 2022 [31]. We add latency stage of cells from getting dengue virus to being infected cells. To make the model less complex for analysis, we omit an innate immune response i.e., interferon, rather we focus on adaptive immune response which is more powerful and more specific to the invading pathogen. The model consists of seven classes of cells. The first three classes are x, e and y representing the concentration of healthy target cells (monocytes, macrophages, dendritic cells or hepatocytes etc.), exposed cells and infected cells. Another four classes are the concentration of free viruses (v), the concentration of B-cells (b), the concentration of antibodies (a), and the concentration of cytotoxic T lymphocytes (z). Here, the healthy target cells are produced at a rate Λ and they are infected by dengue virus at a rate β. Both healthy target cells and exposed cells die naturally at a rate μ. Exposed cells are transitioned to infected cells at a rate α. Infected cells are declined due to both natural death and infection-induced death at a rate d and they are lysed by CTLs at a rate q. Free viruses are produced by infected cells at a rate k, die at a rate γ, and are neutralized by antibodies at a rate p. The presence of viruses activates B-cells at a rate c, where B-cells death rate is δ. Further, antibodies production and death rate are f and s, respectively. Antibodies are also killed by viruses at a rate ε. Finally, CTLs are expanded by derivation from infected cells at a rate m and died at a rate n. This model can be described as diagram shown in Fig. 1 and as system of ODE equations as (2.1)-(2.7) below. Later, in section 6, an optimal control problem is applied into our model in which a vaccination is added.

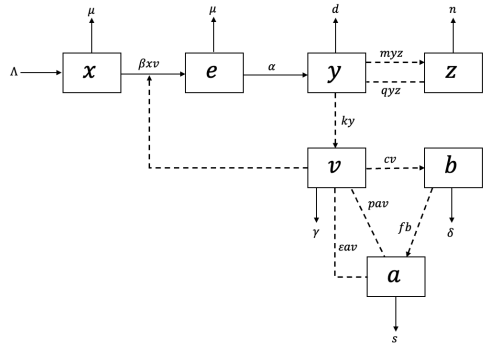

Fig. 1. A diagram for our dengue viral infection model.

$$\frac{dx}{dt} = \Lambda - \beta xv - \mu x, \tag{2.1}$$

$$\frac{de}{dt} = \beta xv - \alpha e - \mu e, \tag{2.2}$$

$$\frac{dy}{dt} = \alpha e - dy - qyz, \tag{2.3}$$

$$\frac{dv}{dt} = ky - \gamma v - pav, \tag{2.4}$$

$$\frac{db}{dt} = cv - \delta b, \tag{2.5}$$

$$\frac{da}{dt} = fb - \varepsilon av - sa, \qquad (2.6)$$

$$\frac{dz}{dt} = myz - nz. \qquad (2.7)$$

The initial conditions are $x(0) \geq 0$, $e(0) \geq 0$, $y(0) \geq 0$, $v(0) \geq 0$, $b(0) \geq 0$, $a(0) \geq 0$, and $z(0) \geq 0$.

3. Model Analysis

3.1 Positivity and boundedness of the solutions

Theorem 3.1. *With nonnegative initial conditions, all solutions of Eqs.* (2.1) – (2.7) *remain nonnegative and bounded for all* $t > 0$.

Proof. For $t > 0$, we have the following:

$$\left.\frac{dx}{dt}\right|_{x=0} = \Lambda \geq 0, \left.\frac{de}{dt}\right|_{e=0} = \beta xv \geq 0,$$
$$\left.\frac{dy}{dt}\right|_{y=0} = \alpha e \geq 0, \left.\frac{dv}{dt}\right|_{v=0} = ky \geq 0,$$
$$\left.\frac{db}{dt}\right|_{b=0} = cv \geq 0, \left.\frac{da}{dt}\right|_{a=0} = fb \geq 0,$$
$$\left.\frac{dz}{dt}\right|_{z=0} = 0.$$

Therefore, with the use of functional differential equations theory, the positivity of all solutions initiating in $\mathbb{R}^7_+$ is guaranteed for all $t > 0$. Next, the boundedness of solutions is verified.

Consider the total number of poputation, $N = x + e + y + \frac{q}{m}z$. Then,

$$\begin{aligned}\frac{dN}{dt} &= \frac{dx}{dt} + \frac{de}{dt} + \frac{dy}{dt} + \left(\frac{q}{m}\right)\frac{dz}{dt} \\ &= \Lambda - \beta xv - \mu x + \beta xv - \alpha e \\ &\quad -\mu e + \alpha e - dy - qyz + qyz \\ &\quad -\frac{qnz}{m} \\ &= \Lambda - \mu x - \mu e - dy - \frac{qnz}{m} \\ &\leq \Lambda - \phi N, \qquad (3.1)\end{aligned}$$

where, $\phi = min(\mu, d, n)$.
Hence,

$$\frac{dN}{dt} \leq \Lambda - \phi N. \qquad (3.2)$$

We next solve Eq. (3.2) by integration, we have

$$N \leq \frac{\Lambda}{\phi} + C_1 e^{-\phi t}. \qquad (3.3)$$

When $t \to \infty$, then $N \to \frac{\Lambda}{\phi}$, implying that $0 \leq N \leq \frac{\Lambda}{\phi}$.
Next, consider the concentration of free viruses, and since $y \leq N \leq \frac{\Lambda}{\phi}$, then

$$\begin{aligned}\frac{dv}{dt} &= ky - \gamma v - pva \\ &\leq k\frac{\Lambda}{\phi} - \gamma v. \qquad (3.4)\end{aligned}$$

Similarly, by integration, we have

$$v \leq \frac{k\Lambda}{\gamma\phi} + C_2 e^{-\gamma t}. \qquad (3.5)$$

And when $t \to \infty$, we have $v \to \frac{k\Lambda}{\gamma\phi}$, implying that $0 \leq v \leq \frac{k\Lambda}{\gamma\phi}$.
And, consider the concentration of B-cells, and since $v \leq \frac{k\Lambda}{\gamma\phi}$, then

$$\begin{aligned}\frac{db}{dt} &= cv - \delta b \\ &\leq \frac{ck\Lambda}{\gamma\phi} - \delta b. \qquad (3.6)\end{aligned}$$

Similarly, by integration, we have

$$b \leq \frac{ck\Lambda}{\gamma\phi\delta} + C_3 e^{-\delta t}. \qquad (3.7)$$

Consider when $t \to \infty$, then $b \to \frac{ck\Lambda}{\gamma\phi\delta}$, implying that $0 \le b \le \frac{ck\Lambda}{\gamma\phi\delta}$.
Finally, consider the concentration of antibodies, and since $b \le \frac{ck\Lambda}{\gamma\phi\delta}$, then

$$\begin{aligned}\frac{da}{dt} &= fb - \varepsilon av - sa \\ &\le \frac{fck\Lambda}{\gamma\phi\delta} - sa. \qquad (3.8)\end{aligned}$$

By integration, we have

$$a \le \frac{fck\Lambda}{\gamma\phi\delta s} + C_4 e^{-st}. \qquad (3.9)$$

Consider when $t \to \infty$, then $a \to \frac{fck\Lambda}{\gamma\phi\delta s}$, implying that $0 \le a \le \frac{fck\Lambda}{\gamma\phi\delta s}$.
Hence, all solutions of Eqs. (2.1) – (2.7) are bounded and the following compact set $\Omega = \left\{(x, e, y, v, b, a, z) \in \mathbb{R}^7_+ : N \le \frac{\Lambda}{\phi}, v \le \frac{k\Lambda}{\gamma\phi}, b \le \frac{ck\Lambda}{\gamma\phi\delta} \text{ and } a \le \frac{fck\Lambda}{\gamma\phi\delta s}\right\}$, where $N = x + e + y + \frac{q}{m}z$

is the biologically feasible region for Eqs. (2.1) – (2.7).
This completes the proof.

3.2 Equilibrium points

We determine two equilibrium points for this model.

