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Research Article

Global Stability Analysis of Secondary DENV Infection Models with Antibody-Mediated Immunity and Distributed Time Delays

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Abstract: This study develops and analyzes mathematical models describing secondary infection with the Dengue Virus (DENV), explicitly incorporating the effects of both non-specific and strain-specific antibodies. The first model introduces two distributed time delays corresponding to monocyte infection and virion maturation. An extended model further differentiates between latent and actively infected monocytes and includes two additional delays that represent the latency and activation phases of monocyte infection. Analytical investigations focus on the non-negativity and boundedness of model solutions, and the basic reproduction number (R_0) is derived to examine the existence and stability of equilibrium points. Global stability of equilibria is established using Lyapunov technique. To validate the theoretical findings, numerical simulations and sensitivity analyses are performed. Results demonstrate that incorporating latent infection and time delays can reduce the value of R_0, suggesting that their omission may lead to overestimation of antiviral treatment requirements. Moreover, prolonged delays can mimic the effects of antiviral interventions by slowing viral propagation, indicating potential therapeutic strategies that target viral replication and maturation timing.

Keywords: secondary DENV infection, antibody-mediated immunity, global stability, time delay, lyapunov function

MSC: 34D20, 34D23, 37N25, 92B05

1. Introduction

Dengue Virus (DENV) is a mosquito-borne virus mainly transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. It causes dengue fever, which presents with symptoms such as high fever, severe headaches, eye pain, muscle and joint aches, skin rash, and mild bleeding [1]. The disease is triggered by any one of the four distinct dengue virus serotypes, labeled DENV-1 through DENV-4. Unlike diseases that spread through direct human contact, dengue is only passed on through mosquito bites. After recovering from an infection, a person gains long-term immunity to that specific serotype but remains susceptible to the other three [2]. Contracting dengue again with a different serotype increases the risk of developing severe dengue fever [3]. Dengue infection causes a substantial number of fatalities, primarily in tropical and subtropical regions worldwide. In 2024, the disease affected over 14 million individuals globally, leading to more than 10,000 deaths [4].

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DENV is a single-stranded Ribonucleic Acid (RNA) virus from the *Flaviviridae* family and primarily targets monocytes [5]. When a person is infected with DENV, the body's innate and adaptive immune systems work together to fight the infection [2]. As the infection progresses, the adaptive immune system becomes more active. When the immune system detects an increase in the number of infected cells, it stimulates T-cells, which in turn activate B-cells. Cytotoxic T Lymphocytes (CTLs) ($CD8^+$ T cells) target and destroy virus-infected cells, while helper T-cells ($CD4^+$ T cells) support the immune response by secreting signaling molecules. B-cells, once activated, produce virus-specific antibodies, which help neutralize free viral particles and prevent further infection. This coordinated immune response plays a key role in controlling the virus [5].

The use of mathematical models to describe natural phenomena is fundamental across various disciplines of applied science. In fields like physics, chemistry, and biology, these models provide a structured framework for analyzing complex systems and predicting real-world behaviors. In recent years, infectious diseases, including dengue fever [6–9], COVID-19 [10], pneumonia [11], tuberculosis [12], monkeypox [13], ebola [14] have drawn significant attention in mathematical modeling, helping researchers better understand disease dynamics and develop effective control strategies.

Dengue infection models are broadly categorized into epidemiological models and within-host models, each serving a distinct purpose in understanding the disease. Epidemiological models focus on the transmission dynamics of dengue within a population, helping to predict outbreaks and assess control measures. These models are instrumental in guiding public health policies, optimizing resource distribution, and formulating intervention strategies to reduce disease burden. On the other hand, within-host models explore the interactions between the DENV and the host's immune system at a cellular level. By examining viral replication, immune responses, and disease progression, these models offer crucial insights into pathogenesis and treatment approaches. They play a key role in vaccine development, antiviral drug research, and the study of severe dengue complications, such as Antibody-Dependent Enhancement (ADE) and cytokine storms.