3.2.1 Infection-free equilibrium point (E_0)

$$E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0\right). \qquad (3.10)$$

3.2.2 The infected steady state (E_1^*)

$E_1^* = (x^*, e^*, y^*, v^*, b^*, a^*, z^*)$, where

$$x^* = \frac{\Lambda c}{\beta\delta b^* + \mu c}, e^* = \frac{\beta\Lambda\delta b^*}{(\beta\delta b^* + \mu c)(\alpha + \mu)},$$

$$y^* = \frac{n}{m}, v^* = \frac{\delta b^*}{c},$$

$$a^* = \frac{knc - \gamma\delta b^* m}{mp\delta b^*}, \text{ where } knc > \gamma\delta b^* m$$

$$z^* = \frac{\alpha\beta\Lambda\delta b^* m - dn(\beta\delta b^* + \mu c)(\alpha + \mu)}{qn(\beta\delta b^* + \mu c)(\alpha + \mu)},$$

where $\alpha\beta\Lambda\delta b^* m > dn(\beta\delta b^* + \mu c)(\alpha + \mu)$,

b^* is a positive solution of equation $A_1 b^2 + A_2 b + A_3 = 0$, where

$$\begin{aligned}A_1 &= fmp\delta c + \varepsilon\gamma m\delta^2 > 0 \\ A_2 &= cs\gamma\delta m - \varepsilon knc\delta \\ A_3 &= -c^2 skn < 0.\end{aligned}$$

Since $A_1 > 0$ and $A_3 < 0$, whether or not $A_2 < 0$ or $A_2 > 0$, there is one time change of sign. By Descartes' rule of sign, it guarantees that there is one positive solution of b^*.

3.3 Basic reproduction number $\mathcal{R}_0$

The basic reproduction number ($\mathcal{R}_0$) is an epidemiologic metric used to describe the contagiousness of infectious agents. It is an average number of secondary infections caused by a typical case of an infection, which in this case it is the expected number of secondary cases of dengue infection caused by a typical case of an infected cell. In this study, the next-generation matrix method [34] is used to compute $\mathcal{R}_0$. $\mathcal{F}$ is a matrix of the rate of new infections appearance which is the rate of all flows from x to e, and $\mathcal{V}$ is a matrix of the transfer rate of individual infections, i.e., represents rates of all other flows.
For our model, we have

$$\mathcal{F} = \begin{bmatrix} \beta xv \\ 0 \\ 0 \end{bmatrix} \text{ and } \mathcal{V} = \begin{bmatrix} \alpha e + \mu e \\ dy + qyz - \alpha e \\ \gamma v + pav - ky \end{bmatrix}.$$

The Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$ are

$$F = \begin{bmatrix} 0 & 0 & \beta x \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

and

$$V = \begin{bmatrix} \alpha+\mu & 0 & 0 \\ -\alpha & d+qz & 0 \\ 0 & -k & \gamma+pa \end{bmatrix}.$$

And, the next generation matrix is

$$F(E_0)V^{-1}(E_0) = \begin{bmatrix} \dfrac{\beta\Lambda\alpha k}{\gamma d\mu(\alpha+\mu)} & \dfrac{\beta\Lambda k}{\gamma d\mu} & \dfrac{\beta\Lambda}{\gamma\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

The basic reproduction number is given by the spectral radius of the martrix FV^{-1}, thus

$$\mathcal{R}_0 = \frac{\beta\Lambda\alpha k}{\gamma d\mu(\alpha+\mu)}.$$

3.4 Stability of infection-free equilibrium point

3.4.1 Local stability of infection-free equilibrium point

Theorem 3.2. *If $\mathcal{R}_0 < 1$, then the infection- free equilibrium point (E_0) is locally asymptotically stable, otherwise it is unstable.*

Proof. The Jacobian matrix at the infection-free equilibrium point is $J(E_0)$

$$= \begin{bmatrix} -\mu & 0 & 0 & \dfrac{-\beta\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & -\alpha-\mu & 0 & \dfrac{\beta\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & \alpha & -d & 0 & 0 & 0 & 0 \\ 0 & 0 & k & -\gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & c & -\delta & 0 & 0 \\ 0 & 0 & 0 & 0 & f & -s & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -n \end{bmatrix}.$$

To guarantee that the infection-free equilibrium point is stable, all eigenvalues of above $J(E_0)$ are required to be negative. Then, we find eigenvalues from $det(J(E_0) - \lambda I) = 0$,

$$\begin{vmatrix} -\mu-\lambda & 0 & 0 & \dfrac{-\beta\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & -\alpha-\mu-\lambda & 0 & \dfrac{\beta\Lambda}{\mu} & 0 & 0 & 0 \\ 0 & \alpha & -d-\lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & k & -\gamma-\lambda & 0 & 0 & 0 \\ 0 & 0 & 0 & c & -\delta-\lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & f & -s-\lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -n-\lambda \end{vmatrix} = 0.$$

By cofactor expansion, we have

$$(-\mu-\lambda)(-n-\lambda)(-s-\lambda)(-\delta-\lambda)\begin{vmatrix} -\alpha-\mu-\lambda & \dfrac{\beta\Lambda}{\mu} & 0 \\ \alpha & 0 & 0 \\ 0 & -d-\lambda & k \\ 0 & k & -\gamma-\lambda \end{vmatrix} = 0.$$

Then, the first four eigenvalues are

$$\lambda_1 = -\mu < 0, \lambda_2 = -n < 0,$$
$$\lambda_3 = -s < 0, \lambda_4 = -\delta < 0.$$

And, the rest of a characterestic equation is

$$(-\alpha-\mu-\lambda)\begin{vmatrix} -d-\lambda & 0 \\ k & -\gamma-\lambda \end{vmatrix} + \frac{\beta\Lambda}{\mu}\begin{vmatrix} \alpha & d-\lambda \\ 0 & k \end{vmatrix} = 0,$$

$$\lambda^3 + (\alpha+\mu+d+\gamma)\lambda^2 + \Big[\gamma d + (\gamma+d)(\alpha+\mu)\Big]\lambda + \gamma d(\alpha+\mu) - \frac{\beta\Lambda\alpha k}{\mu} = 0.$$

Consider the above characteristic equation by using the Routh-Hurwitz Criterion and consider it in the form of

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

we have

$$\begin{aligned} a_1 &= \alpha+\mu+d+\gamma > 0, \\ a_3 &= \gamma d(\alpha+\mu) - \frac{\beta\Lambda\alpha k}{\mu} \\ &= \gamma d(\alpha+\mu)(1-\mathcal{R}_0). \end{aligned}$$

Thus, $a_3 > 0$ when $\mathcal{R}_0 < 1$. Next, consider

$$a_1a_2 - a_3 = (\alpha+\mu+d+\gamma)\,[\gamma d + (d+\gamma)(\alpha+\mu)]$$

$$-\gamma d(\alpha+\mu)+\frac{\beta\Lambda\alpha k}{\mu}$$
$$=(d+\gamma)\left[\gamma d+(\alpha+\mu)(\alpha+\mu+d+\gamma)\right]$$
$$+\frac{\beta\Lambda\alpha k}{\mu}>0.$$

Hence, by the Routh-Hurwitz Criterion, the infection-free equilibrium point is locally asymptotically stable if $\mathcal{R}_0 < 1$, when $\mathcal{R}_0 > 1$ it is unstable. This completes the proof. This means when $\mathcal{R}_0 < 1$, the infection will be eliminated eventually towards infection-free equilibrium point. □

3.4.2 Global stability of infection-free equilibrium point

Theorem 3.3. *The infection-free equilibrium point* (E_0) *is globally asymptotically stable if* $\mathcal{R}_0 < 1$.

Proof. Lyapunov function method is used and it is defined as

$$L=\alpha e+(\alpha+\mu)y+\frac{(\alpha+\mu)d}{k}v. \quad (3.11)$$

Clearly, L is positive definite.
Then, calculate the derivative of L along the solutions of the model, and we obtain

$$\begin{aligned}
L' &= \frac{\partial L}{\partial e}\cdot\frac{de}{dt}+\frac{\partial L}{\partial y}\cdot\frac{dy}{dt}+\frac{\partial L}{\partial v}\cdot\frac{dv}{dt}\\
&= \alpha[\beta xv-\alpha e-\mu e]+(\alpha+\mu)[\alpha e-dy-qyz]\\
&\quad +\frac{(\alpha+\mu)d}{k}[ky-\gamma v-pav]\\
&= \alpha\beta xv-qyz(\alpha+\mu)-\frac{dv(\alpha+\mu)(\gamma+pa)}{k}\\
&\le \alpha\beta xv-\frac{dv\gamma(\alpha+\mu)}{k}-qyz(\alpha+\mu)\\
&= v\left[\alpha\beta x-\frac{d\gamma(\alpha+\mu)}{k}\right]-qyz(\alpha+\mu)\\
&\le v\left[\frac{\alpha\beta\Lambda}{\mu}-\frac{d\gamma(\alpha+\mu)}{k}\right]-qyz(\alpha+\mu)\\
&= \frac{vd\gamma(\alpha+\mu)}{k}\left[\frac{\beta\Lambda\alpha k}{\gamma d\mu(\alpha+\mu)}-1\right]-qyz(\alpha+\mu)\\
&= \frac{vd\gamma(\alpha+\mu)}{k}(\mathcal{R}_0-1)-qyz(\alpha+\mu).
\end{aligned}$$

Here, $L' = 0$, when $v = y = z = 0$ and $L' < 0$ when $\mathcal{R}_0 < 1$. Lasalle's invariance principle [35] requires that L' be negative semi-definite, i.e., $L' \le 0$, to ensure that the dynamics measured by the Lyapunov function does not increase over time. And, if $L' \le 0$, LaSalle's invariance principle can be applied to conclude that the system trajectories will eventually converge to the largest invariant set within the region where $L' = 0$.