In recent years, numerous investigations have concentrated on developing within-host models of primary DENV infection. Nuraini et al. [15] introduced a within-host model that incorporates the role of CTLs. The combined effects of the innate immune system and CTLs on primary DENV infection were explored in [16]. Perera and Perera [17] constructed a computational mathematical model that integrates both innate and humoral immune responses to analyze the within-host behavior of DENV infection. The long-term behavior of the model introduced in [17] was further examined in [18]. Clapham et al. [19] examined the influence of antiviral therapy that inhibits viral replication in their DENV infection model. In another approach, Ansari and Hesaaraki [20] applied the Beddington-DeAngelis functional form to describe the interaction between DENV and monocytes. The model by Nuraini was further expanded by Thibodeaux et al. [21], who considered monocyte production to be regulated by macrophage colony-stimulating factor. Liu et al. [22] extended Nuraini's framework by introducing stochastic elements to account for random fluctuations. Modak and Muthu [23] analyzed the influence of stochastic noise on a delayed within-host model of DENV transmission. Additionally, models that account for both CTL and humoral immune responses have been developed in works such as [2, 24, 25].

Several mathematical models for secondary DENV infection have been studied. Sasmal et al. [26] have included both humoral and CTL immunities into the secondary DENV infection model. Boisov et al. [27] have investigated a secondary DENV infection model with infectious and noninfectious dengue viruses taking into account both humoral and CTL immunities. Camargo et al. [28] have developed a secondary DENV infection model in scenarios of infection-enhancing and infection-neutralizing antibody competition. Nikin-Beers and Ciupe [29] have formulated two DENV models for primary and secondary infections taking into consideration the influence of T cell cross-reactivity in disease acuteness. The role of cross-reactive antibodies in disease enhancement in primary and secondary infections has been studied in [30]. Ben-Shachar and Koelle [31] have developed a secondary DENV infection model and have shown that how the T cells increase the production of cytokine which increase the risk of disease severity. Elaiw and Alofi [32] have included the mobility of cells and viruses into the secondary DENV infection model. Alshaikh et al. [33] proposed a model for secondary DENV infection that incorporates the virus's ability to target and infect various types of host cells. The model presented in [33] was further expanded in [34] to incorporate the spatial movement of both host cells and viral particles. Alves Rubio et al. [35] examined a mathematical model to investigate antibody-dependent enhancement during heterologous secondary DENV infections and evaluated the impact of restricted plasma cell cloning on the immune response. Rashid et al. [36] explored a secondary dengue infection model that combines deterministic and stochastic

dynamics, incorporating logistic cell growth and a nonlinear transmission rate. Their approach utilizes piecewise fractional differential equations to capture the complexity of the system. Gujarati and Ambika [37] developed a model for secondary DENV infection that incorporates the dynamics of two distinct antibody types.

In a recent study, Elaiw et al. [38] developed a mathematical model for viral infection that incorporates the influence of two different types of antibodies. The model presented in [38] captures the temporal dynamics of five key compartments: target cells, $M(t)$, infected cells, $E(t)$, free virus particles, $V(t)$, non-specific antibodies, $W^N(t)$, and strain-specific antibodies, $W^S(t)$, and is expressed as follows:

$$\frac{dM}{dt} = \underbrace{\phi}_{\text{production rate of target cells}} - \underbrace{\rho M}_{\text{death rate}} - \underbrace{\kappa MV}_{\text{infection rate}}, \tag{1}$$

$$\frac{dE}{dt} = \underbrace{\kappa MV}_{\text{infection rate}} - \underbrace{\delta E}_{\text{death rate}}, \tag{2}$$

$$\frac{dV}{dt} = \underbrace{\eta E}_{\text{generation rate of viruses}} - \underbrace{\rho V}_{\text{clearance rate}} - \underbrace{\beta_1 V W^N}_{\text{neutralization rate via } W^N} - \underbrace{\beta_2 V W^S}_{\text{neutralization rate via } W^S}, \tag{3}$$

$$\frac{dW^N}{dt} = \underbrace{\gamma_1}_{\text{generation rate of non-specific antibodies}} + \underbrace{\lambda_1 V W^N}_{\text{antibody stimulation rate}} - \underbrace{\psi_1 W^N}_{\text{death rate}}, \tag{4}$$

$$\frac{dW^S}{dt} = \underbrace{\gamma_2}_{\text{generation rate of strain-specific antibodies}} + \underbrace{\lambda_2 V W^S}_{\text{antibody stimulation rate}} - \underbrace{\psi_2 W^S}_{\text{death rate}}. \tag{5}$$

Models (1)-(5) do not incorporate time delays in the infection process or viral maturation. However, time delays are crucial for accurately capturing the progression of infections, particularly in relation to how the virus infects host cells and matures over time. In our proposed models, we introduce time delays to account for these natural lags in the infection and maturation processes. This modification provides a more precise representation of the time-dependent dynamics of the infection.

This paper aims to develop two mathematical models for secondary DENV infection, incorporating both strain-specific and non-specific antibodies. The first model introduces two types of distributed time delays: one associated with the formation of DENV-infected monocytes and another representing the maturation process of newly released virions. The second model expands on this by distinguishing between latent and active DENV-infected monocytes and incorporating two additional delays: the time lag associated with the development of latently infected monocytes and the subsequent delay before their activation. The study conducts a comprehensive analysis of fundamental and global properties, performs sensitivity assessments, and validates theoretical findings through numerical simulations.

2. Model with two antibodies

This part offers a detailed description of the formulated model, constructed under the following set of assumptions:

(A1) The model consists of five populations: uninfected monocytes (M), DENV-infected monocytes (E), free DENV particles (V), non-specific antibodies (heterogeneous antibodies) (W^N), and strain-specific antibodies (homogeneous antibodies) (W^S). These components are die at rates ρM, δE, ρV, $\psi_1 W^N$, and $\psi_2 W^S$, respectively.

(A2) There are two distinct populations of antibodies: non-specific antibodies, which were produced during the primary infection against one of the DENV serotypes, and strain-specific antibodies, which target the new DENV serotype during the secondary infection.

(A3) Uninfected monocytes, the primary targets of DENV, are produced at a rate of ϕ and become infected by DENV at a rate of κMV (see Eq. (6)). In addition, the DENV-infected monocytes are formed at rate κMV (see Eq. (7)).

(A4) The DENV particles are generated by DENV-infected monocytes at a rate ηE (see Eq. (8)).

(A5) Non-specific and strain-specific antibodies neutralize the DENV particles at rates of $\beta_1 VW^N$ and $\beta_2 VW^S$, respectively (see Eq. (8)).

(A6) The non-specific and strain-specific antibodies are generated at rates γ_1 and γ_2, respectively, and proliferate in response to the presence of DENV particles at rates $\lambda_1 EW^N$ and $\lambda_2 EW^S$, respectively (see Eqs. (9)-(10)).

(A7) The model includes two types of distributed time delays, with the delay parameter τ being randomly selected according to a probability distribution function $f_j(\tau)$ over the time interval $[0,\ h_j]$, $j = 1,\ 2$, where h_j is the limit superior of the delay period. These two types are:

(I) The formation delay of DENV-infected monocytes. In this context, the expression $f_1(\tau)e^{m_1\tau}$ denotes the probability that uninfected monocytes exposed to free DENV at time $t-\tau$ persist for τ units and transition into DENV-infected monocytes by time t, where, $\dfrac{1}{m_1}$ is the average life time of the monocytes during the infection delay period.

(II) The maturation period of newly released virions is considered here. The term $f_2(\tau)e^{-m_2\tau}$ represents the probability that immature free DENV particles present at time $t-\tau$ remain viable over a duration τ and complete maturation by time t, where, $\dfrac{1}{m_2}$ is the average life time of immature DENV virions during maturation delay period.