From above we obtain that the largest invariant set where $L' = 0$ is the set that $v = y = z = 0$ i.e., the equilibrium point E_0. Therefore, by Lasalle's invariance principle [36] when $\mathcal{R}_0 < 1$, the system trajectories will converge to E_0, i.e., E_0 is globally asymptotically stable. This completes the proof. □

3.5 Stability of the infected steady state

3.5.1 Local stability of the infected steady state

Theorem 3.4. *When* $R_0 > 1$, *the infected steady state* (E_1^*) *is locally stable if it satisfies the Routh-Array criteria.*

Proof. The Jacobian matrix at the infected steady state is $J\left(E_1^*\right)$

$$=\begin{bmatrix}
-\beta v^*-\mu & 0 & 0 & 0\\
\beta v^* & -\alpha-\mu & 0 & 0\\
0 & \alpha & -d-qz^* & \frac{-qn}{m}\\
0 & 0 & k & 0\\
0 & 0 & 0 & -pv^*\\
0 & 0 & 0 & 0\\
0 & 0 & mz^* & 0
\end{bmatrix}
\begin{bmatrix}
-\beta x^* & 0 & 0 & 0\\
\beta x^* & 0 & 0 & 0\\
0 & 0 & 0 & \frac{-qn}{m}\\
-\gamma-pa^* & 0 & -pv^* & 0\\
c & -\delta & 0 & 0\\
-\varepsilon a^* & f & -\varepsilon v^*-s & 0\\
0 & 0 & 0 & 0
\end{bmatrix}.$$

Similar to Theorem 3.2, we calculate the characteristic equation of above $J(E_1)$ by using cofactor expansion.

Then, the characteristic equation of Jacobian matrix above is written in the form of $a_0\lambda^7+a_1\lambda^6+a_2\lambda^5+a_3\lambda^4+a_4\lambda^3+a_5\lambda^2+a_6\lambda+a_7=0$,
where

$a_0 = 1$

$$
\begin{aligned}
a_1 &= B_6 + B_3 + B_1,\\
a_2 &= B_4 + B_1B_3 + B_2 + B_6(B_3 + B_1) + B_7,\\
a_3 &= B_5 + B_1B_4 + B_2B_3 + B_6(B_4 + B_1B_3 + B_2)\\
&\quad + B_7(B_3 + B_1) - k\alpha\beta x^*,\\
a_4 &= B_1B_5 + B_2B_4 + B_6(B_5 + B_1B_4 + B_2B_3)\\
&\quad + B_7(B_4 + B_1B_3 + B_2) - \left[\beta x^* B_9 + k\alpha B_{10}\right],\\
a_5 &= B_2B_5 + B_6(B_1B_5 + B_2B_4) + B_7(B_5 + B_1B_4\\
&\quad + B_2B_3) - \left[\beta x^* B_8 + B_9B_{10}\right],\\
a_6 &= B_2B_5B_6 + B_7(B_1B_5 + B_2B_4) - B_8B_{10},\\
a_7 &= B_2B_5B_7.
\end{aligned}
$$

Here,

$$
\begin{aligned}
&B_1 = \mu + \beta v^* + \alpha + \mu, B_2 = (\alpha + \mu)(\mu + \beta v^*),\\
&B_3 = (\varepsilon v^* + s) + (\gamma + pa^* + \delta),\\
&B_4 = (\gamma + pa^*)\delta + (\gamma + pa^* + \delta)(\varepsilon v^* + s) - pv^*\varepsilon a^*,\\
&B_5 = (\gamma + pa^*)(\varepsilon v^* + s)\delta + pv^* cf - pv^*\varepsilon a^* s,\\
&B_6 = (d + qz^*), B_7 = \frac{qn}{m}(mz^*), B_8 = k\alpha\delta(\varepsilon v^* + s),\\
&B_9 = k\alpha(\varepsilon v^* + s) + k\alpha\delta, B_{10} = \beta x^*\mu.
\end{aligned}
$$

Therefore, the infected steady state is stable if satisfies the Routh-Array criteria for n = 7, i.e.,

$$
\begin{aligned}
&a_0 \geq 0,\ a_1 \geq 0,\ a_2 \geq 0,\ \frac{a_1a_2 - a_0a_3}{a_1} \geq 0,\\
&\frac{b_1a_3 - a_1b_2}{b_1} \geq 0,\ \frac{c_1b_2 - b_1c_2}{c_1} \geq 0,\\
&\frac{d_1c_2 - c_1c_2}{d_1} \geq 0,\ \frac{e_1d_2 - d_1e_2}{e_1} \geq 0,\\
&\frac{f_1e_2 - e_1f_2}{f_1} \geq 0.
\end{aligned}
$$

This means that if the conditions above are met, an infection will spread out to the value of all cell population as infected steady state. □

3.5.2 Global stability of the infected steady state

We use the geometric approach by Li and Muldowney [37] to analyze global stability of infected equilibrium point. Geometric approach [37] can be recognized as a special case of classical result of Lyapunov method. It gives a new criterion for the global stability of equilibria for nonlinear autonomous ordinary differential equations in any finite dimension based on the criteria of Bendixon and Dulac for planar systems and on a local version of the C^1 closing lemma of Pugh [38].

The concept of this approach is explained below.

Let the autonomous dynamical system is

$$\dot{x} = f(x), x \in \Omega \subset \mathbb{R}^n, \tag{3.12}$$

where $f : \Omega \to \mathbb{R}^n$, and $f \in C^1(\Omega)$.

The assumptions below are made:

(H1) Ω is simply connected.

(H2) there is a compact absorbing set $\Gamma \subset \Omega$.

(H3) $\bar{x}$ is the unique equilibrium point of (3.12) in Ω.

Then, the result following Li and Muldowney approach is presented in the theory below.

Theorem 3.5. Under the assumptions **(H1) - (H3)** above, the unique equilibrium point $\bar{x}$ of (3.12) is globally asymptotically stable int Ω when $\bar{q}_2 < 0$, where

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{x_0 \in E} \frac{1}{t}\int_0^t v(B(x(s, x_0)))ds. \tag{3.13}$$

Here, the matrix B is defined as $B = Q_f Q^{-1} + QJ^{[2]}Q^{-1}$, where Q_f is the derivative in the direction of solution of f and $J^{[2]}$ is the second additive compound matrix of Jacobian J of the system Eq. (3.12). In addition, the $v(B)$ is the *Lozinskiĭ* measure with respect to a vector norm $\|\cdot\|$ in $\mathbb{R}^n$, where

$$v(B) = \lim_{h\to 0^+} \frac{\|I + hB\| - 1}{h}.$$

Next, we shall analyze the global stability of the infected steady state for our model.

Lemma 3.1. *When* $\mathcal{R}_0 > 1$, *the Eqs. (2.1)-(2.7) is uniformly persistent in int* (Ω).

Proof. From Theorem 3.3 when $\mathcal{R}_0 < 1$, we have $\frac{dL}{dt} \leq 0$, and when $\mathcal{R}_0 > 1$, $\frac{dL}{dt} > 0$. This leads to the instability of E_0. By the result of Freedman et al., 1994 [39] and Butler et al., 1986 [40], therefore, the system is uniformly persistent in the interior of Ω i.e., there exists a constant $w > 0$ such that

$$\liminf_{t\to\infty} x(t) > w, \liminf_{t\to\infty} e(t) > w, \liminf_{t\to\infty} y(t) > w,$$
$$\liminf_{t\to\infty} v(t) > w, \liminf_{t\to\infty} b(t) > w, \liminf_{t\to\infty} a(t) > w,$$
$$\liminf_{t\to\infty} z(t) > w,$$

provided $(x(0), e(0), y(0), v(0), b(0), a(0), z(0)) \in \Omega$. With two properties which are the uniformly persistence and the boundedness of Ω, it is therefore equivalent to the existence of a compact set. This set is absorbing for our Eqs. (2.1)-(2.7) in the interior of Ω. Hence, the assumption ***(H1)*** and ***(H2)*** hold.

Theorem 3.6. When $\mathcal{R}_0 > 1$ and when $\bar{b} > 0$ ($\bar{b}$ is defined in the proof), the infected steady state (E_1^*) is globally asymptotically stable in *int* Ω.