Denote

$$(M,\ E,\ V,\ W^N,\ W^S) = (M,\ E,\ V,\ W^N,\ W^S)(t),$$

$$(M_\tau,\ E_\tau,\ V_\tau) = (M,\ E,\ V)(t-\tau).$$

Figure 1 presents a schematic representation depicting the dynamics involved in secondary DENV infection. Based on the assumptions A1 to A7 outlined above, we formulate a secondary DENV infection model with distributed-time delays, represented as a system of five Delay Differential Equations (DDEs):

$$\frac{dM}{dt} = \phi - \rho M - \kappa MV, \tag{6}$$

$$\frac{dE}{dt} = \kappa \int_0^{h_1} f_1(\tau)e^{-m_1\tau}M_\tau V_\tau d\tau - \delta E, \tag{7}$$

$$\frac{dV}{dt} = \eta \int_0^{h_2} f_2(\tau)e^{-m_2\tau}E_\tau d\tau - \rho V - \beta_1 VW^N - \beta_2 VW^S, \tag{8}$$

$$\frac{dW^N}{dt} = \gamma_1 + \lambda_1 VW^N - \psi_1 W^N, \tag{9}$$

$$\frac{dW^S}{dt} = \gamma_2 + \lambda_2 VW^S - \psi_2 W^S. \tag{10}$$

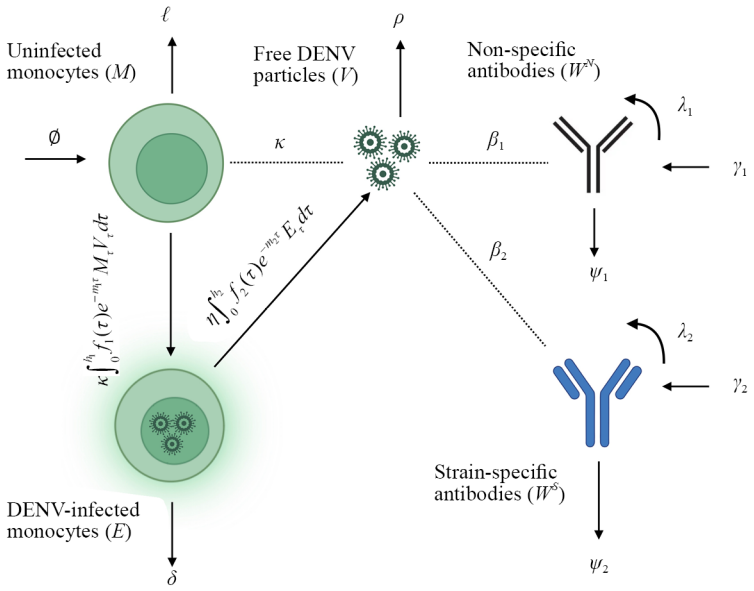


Figure 1. The diagram illustrates the dynamics of secondary DENV infection.

It is important to note that the functions $f_j(\tau)$, where $j = 1,\ 2$ satisfy the conditions [39]:

$$f_j(\tau) > 0,\ \int_0^{h_j} f_j(\tau)d\tau = 1,\ \int_0^{h_j} f_j(\tau)e^{\varsigma\tau}d\tau < \infty,\ \ \varsigma > 0.$$

Let us define $\Lambda_j(\tau) = f_j(\tau)e^{-m_j\tau}$ and $\digamma_j = \int_0^{h_j} \Lambda_j(\tau)d\tau$, where $j = 1,\ 2$, which ensures that $0 < \digamma_j \leq 1$. The initial conditions for the model described in equations (6)-(10) are as follows:

$$\begin{cases} M(\theta) = \varepsilon_1(\theta),\ E(\theta) = \varepsilon_2(\theta),\ V(\theta) = \varepsilon_3(\theta),\ W^N(\theta) = \varepsilon_4(\theta),\ W^S(\theta) = \varepsilon_5(\theta), \\ \\ \varepsilon_j(\theta) \geq 0,\ \theta \in [-\tau^*,\ 0],\ \varepsilon_j(\theta) \in \mathscr{C}\left([-\tau^*, 0], \mathbb{R}_{\geq 0}\right),\ j = 1,\ 2,\ \cdots,\ 5, \end{cases} \tag{11}$$

where, $\tau^* = \max\{h_1,\ h_2\}$, and $\mathscr{C}$ is the Banach space of continuous functions mapping from $[-\tau^*,\ 0]$ to $\mathbb{R}_{\geq 0}$ with the norm

$$\left\|\varepsilon_j\right\| = \sup_{-\tau^* \leq \theta \leq 0} \left|\varepsilon_j(\theta)\right| \text{ for } \varepsilon_j \in \mathscr{C},\ \ j = 1,\ 2,\ \cdots,\ 5.$$