Proof. It can be obtained from above that the assumptions ***(H1) - (H3)*** hold.
Then, we consider the Jacobian matrix of (2.1)-(2.4) as follows:

$$J(x,e,y,v) = \begin{bmatrix} -(\beta v+\mu) & 0 & 0 & -\beta x \\ \beta v & -(\alpha+\mu) & 0 & \beta x \\ 0 & \alpha & -(d+qz) & 0 \\ 0 & 0 & k & -(\gamma+pa) \end{bmatrix}.$$

Let

$$M_{11} = \beta v + \mu, M_{22} = \alpha + \mu, M_{33} = d + qz$$
and $M_{44} = \gamma + pa$.

The second additive compound matrix of the Eqs. (2.1)-(2.4) is

$$J^{[2]} = \begin{bmatrix} -(M_{11}+M_{22}) & 0 & \beta x & 0 & \beta x & 0 \\ \alpha & -(M_{11}+M_{33}) & 0 & \beta x & 0 & \beta x \\ 0 & k & -(M_{11}+M_{44}) & 0 & 0 & 0 \\ 0 & \beta v & 0 & -(M_{22}+M_{33}) & 0 & -\beta x \\ 0 & 0 & \beta v & k & -(M_{22}+M_{44}) & 0 \\ 0 & 0 & 0 & 0 & \alpha & -(M_{33}+M_{44}) \end{bmatrix}.$$

We then define the matrix function Q by

$$Q(x,e,y,v) = \text{diag}\left\{1,1,1,1,\frac{y}{v},\frac{y}{v}\right\}.$$

Then, we obtain

$$Q_f Q^{-1} = \text{diag}\left\{0,0,0,0,\frac{y'}{y}-\frac{v'}{v},\frac{y'}{y}-\frac{v'}{v}\right\}.$$

Next, we determine $QJ^{[2]}Q^{-1}$, and

$$QJ^{[2]}Q^{-1} = \begin{bmatrix} -(M_{11}+M_{22}) & 0 & \beta x & 0 & \beta x\frac{v}{y} & 0 \\ \alpha & -(M_{11}+M_{33}) & 0 & \beta x & 0 & \beta x\frac{v}{y} \\ 0 & k & -(M_{11}+M_{44}) & 0 & 0 & 0 \\ 0 & \beta v & 0 & -(M_{22}+M_{33}) & 0 & -\beta x\frac{v}{y} \\ 0 & 0 & \beta y & k\frac{y}{v} & -(M_{22}+M_{44}) & 0 \\ 0 & 0 & 0 & 0 & \alpha & -(M_{33}+M_{44}) \end{bmatrix}.$$

Then, $B = Q_f Q^{-1} + QJ^{[2]}Q^{-1}$

$$B = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix},$$

where

$$B_{11} = \left[-(M_{11}+M_{22})\right],$$

$$B_{12} = \begin{bmatrix} 0 & \beta x & 0 & \beta x\frac{v}{y} & 0 \end{bmatrix},$$

$$B_{21} = \begin{bmatrix} \alpha \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

$$B_{22} = \begin{bmatrix} -(M_{11}+M_{33}) & 0 & 0 & 0 & \beta x\frac{v}{y} \\ k & -(M_{11}+M_{44}) & 0 & 0 & -\beta x\frac{v}{y} \\ \beta v & 0 & -(M_{22}+M_{33}) & \beta y & 0 \\ 0 & \beta y & k\frac{y}{v} & -(M_{22}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) & 0 \\ 0 & 0 & 0 & \alpha & -(M_{33}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) \end{bmatrix}.$$

The *Lozinskiĭ* measure of matrix B is defined as follows:

$$v(B) \leqslant \max\{g_1, g_2\},$$

where $g_1 = v(B_{11}) + \|B_{12}\|$, and $g_2 = \|B_{21}\| + v(B_{22})$.

Here,

$v(B_{11}) = -(M_{11}+M_{22}), \|B_{12}\| = \max\{\beta x, \beta x\frac{v}{y}\}$, $\|B_{21}\| = \alpha$, and

$v(B_{22})$ is to be determined.
Thus, we have

$$\begin{aligned} g_1 &= v(B_{11}) + \|B_{12}\| \\ &= -(M_{11}+M_{22}) + \max\{\beta x, \beta x\frac{v}{y}\}. \end{aligned}$$

$$g_2 = \|B_{21}\| + v(B_{22}) = \alpha + v(B_{22}).$$

We next partition the matrix B_{22} as

$$B_{22} = F = \begin{bmatrix} F_{11} & F_{12} \\ F_{21} & F_{22} \end{bmatrix}$$

where

$$F_{11} = \begin{bmatrix} -(M_{11}+M_{33}) \end{bmatrix},$$

$$F_{12} = \begin{bmatrix} 0 & 0 & 0 & \beta x\frac{v}{y} \end{bmatrix},$$

$$F_{21} = \begin{bmatrix} k \\ \beta v \\ 0 \\ 0 \end{bmatrix},$$

$$F_{22} = \begin{bmatrix} -(M_{11}+M_{44}) & 0 & 0 \\ 0 & -(M_{22}+M_{33}) & 0 \\ \beta y & k\frac{y}{v} & -\beta x\frac{v}{y} \\ 0 & 0 & -(M_{22}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) \\ 0 & 0 & \alpha \end{bmatrix}$$

$$\begin{bmatrix} 0 & 0 \\ 0 & -\beta x\frac{v}{y} \\ -(M_{22}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) & 0 \\ \alpha & -(M_{33}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) \end{bmatrix}.$$

Similarly, we define the *Lozinskiĭ* measure of matrix F as

$$v(F) \leqslant \max\{g_3, g_4\},$$

where $g_3 = v(F_{11}) + \|F_{12}\|$ and $g_4 = \|F_{21}\| + v(F_{22})$.
We obtain

$$v(F_{11}) = -(M_{11}+M_{33}), \|F_{12}\| = \beta x\frac{v}{y},$$

$\|F_{21}\| = k + \beta v$, and

$v(F_{22})$ is to be determined.
Therefore, we have

$$\begin{aligned} g_3 &= v(F_{11}) + \|F_{12}\| \\ &= -(M_{11}+M_{33}) + \beta x\frac{v}{y}, \\ g_4 &= \|F_{21}\| + v(F_{22}) \\ &= k + \beta v + v(F_{22}). \end{aligned}$$

Next, we partition the matrix F_{22} as

$$F_{22} = G = \begin{bmatrix} G_{11} & G_{12} \\ G_{21} & G_{22} \end{bmatrix}$$

where

$$G_{11} = \begin{bmatrix} -(M_{11}+M_{44}) \end{bmatrix}, \; G_{12} = \begin{bmatrix} 0 & 0 & 0 \end{bmatrix},$$

$$G_{21} = \begin{bmatrix} 0 \\ \beta y \\ 0 \end{bmatrix},$$

$$G_{22} = \begin{bmatrix} -(M_{22}+M_{33}) & 0 \\ k\frac{y}{v} & -(M_{22}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) \\ 0 & \alpha \end{bmatrix}$$

$$\begin{bmatrix} -\beta x\frac{v}{y} \\ 0 \\ -(M_{33}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) \end{bmatrix}.$$

Now, we define the *Lozinskiĭ* measure of matrix G as

$$v(G) \leq \max\{g_5, g_6\},$$

where $g_5 = v(G_{11}) + \|G_{12}\|$ and $g_6 = \|G_{21}\| + v(G_{22})$.
We have,

$$v(G_{11}) = -(M_{11}+M_{44}), \|G_{12}\| = 0,$$
$$\|G_{21}\| = \beta y, \text{and}$$

$v(G_{22})$ is to be determined.
Thus, we have

$$g_5 = v(G_{11}) + \|G_{12}\| = -(M_{11}+M_{44}),$$
$$g_6 = \|G_{21}\| + v(G_{22}) = \beta y + v(G_{22}).$$

Next, we partition the matrix G_{22} as

$$G_{22} = H = \begin{bmatrix} H_{11} & H_{12} \\ H_{21} & H_{22} \end{bmatrix}$$

where $H_{11} = \left[-(M_{22}+M_{33})\right]$,

$$H_{12} = \begin{bmatrix} 0 & -\beta x\frac{v}{y} \end{bmatrix},$$

$$H_{21} = \begin{bmatrix} k\frac{y}{v} \\ 0 \end{bmatrix},$$

$$H_{22} = \begin{bmatrix} -(M_{22}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) & 0 \\ \alpha & -(M_{33}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right) \end{bmatrix}.$$

The *Lozinskii* measure of matrix H is

$$v(H) \leq \max\{g_7, g_8\},$$

where $g_7 = v(H_{11}) + \|H_{12}\|$ and $g_8 = \|H_{21}\| + v(H_{22})$.
We obtain,

$$v(H_{11}) = -(M_{22}+M_{33}),$$
$$\|H_{12}\| = \beta x\frac{v}{y}, \|H_{21}\| = k\frac{y}{v}.$$