Based on the established theory of functional differential equations, the model described by Equations (6)-(10), along with the initial conditions (11), possesses a unique solution, as shown by [40, 41].

2.1 *Preliminary results*

We start by establishing that the model outlined in Equations (6)-(10) is well-posed, guaranteeing that its solutions remain nonnegative and bounded in the long term. Next, we identify all potential equilibrium points and examine the critical parameters that determine their existence and stability.

Lemma 1 The solutions to Equations (6)-(10), subject to the initial conditions (11), are guaranteed to be non-negative and bounded over time.

Proof. We will demonstrate the non-negativity of the solutions to the model described by Equations (6)-(10). Obviously,

$$\frac{dM}{dt}|_{M=0} = \phi > 0, \quad \frac{dW^N}{dt}|_{W^N=0} = \gamma_1 > 0, \quad \frac{dW^S}{dt}|_{W^S=0} = \gamma_2 > 0.$$

Therefore, $M(t) > 0$, $W^N(t) > 0$, and $W^S(t) > 0$ for all $t \geq 0$. Moreover,

$$E(t) = e^{-\delta t}\varepsilon_2(0) + \kappa \int_0^t e^{-\delta(t-\theta)} \int_0^{h_1} \Lambda_1(\tau) M(\theta-\tau) V(\theta-\tau) d\tau d\theta \geq 0,$$

$$V(t) = e^{-\int_0^t (\rho+\beta_1 W^N(x)+\beta_2 W^S(x))dx}\varepsilon_3(0) + \eta \int_0^t e^{-\int_\theta^t (\rho+\beta_1 W^N(x)+\beta_2 W^S(x))dx} \int_0^{h_2} \Lambda_2(\tau) E(\theta-\tau) d\tau d\theta \geq 0,$$

for any $t \in [0,\ \tau^*]$. Thus, by recursive argumentation, we find that $(E,\ V)(t) \geq 0$ for any $t \geq 0$.

Let's demonstrate that the solution $(M,\ E,\ V,\ W^N,\ W^S)(t)$ is ultimately bounded. Eq. (6) gives $\limsup_{t\to\infty} M(t) \leq \Omega_1$ where $\Omega_1 = \dfrac{\phi}{\rho}$. To prove the ultimate boundedness of $E(t)$, we consider

$$\mathscr{H}_1 = \int_0^{h_1} \Lambda_1(\tau) M_\tau d\tau + E.$$

Then, we get

$$\begin{aligned}
\frac{d\mathscr{H}_1}{dt} &= \int_0^{h_1} \Lambda_1(\tau) \frac{dM_\tau}{dt} d\tau + \frac{dE}{dt} \\
&= \int_0^{h_1} \Lambda_1(\tau) \left(\phi - \rho M_\tau - \kappa M_\tau V_\tau\right) d\tau + \kappa \int_0^{h_1} \Lambda_1(\tau) M_\tau V_\tau d\tau - \delta E \\
&= \phi \int_0^{h_1} \Lambda_1(\tau) d\tau - \rho \int_0^{h_1} \Lambda_1(\tau) M_\tau d\tau - \delta E \\
&\leq \phi \digamma_1 - \mathscr{T}_1 \left[\int_0^{h_1} \Lambda_1(\tau) M_\tau d\tau + E\right] \\
&\leq \phi - \mathscr{T}_1 \mathscr{H}_1,
\end{aligned}$$

where $\mathscr{T}_1 = \min\{\rho,\ \delta\}$. Hence, $\limsup_{t\to\infty} \mathscr{H}_1(t) \le \Omega_2$, and $\limsup_{t\to\infty} E(t) \le \Omega_2$, where $\Omega_2 = \dfrac{\phi}{\mathscr{T}_1}$. Define

$$\mathscr{H}_2 = V + \frac{\beta_1}{\lambda_1} W^N + \frac{\beta_2}{\lambda_2} W^S.$$

Then, we get

$$\begin{aligned}
\frac{d\mathscr{H}_2}{dt} &= \frac{dV}{dt} + \frac{\beta_1}{\lambda_1}\frac{dW^N}{dt} + \frac{\beta_2}{\lambda_2}\frac{dW^S}{dt} \\
&= \eta \int_0^{h_2} \Lambda_2(\tau) E_\tau d\tau - \rho V - \beta_1 V W^N - \beta_2 V W^S + \frac{\beta_1}{\lambda_1}\left(\gamma_1 + \lambda_1 V W^N - \psi_1 W^N\right) \\
&\quad + \frac{\beta_2}{\lambda_2}\left(\gamma_2 + \lambda_2 V W^S - \psi_2 W^S\right) \\
&= \eta \int_0^{h_2} \Lambda_2(\tau) E_\tau d\tau + \frac{\beta_1\gamma_1}{\lambda_1} + \frac{\beta_2\gamma_2}{\lambda_2} - \rho V - \frac{\beta_1\psi_1}{\lambda_1} W^N - \frac{\beta_2\psi_2}{\lambda_2} W^S \\
&\le \eta F_2 \Omega_2 + \frac{\beta_1\gamma_1}{\lambda_1} + \frac{\beta_2\gamma_2}{\lambda_2} - \mathscr{T}_2\left[V + \frac{\beta_1}{\lambda_1} W^N + \frac{\beta_2}{\lambda_2} W^S\right] \\
&\le \eta\Omega_2 + \frac{\beta_1\gamma_1}{\lambda_1} + \frac{\beta_2\gamma_2}{\lambda_2} - \mathscr{T}_2\mathscr{H}_2,
\end{aligned}$$

where $\mathscr{T}_2 = \min\{\rho,\ \psi_1,\ \psi_2\}$. It follows that $\limsup_{t\to\infty} \mathscr{H}_2(t) \le \Omega_3$ where $\Omega_3 = \dfrac{\eta\Omega_2}{\mathscr{T}_2} + \dfrac{\beta_1\gamma_1}{\lambda_1\mathscr{T}_2} + \dfrac{\beta_2\gamma_2}{\lambda_2\mathscr{T}_2}$, then $\limsup_{t\to\infty} V(t) \le \Omega_3$, $\limsup_{t\to\infty} W^N(t) \le \Omega_4$, and $\limsup_{t\to\infty} W^S(t) \le \Omega_5$ where $\Omega_4 = \dfrac{\lambda_1\Omega_3}{\beta_1}$ and $\Omega_5 = \dfrac{\lambda_2\Omega_3}{\beta_2}$. □

Consequently, based on Lemma 1, the set

$$\Gamma = \left\{\left(M,\ E,\ V,\ W^N,\ W^S\right) \in \mathscr{C}^5_{\ge 0} : \|M\| \le \Omega_1,\ \|E\| \le \Omega_2,\ \|V\| \le \Omega_3,\ \|W^N\| \le \Omega_4,\ \|W^S\| \le \Omega_5\right\}$$

is positively invariant with respect to system (6)-(10).

Lemma 2 Let R_0 be the basic reproductive number for system (6)-(10), then

(I) If $R_0 \le 1$, then there exists a unique infection-free equilibrium $\mathscr{E}\mathscr{P}_0$.

(II) If $R_0 > 1$, then there exists an endemic equilibrium $\mathscr{E}\mathscr{P}_1$ in addition to $\mathscr{E}\mathscr{P}_0$.