Then,

$$\begin{aligned} v(H_{22}) &= \max\{-(M_{22}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right)+\alpha, \\ &\quad -(M_{33}+M_{44})+\left(\frac{y'}{y}-\frac{v'}{v}\right)\} \\ &= \max\{-(\mu+\gamma+pa)+\left(\frac{y'}{y}-\frac{v'}{v}\right), \\ &\quad -(d+qz+\gamma+pa)+\left(\frac{y'}{y}-\frac{v'}{v}\right)\}. \end{aligned}$$

From the equation (2.4), we have

$$\frac{dv}{dt} = ky - \gamma v - pav$$
$$\frac{v'}{v} = \frac{ky}{v} - \gamma - pa.$$

Substitute above expression in $v(H_{22})$, we then have

$$v(H_{22}) = \max\{-\mu + \frac{y'}{y} - \frac{ky}{v}, -(d+qz) + \frac{y'}{y} - \frac{ky}{v}\}.$$

Therefore,

$$\begin{aligned} g_7 &= v(H_{11}) + \|H_{12}\| \\ &= -(M_{22}+M_{33}) + \beta x\frac{v}{y} \\ &= -(\alpha+\mu+d+qz) + \beta x\frac{v}{y}, \end{aligned}$$

$$g_8 = \|H_{21}\| + v(H_{22})$$
$$= k\frac{y}{v} + \max\{-\mu + \frac{y'}{y} - \frac{ky}{v}, -(d+qz)$$
$$+ \frac{y'}{y} - \frac{ky}{v}\}$$
$$= \frac{y'}{y} + \max\{-\mu, -(d+qz)\}.$$

And from the equation (2.3), we have

$$\frac{dy}{dt} = \alpha e - dy - qyz$$
$$\frac{y'}{y} = \frac{\alpha e}{y} - d - qz.$$

We consider

$$g_7 = -(\alpha + \mu + d + qz) + \beta x\frac{v}{y}$$
$$= \frac{y'}{y} - \frac{\alpha e}{y} - (\alpha + \mu) + \beta x\frac{v}{y}.$$

Therefore,

$$v(H) \le \max\{g_7, g_8\}$$
$$\le \frac{y'}{y} + \max\left\{-\frac{\alpha e}{y} - (\alpha+\mu) + \beta x\frac{v}{y},\right.$$
$$\left.\sup\{-\mu, -(d+qz)\}\right\}.$$

Then, we have

$$v(G) \le \max\{g_5, g_6\},$$

where

$$g_5 = -(M_{11} + M_{44})$$
$$= \frac{y'}{y} - (M_{11} + M_{44}) - \frac{\alpha e}{y} + d + qz.$$
$$g_6 = \beta y + v(G_{22}).$$

Therefore,

$$v(G) \le \frac{y'}{y} + \max\left\{d + qz - (M_{11} + M_{44})\right.$$
$$-\frac{\alpha e}{y}, \beta y + \beta x\frac{v}{y} - \frac{\alpha e}{y} - (\alpha+\mu),$$
$$\left.+\beta y + \sup\{-\mu, -(d+qz)\}\right\}.$$

Next, consider

$$v(F) \le \max\{g_3, g_4\},$$

where

$$g_3 = -(M_{11} + M_{33}) + \beta x\frac{v}{y}$$
$$= \frac{y'}{y} - (M_{11} + M_{33}) + \beta x\frac{v}{y} - \frac{\alpha e}{y}$$
$$+ d + qz.$$
and $g_4 = k + \beta v + v(F_{22})$.

Therefore

$$v(F) \le \frac{y'}{y} + \max\left\{-(M_{11} + M_{33}) + \beta x\frac{v}{y} - \frac{\alpha e}{y}\right.$$
$$+d + qz, k + \beta v + d + qz - (M_{11} + M_{44})$$
$$-\frac{\alpha e}{y}, k + \beta v + \beta y + \beta x\frac{v}{y} - \frac{\alpha e}{y}$$
$$-(\alpha+\mu), k + \beta v + \beta y + \sup\{-\mu,$$
$$\left.-(d+qz)\}\right\}.$$

Since $v(B) \le \max\{g_1, g_2\}$,

where

$$g_1 = -(M_{11} + M_{22}) + \max\{\beta x, \beta x\frac{v}{y}\}$$
$$= \frac{y'}{y} - (M_{11} + M_{22}) + \max\left\{\beta x, \beta x\frac{v}{y}\right\}$$
$$- \frac{\alpha e}{y} + d + qz.$$
and $g_2 = \alpha + v(B_{22})$.

Hence,

$$v(B) \le \frac{y'}{y} + \max\left\{-(M_{11} + M_{22}) + \sup\{\beta x, \beta x\frac{v}{y}\}\right.$$
$$-\frac{\alpha e}{y} + d + qz, \alpha - (M_{11} + M_{33}) + \beta x\frac{v}{y}$$
$$-\frac{\alpha e}{y} + d + qz, \alpha + k + \beta v + d + qz$$

$$
\begin{aligned}
&- (M_{11} + M_{44}) - \frac{\alpha e}{y}, \alpha + k + \beta v + \beta y \\
&+ \beta x \frac{v}{y} - \frac{\alpha e}{y} - (\alpha + \mu), \alpha + k + \beta v + \beta y \\
&+ \sup\{-\mu, -(d + qz)\}\Big\}. \\
&= \frac{y'}{y} - \bar{b},
\end{aligned}
$$

where

$$
\begin{aligned}
\bar{b} = \min \Big\{ & \beta v + \mu + \alpha + \mu - \inf\{-\beta x, -\beta x \frac{v}{y}\} \\
& + \frac{\alpha e}{y} - d - qz, \beta v + \mu - \alpha - \beta x \frac{v}{y} + \frac{\alpha e}{y}, \\
& \gamma + pa + \frac{\alpha e}{y} + \mu - \alpha - k - d - qz, \\
& \mu + \frac{\alpha e}{y} - k - \beta v - \beta y - \beta x \frac{v}{y}, -\alpha - k \\
& - \beta v - \beta y - \inf\{\mu, (d + qz)\}\Big\}.
\end{aligned}
$$

Let $\bar{t}$ be large enough such that the system is persistent and $(x(t), e(t), y(t), v(t)) \subset \Gamma$ for all $t \geq \bar{t}$. Then, for $t > \bar{t}$ along each solution $x(t), e(t), y(t), v(t)$ such that $(x(0), e(0), y(0), v(0)) \in \Gamma$, $\frac{1}{t}[\ln y(t) - \ln y(0)] < \frac{\bar{b}}{2}$.
Thus,

$$
\begin{aligned}
\bar{q_2} = \frac{1}{t}\int_0^t v(B)ds &\leq \frac{1}{t}\int_0^t \Big(\frac{y'}{y} - \bar{b}\Big)ds \\
&= \Big(\frac{\ln y(t) - \ln y(0)}{t}\Big) - \bar{b} \\
&< -\frac{\bar{b}}{2},
\end{aligned}
$$

which implies $\bar{q_2} \leq -\frac{\bar{b}}{2} < 0$.
Hence, by Theorem 3.5, (x, e, y, v) is globally asymptotically stable in *int* Ω when $\mathcal{R}_0 > 1$ and $\bar{b} > 0$. Next, consider the fifth equation of the system,

$$\frac{db}{dt} = cv - \delta b. \tag{3.14}$$

We have its limit system as $\frac{db}{dt} = cv^* - \delta b$.

Since $cv^* = \delta b^*$, we get

$$
\begin{aligned}
\frac{db}{dt} &= \delta b^* - \delta b, \\
\frac{db}{dt} &+ \delta b = \delta b^*.
\end{aligned} \tag{3.15}
$$

By using integrating factor method, we obtain

$$b = b^* + Ce^{-\delta t}. \tag{3.16}$$

When $t \longrightarrow \infty$, we have $\lim_{t\to\infty} b(t) = b^*$.
Next, consider the sixth equation of the system,

$$\frac{da}{dt} = fb - \varepsilon av - sa.$$

Its limit system is $\frac{da}{dt} = fb^* - \varepsilon av^* - sa$.
Since $fb^* = (\varepsilon v^* + s)a^*$, we get

$$
\begin{aligned}
\frac{da}{dt} &= (\varepsilon v^* + s)(a^* - a), \\
\frac{da}{dt} &+ (\varepsilon v^* + s)a = (\varepsilon v^* + s)a^*.
\end{aligned} \tag{3.17}
$$

Therefore, by using integrating factor method, we have

$$a = a^* + Ce^{-(\varepsilon v^* + s)t}. \tag{3.18}$$

When $t \longrightarrow \infty$, we have $\lim_{t\to\infty} a(t) = a^*$.
Finally, consider the seventh equation of the system,

$$\frac{dz}{dt} = myz - nz.$$

We have its limit system as $\frac{dz}{dt} = (my^* - n)z$.
Since $my^* = n$, we get

$$
\begin{aligned}
\frac{dz}{dt} &= nz - nz, \\
\frac{dz}{dt} &= 0.
\end{aligned} \tag{3.19}
$$

This matches the definition that $z = z^*$.
Hence, E_1^* is globally asymptotically stable when $\mathcal{R}_0 > 1$ and $\bar{b} > 0$.
Thus, the proof of Theorem 3.6 is complete. □

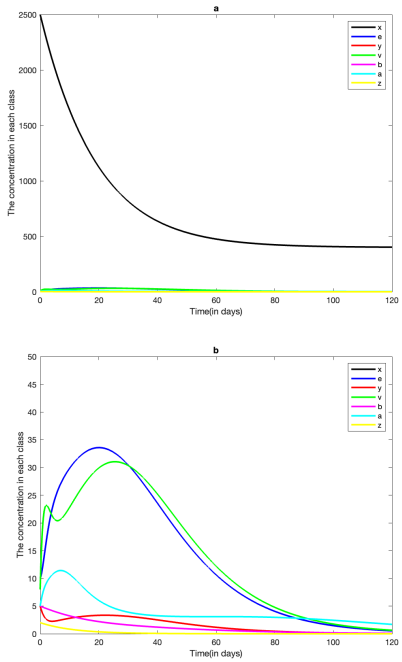

Fig. 2. The dynamics of the seven classes of cells when $\mathcal{R}_0 < 1$. Here we use $\beta = 0.0001$, where (b) is a zoom-in version of (a).

4. Numerical Results

To verify the validity of Theorem 3.3 and 3.6, the system of Eqs. (2.1)-(2.7) is solved numerically. The parameters within this model are chosen as appropriate following the previous studies of dengue within-host models which are shown in Table 1. The proportion of susceptible cells, exposed cells, infected cells, free viruses, B-cells, antibodies, and T-lymphocytes are 2500, 10, 5, 8, 5, 5 and 2, respectively. Below we demonstrate the dynamics of each class with time for two cases. The first case when $\mathcal{R}_0 < 1$ is shown in Fig. 2. The second case when $\mathcal{R}_0 > 1$ is shown in Fig. 3.

Fig. 2 shows that the system is asymptotically stable at the infection-free equilibrium point $(400, 0, 0, 0, 0, 0, 0)$, which is as expected from our analysis as basic reproduction number is $\mathcal{R}_0 = 0.4000 < 1$.

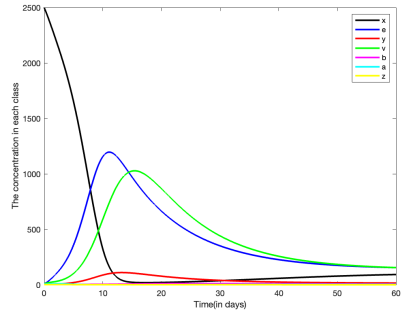

Fig. 3. The dynamics of the seven classes of cells when $\mathcal{R}_0 > 1$. Here we use $\beta = 0.001$.

Fig. 3 shows that the asymptotically stable of infected equilibrium point has been obtained and it is $(90, 166, 60, 160, 140, 5, 2, 10)$, where $\mathcal{R}_0 = 4.000 > 1$.

5. Sensitivity Analysis

In this section, the sensitivity analysis of the basic reproduction number $(\mathcal{R}_0)$ is performed. With this analysis, we can investigate how each parameter used in the model would affect the basic reproduction value. Hence, it is useful to use as a target to prevent and control the spread of dengue infection. This then will help public health authorities to focus on designing intervention strategy to effectively control the transmission of dengue. These sensitivity indices are calculated by using the technique of the normalized forward sensitivity index (see e.g., Samsuzzoha et al., 2013 [41] and Ngoteya et al., 2015 [42]). The normalized forward sensitivity index of $\mathcal{R}_0$ with respect to a parameter W is given by

$$S_W^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial W} \times \frac{W}{\mathcal{R}_0}.$$

The normalized sensitivity indices are calculated by using the parameters value in

Table 1 and they are presented in Table 2.

From Table 2, we obtain that the positive sign of sensitivity index of $\mathcal{R}_0$ (i.e., with respect to λ, β, k, and α) leads to the result that when these parameters increase, the value of $\mathcal{R}_0$ increases. On the other hand, the negative sign of sensitivity index of $\mathcal{R}_0$ (i.e., with respect to γ, d, and μ) gives a result that when these parameters increase, the value of $\mathcal{R}_0$ decreases. Here, we could see that a parameter that we could manage to control and gives a great impact on $\mathcal{R}_0$ is infection rate (β), therefore, trying to reduce this parameter or an infection term βxv would be potential intervention. Hence, in the next section we then employ a vaccination control in order to reduce this infection term.

6. Optimal Control Model

Optimal control is a method to determine control trajectories for a system over a period of time to optimize (maximize or minimize) an objective function. Here we use the optimal control theory of Pontryagin's Minimum Principle (PMP) [43] to minimize our objective function. In this study, we employ one control measure and it is a preventive vaccine control, denoted as $u(t)$, which is time-dependent vaccination control. The control is in the interval [0,1] for any time $t \geq 0$ on the interval $[0, T]$. Here 0 means that a control is not implemented whereas 1 means the full implementation of the control. An optimal control of Eqs. (2.1) - (2.7) then becomes

$$\begin{aligned}
\frac{dx}{dt} &= \Lambda - (1-u(t))\beta xv - \mu x,\\
\frac{de}{dt} &= (1-u(t))\beta xv - \alpha e - \mu e,\\
\frac{dy}{dt} &= \alpha e - dy - qyz,\\
\frac{dv}{dt} &= ky - \gamma v - pav,\\
\frac{db}{dt} &= cv - \delta b,\\
\frac{da}{dt} &= fb - \varepsilon av - sa,\\
\frac{dz}{dt} &= myz - nz. \qquad (4.1)
\end{aligned}$$

Our objective is to minimize the concentration of exposed cells, the concentration of infected cells and the concentration of free virus at a minimal cost of control $u(t)$ over the time interval $[0, T]$.
The objective functional $P(u)$ for control problem is

$$P(u) = \int_0^T \Big[W_1 e(t) + W_2 y(t) + W_3 v(t) + \frac{1}{2}(W_4 u^2(t)) \Big] dt, \qquad (4.2)$$

with initial conditions

$x(0) \geq 0,\ e(0) \geq 0,\ y(0) \geq 0,\ v(0) \geq 0,\ b(0) \geq 0,$ $a(0) \geq 0$ and $z(0) \geq 0$.

The weight constants are represented by W_1, W_2, W_3 and W_4 and the terms $W_4 u^2(t)$ represent the costs associated with preventive vaccine control. It is assumed the control is nonlinear and takes a quadratic nature. Our aim is to find the control u such that

$$P(u^*) = \min P(u).$$

The set of admissible control includes all possible Lebesgue measurable function $u(t)$ that is defined on the interval [0, T] and for $t \in [0, T]$ satisfy the condition $u(t) \in$ U, where U is the control set of Lebesgue measurable function given as $\mathrm{U} = \{u(t) : 0 \leq u \leq 1\}$. We can determine an optimal solution of this optimal control problem by considering the Lagrangian and the Hamiltonian for the problem.

The Lagrangian of the optimal control problem is given by

$$g(e, y, v, u) = W_1 e(t) + W_2 y(t) + W_3 v(t) + \frac{1}{2}\big(W_4 u^2(t)\big). \qquad (4.3)$$

Table 1. Parameters values used in numerical study.

Parameter	Description	Value	Unit	Reference
Λ	The production rate of susceptible cells	20	$cells/day$	Perera and Perera, 2022
β	The infection rate of susceeptible cells due to interaction with virus	0.001	$cells/day$	Kanumoori et al., 2021
μ	The natural death rate of susceptiple and exposed cells	0.05	day	Estimated
α	The transition rate of cells from being exposed to infected	0.05	day	Estimated
d	The decline rate of infected cells due to both natural death and infection-induced death	0.5	day	Perera and Perera, 2022
q	The rate at which infected cells are lysed by T-lymphocytes	0.001	–	Perera and Perera, 2022
k	The production rate of free viruses which produced by infected cells	5	day	Kanumoori et al., 2021
γ	The death rate of free virus	0.5	day	Perera and Perera, 2022
p	The the rate at which virus particles are neutralized by antibodies	0.007	$cells/day$	Perera and Perera, 2022
c	The activation rate of B-cells	0.001	$cells/day$	Perera and Perera, 2022
δ	The death rate of B-cells	0.049	day	Perera and Perera, 2022
f	The production rate of antibodies	0.8	$cells/day$	Perera and Perera, 2022
ε	The rate at which virus kills antibodies	0.01	day	Perera and Perera, 2022
s	The death rate of antibody	0.051	day	Kanumoori et al., 2021
m	The expansion rate of T-lymphocytes that are derived from infected cells	0.001	$cells/day$	Kanumoori et al., 2021
n	The death rate of T-lymphocytes	0.01	day	Perera and Perera, 2022

Applying Pontryagin's Minimum Principle (PMP), the Hamiltonian is obtained

$$\begin{aligned} H &= W_1 e(t) + W_2 y(t) + W_3 v(t) + \frac{1}{2}\left(W_4 u^2(t)\right) \\ &+ \lambda_x[\Lambda - (1-u(t))\beta xv - \mu x] \\ &+ \lambda_e[(1-u(t))\beta xv - \alpha e - \mu e] \\ &+ \lambda_y[\mu e - dy - gyz] + \lambda_v[ky - \gamma v - pav] \\ &+ \lambda_b[cv - \delta b] + \lambda_a[fb - \varepsilon av - sa] \\ &+ \lambda_z[myz - nz], \end{aligned} \tag{4.4}$$

where $\lambda_x, \lambda_e, \lambda_y, \lambda_v, \lambda_b, \lambda_a$ and λ_z are the

Table 2. Sensitivity indices values of the basic reproduction number.

Parameter	Sensitivity index at parameter value	Sign
Λ	+ 1.0000	positive
β	+ 1.0000	positive
k	+ 1.0000	positive
α	+ 0.5000	positive
γ	- 1.0000	negative
d	- 1.0000	negative
μ	- 1.0000	negative

adjoint functions associated with the state equations for x, e, y, v, b, a and z, respectively.
Next, we clarify the existence of our control.

Theorem 6.1. *There exists optimal control* $u_1^* \in \mathrm{U}$ *to system (4.1) in the interval [0, T].*

Proof. Sufficient condition in optimal control theory [44, 45].
Let $r(t, \vec{x}, \vec{u})$ be the right-hand side of system (4.1).
We then are required to show that the following conditions are satisfied.

1. r is a C^1 function, and there exists a constant C such that
$|r(t,0,0)| \le C, \quad |r_{\vec{x}}(t,\vec{x},\vec{u})| \le C(1+|\vec{u}|)$, $|r_{\vec{u}}(t,\vec{x},\vec{u})| \le C$.

2. The admissible set $\mathcal{S}$ of all solutions to the system (4.1) with corresponding control is nonempty.

3. $r(t,\vec{x},\vec{u}) = i(t,\vec{x}) + j(t,\vec{x})\vec{u}$.

4. The control set $\mathrm{U} = [0,1]$.

5. The integrand of the objective functional is convex in U.

We start from writing

$$r(t,\vec{x},\vec{u}) = \begin{bmatrix} \Lambda - (1-u(t))\beta xv - \mu x \\ (1-u(t))\beta xv - \alpha e - \mu e \\ \alpha e - dy - qyz \\ ky - \gamma v - pav \\ cv - \delta b \\ fb - \varepsilon av - sa \\ myz - nz \end{bmatrix}.$$

It is trivial to see that $r(t,\vec{x},\vec{u})$ is a C^1 function and $|r(t,0,0)| = \Lambda$.
And,

$$r_{\vec{x}}(t,\vec{x},\vec{u}) = \begin{bmatrix} -\beta v - \mu & 0 & 0 \\ \beta v & -\alpha - \mu & 0 \\ 0 & \alpha & -d - qz \\ 0 & 0 & k \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & mz \end{bmatrix}$$

$$\begin{bmatrix} -\beta x & 0 & 0 & 0 \\ \beta x & 0 & 0 & 0 \\ 0 & 0 & 0 & -qy \\ -\gamma - pa & 0 & -pv & 0 \\ c & -\delta & 0 & 0 \\ -\varepsilon a & f & -\varepsilon v - s & 0 \\ 0 & 0 & 0 & my - n \end{bmatrix},$$

$$r_{\vec{u}}(t,\vec{x},\vec{u}) = \begin{bmatrix} \beta xv \\ -\beta xv \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

Since all variables, i.e., x, e, y, v, b, a, z are bounded, then there exists a constant C such that

$$|r(t,0,0)| \le C, |r_{\vec{x}}(t,\vec{x},\vec{u})| \le C(1+|\vec{u}|),$$

$$|r_{\vec{u}}(t,\vec{x},\vec{u})| \le C.$$

Thus, condition (1) holds.
Since condition (1) holds, system (4.1) therefore has a unique solution for constant control. Hence, condition (2) holds.
Next, we rewrite $r(t,\vec{x},\vec{u})$ in the form

$$r(t,\vec{x},\vec{u}) = \begin{bmatrix} \Lambda - \beta xv - \mu x \\ \beta xv - \alpha e - \mu e \\ \alpha e - dy - qyz \\ ky - rv - pav \\ cv - \delta b \\ fb - \varepsilon av - sa \\ myz - nz \end{bmatrix} + \begin{bmatrix} \beta xv \\ -\beta xv \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \times [u]$$

Then, condition (3) is satisfied.
And, by a definition of the integrand, condition (4) satisfies. Now condition (5) is left to prove this Theorem.
We then need to prove that

$$(1-\lambda)\, g(t,\vec{x},\vec{u}) + \lambda\, g(t,\vec{x},\vec{w}) \ge g(t,\vec{x},(1-\lambda)\vec{u}+\lambda\vec{w}),$$

where

$$g(t,\vec{x},\vec{u}) = w_1 e + w_2 y + w_3 v + \frac{1}{2} w_4 u^2$$

and $\vec{u}$, and $\vec{w}$ are two control vectors with $\lambda \in [0,1]$.
Here, we have

$$(1-\lambda)\, g(t,\vec{x},\vec{u}) + \lambda\, g(t,\vec{x},\vec{w})$$

$$= w_1 e + w_2 y + w_3 v + \tfrac{(1-\lambda)}{2} w_4 u^2 + \tfrac{\lambda}{2} w_4 w^2.$$

And, $g(t,\vec{x},(1-\lambda)\vec{u}+\lambda\vec{w})$

$$= w_1 e + w_2 y + w_3 v + \tfrac{w_4}{2} \left[(1-\lambda)u + \lambda w\right]^2.$$

Next, we consider

$$(1-\lambda)\, g(t,\vec{x},\vec{u}) + \lambda\, g(t,\vec{x},\vec{w}) - g(t,\vec{x},(1-\lambda)\vec{u}+\lambda\vec{w})$$

$$= \frac{1}{2} A_4 \left[\sqrt{q(1-q)}\, u - \sqrt{q(1-q)}\, w\right]^2$$

$$= \frac{1}{2} A_4 q(1-q)(u-w)^2$$

$$\ge 0.$$

Therefore, all 5 conditions above are satisfied.
This completes the proof. □

Theorem 6.2. *Let $\widetilde{x}, \widetilde{e}, \widetilde{y}, \widetilde{v}, \widetilde{b}, \widetilde{a}$ and $\widetilde{z}$ be optimal state solution with associated optimal control variable $u^*(t)$ for the optimal control problem* (4.1). *Then, there exists adjoint variables $\lambda_x, \lambda_e, \lambda_y, \lambda_v, \lambda_b, \lambda_a$ and λ_z given by:*

$$\lambda_x' = -\Big[-((1-u(t))\beta\widetilde{v} + \mu)\lambda_x + ((1-u(t))\beta\widetilde{v}\lambda_e \Big],$$

$$\lambda_e' = -\Big[W_1 - (\alpha+\mu)\lambda_e + \alpha\lambda_y \Big],$$

$$\lambda_y' = -\Big[W_2 - (d+q\widetilde{z})\lambda_y + k\lambda_v + m\widetilde{z}\lambda_z \Big],$$

$$\lambda_v' = -\Big[W_3 - ((1-u(t))\beta\widetilde{x}\lambda_x + ((1-u(t))\beta\widetilde{x}\lambda_e - (\gamma + p\widetilde{a})\lambda_v + c\lambda_b - \varepsilon\widetilde{a}\lambda_a \Big],$$

$$\lambda_b' = -\Big[-\delta\lambda_b + f\lambda_a \Big],$$

$$\lambda_a' = -\Big[-p\widetilde{v}\lambda_v - (\varepsilon\widetilde{v} + s)\lambda_a \Big],$$

$$\lambda_z' = -\Big[-q\widetilde{y}\lambda_y + (m\widetilde{y} - n)\lambda_z \Big],$$

with $\lambda_x(T) = 0,\ \lambda_e(T) = 0,\ \lambda_y(T) = 0,$ $\lambda_v(T) = 0,\ \lambda_b(T) = 0,\ \lambda_a(T) = 0$ and $\lambda_z(T) = 0$ are transversality conditions.

And, the optimal control variable $u^*(t)$ is given by

$$u^*(t) = \max\left\{0, \min\left\{\frac{(\lambda_e - \lambda_x)\beta\widetilde{x}\widetilde{v}}{W_4}, u_{\max}\right\}\right\}.$$

Proof. The adjoint equations for Eq. (4.4) can be calculated as follows

$$\lambda_x' = -\frac{\partial H}{\partial x} = -\Big[-((1-u(t))\beta\widetilde{v} + \mu)\lambda_x + ((1-u(t))\beta\widetilde{v}\lambda_e \Big],$$

$$\lambda_e' = -\frac{\partial H}{\partial e} = -\Big[W_1 - (\alpha+\mu)\lambda_e + \alpha\lambda_y\Big],$$

$$\lambda_y' = -\frac{\partial H}{\partial y} = -\Big[W_2 - (d+q\widetilde{z})\lambda_y + k\lambda_v + m\widetilde{z}\lambda_z\Big],$$

$$\lambda_v' = -\frac{\partial H}{\partial v} = -\Big[W_3 - ((1-u(t))\beta\widetilde{x}\lambda_x + ((1-u(t))\beta\widetilde{x}\lambda_e - (\gamma+p\widetilde{a})\lambda_v + c\lambda_b - \varepsilon\widetilde{a}\lambda_a\Big],$$

$$\lambda_b' = -\frac{\partial H}{\partial b} = -\Big[-\delta\lambda_b + f\lambda_a\Big],$$

$$\lambda_a' = -\frac{\partial H}{\partial a} = -\Big[-p\widetilde{v}\lambda_v - (\varepsilon\widetilde{v}+s)\lambda_a\Big],$$

$$\lambda_z' = -\frac{\partial H}{\partial z} = -\Big[-q\widetilde{y}\lambda_y + (m\widetilde{y}-n)\lambda_z\Big].$$

Next, by Pontryagin et al. [43] approach we solve the equation $\dfrac{\partial H}{\partial u} = 0$ to obtain u^* and we have

$$\frac{\partial H}{\partial u} = W_4 u(t) + \beta\widetilde{x}\widetilde{v}\lambda_x - \beta\widetilde{x}\widetilde{v}\lambda_e = 0$$

$$\therefore\ u(t) = \frac{(\lambda_e - \lambda_x)\beta\widetilde{x}\widetilde{v}}{W_4}. \tag{4.5}$$

Since the control is bounded, we obtain the standard control arguments as the compact form,

$$u^*(t) = \max\left\{0, \min\left\{\frac{(\lambda_e-\lambda_x)\beta\widetilde{x}\widetilde{v}}{W_4}, u_{\max}\right\}\right\}. \tag{4.6}$$

This completes the proof. □

7. Numerical Simulation of Optimal Control Problem

In this section, we study the dynamics of the system (4.1) numerically. The forward-backward sweep method is used to numerically solve the optimal control problem. We first start with an initial feasible control, and solve the optimal state system forward in time. Then, solve the adjoint state system backwards in time. An optimal control is updated according to state variables, adjoint variables, and the Hamiltonian. A new control is then compared with the previous control. If the two controls are the same, then stop, otherwise repeat all steps until a predefined convergence criterion is met. We consider the optimal control continuously for 60 days, with the use of parameter values in Table 1. Here we use $u_{max} = 0.7$.

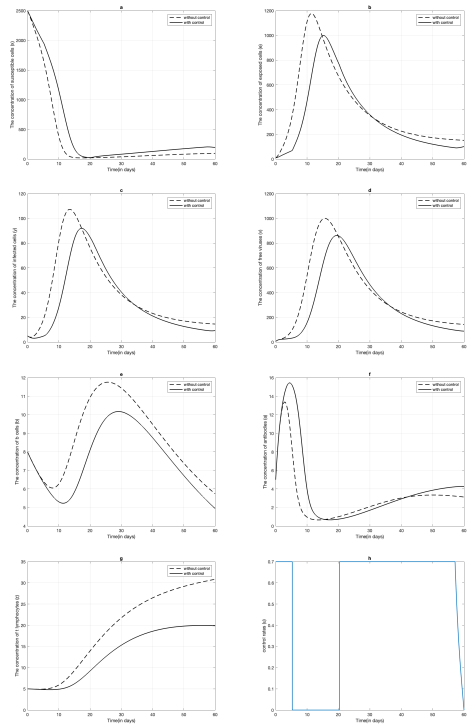

Fig. 4. Numerical simulation of the optimal control model (4.1) with preventive vaccine control. $(a-g)$ the concentration of x, e, y, v, b, a and z, and (h) the strategy guildline of control $u(t)$. The solid line and dashed line represent control and non-control condition, respectively.

Fig. 4 (a) shows that the concentra-

tion of susceptible cells (x) reduces slower in control case than non-control condition and it increases after 20 days to reach higher equilibrium value. Fig. 4(b) shows that the concentration of exposed cells (e) is lower in control case with the peak of about 1,000 $cells/day$, whereas it reaches the peak of almost 1,200 $cells/day$ in non-control one. Further, the peak in control condition occurs a few days later than the peak of non-control one and seems to reach lower equilibrium value in control condition. Similarly, Fig. 4(c) and (d) demonstrate the same pattern as Fig. 4(b) that is in control condition, they are lower than non-control case, the peak occurs a few days later and they reach lower equilibrium value. Fig. 4(e) shows that the concentration of B-cells (b) is lower in control case throughout 60 days. Interestingly, Fig. 4(f) shows that the concentration of antibodies cells (a) is higher in control case for about 16 days, and then it decreases and is lower than non-control case until 42^{nd} day. After that, it becomes higher again in control condition and reach higher equilibrium value. Fig. 4(g) shows that in control condition, the concentration of T-lymphocytes (z) is much lower and tends to reach lower value of equilibrium state than non-control case.

Finally, Fig. 4(h) shows the strategy of ($u(t)$) that it has to start at the maximum rate of 70% for about 5 days then could drop to zero until 20^{th} day. After that it goes up to 70% again until 56^{th} day and sharply goes down to zero towards the 60^{th} day.

Overall, our results show that a control by using vaccine gives an effect in reducing the concentration of e, y, v, b, and z and increasing the concentration of a. Hence, everyone should definitely be encouraged to get vaccine against dengue.

8. Conclusions

Although most people who get dengue infection often have mild or no symptom, there are still cases with high risk of developing severe form which could cause death. Therefore, dengue fever is still a major public health problem worldwide. We develop a within-host model to better understand dengue virus kinetics for cells e.g., monocytes, macrophages, dendritic cells or hepatocytes etc. as shown in Eqs. (2.1)-(2.7). A model consists of seven classes of cells which are the concentration of healthy target cells (x), exposed cells (e), infected cells (y), free viruses (v), B-cells (b), antibodies (a), and cytotoxic T lymphocytes (z). The model dynamical properties i.e., nonnegativity and boundedness of model solutions are verified, two equilibrium points are computed and they are infection-free and infected, and the basic reproduction number is calculated, where it becomes a threshold for equilibrium points stability. An infection-free equilibrium point is both locally and globally stable when basic reproduction number is less than one. In the case when it is greater than one, an infected equilibrium point exists and is stable locally and globally under some certain conditions. We have numerically confirmed these stability properties as shown in Figs. 2-3. Sensitivity analysis is performed and it indicates an effect of β to $\mathcal{R}_0$. Thus, trying to reduce infection term is required. Later, optimal control problem is applied into the model by using Pontryagin's Minimum Principle (PMP). Vaccination which is considered as control variable, is added into the model. This is to seek optimal strategy for preventing dengue viral infection by vaccine.

In control condition, our numerical results demonstrate a great reduction in ex-

posed cells, infected cells, viruses, B-cells and CTLs and an increase in antibody as shown in Fig. $4(a) - (g)$, giving a perfect strategy. This could be interpreted that vaccination could both reduce a viral load and boost immunity. Further, a few days delay of epidemic time is observed in our results for vaccination control condition, giving sign for mitigating infection spread. Our results obtained together with a confirmation recently of high-rate efficacy of new dengue vaccine and an ease to find, dengue vaccination measure is highly recommended for public health concern and policy in particular those who live in dengue risky area are encouraged to have vaccination against dengue infection. Therefore, our proposed model along with the designed control strategy could yield an important guideline for the public health. This not only helps reducing the number of dengue infected patients but also reducing the cost of treatment for dengue patients and making overall economics more sustainable.

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