Proof. The equilibrium points $\mathscr{E}\mathscr{P} = \left(M,\ E,\ V,\ W^N,\ W^S\right)$ of model (6)-(10) are determined by solving the corresponding system of algebraic equations:

$$0 = \phi - \rho M - \kappa M V, \tag{12}$$

$$0 = \kappa F_1 M V - \delta E, \tag{13}$$

$$0 = \eta F_2 E - \rho V - \beta_1 V W^N - \beta_2 V W^S, \tag{14}$$

$$0 = \gamma_1 + \lambda_1 V W^N - \psi_1 W^N, \tag{15}$$

$$0 = \gamma_2 + \lambda_2 V W^S - \psi_2 W^S. \tag{16}$$

Eqs. (12), (13), (15) and (16) give

$$\begin{aligned} M &= \frac{\phi}{\rho + \kappa V}, \qquad & E &= \frac{\kappa \phi F_1 V}{\delta(\rho + \kappa V)}, \\ W^N &= \frac{\gamma_1}{\psi_1 - \lambda_1 V}, \qquad & W^S &= \frac{\gamma_2}{\psi_2 - \lambda_2 V}. \end{aligned} \tag{17}$$

By substituting in Eq. (14), we obtain:

$$\left(-\rho + \frac{\eta \kappa \phi F_1 F_2}{\delta \rho + \delta V \kappa} + \frac{\beta_1 \gamma_1}{\lambda_1 V - \psi_1} + \frac{\beta_2 \gamma_2}{\lambda_2 V - \psi_2} \right) V = 0. \tag{18}$$

Eq. (18) presents two possibilities. The first is $V = 0$ which corresponds to the infection-free equilibrium $\mathscr{E}\mathscr{P}_0 = \left(M_0,\, 0,\, 0,\, W_0^N,\, W_0^S\right)$, where $M_0 = \dfrac{\phi}{\rho}$, $W_0^N = \dfrac{\gamma_1}{\psi_1}$, and $W_0^S = \dfrac{\gamma_2}{\psi_2}$. The second possibility is when $V \neq 0$ and in this case we have

$$-\rho + \frac{\eta \kappa \phi F_1 F_2}{\delta \rho + \delta V \kappa} + \frac{\beta_1 \gamma_1}{\lambda_1 V - \psi_1} + \frac{\beta_2 \gamma_2}{\lambda_2 V - \psi_2} = 0,$$

which gives

$$\frac{\ell_1 V^3 + \ell_2 V^2 + \ell_3 V + \ell_4}{(\delta \rho + \delta V \kappa)(\lambda_1 V - \psi_1)(\lambda_2 V - \psi_2)} = 0, \tag{19}$$

where

$$\ell_1 = \delta \rho \lambda_1 \lambda_2 \kappa,$$

$$\ell_2 = \delta \rho \rho \lambda_1 \lambda_2 - \eta \lambda_1 \lambda_2 \kappa \phi F_1 F_2 - \delta \lambda_2 \beta_1 \kappa \gamma_1 - \delta \lambda_1 \beta_2 \kappa \gamma_2 - \delta \rho \lambda_2 \kappa \psi_1 - \delta \rho \lambda_1 \kappa \psi_2,$$

$$\begin{aligned} \ell_3 = & -\delta \rho \lambda_2 \beta_1 \gamma_1 - \delta \rho \lambda_1 \beta_2 \gamma_2 - \delta \rho \rho \lambda_2 \psi_1 + \eta \lambda_2 \kappa \phi \psi_1 F_1 F_2 + \delta \beta_2 \kappa \gamma_2 \psi_1 \\ & - \delta \rho \rho \lambda_1 \psi_2 + \eta \lambda_1 \kappa \phi \psi_2 F_1 F_2 + \delta \beta_1 \kappa \gamma_1 \psi_2 + \delta \rho \kappa \psi_1 \psi_2, \end{aligned}$$

$$\ell_4 = \delta\rho\beta_2\gamma_2\psi_1 + \delta\rho\beta_1\gamma_1\psi_2 + \delta\rho\rho\psi_1\psi_2 - \eta\kappa\phi\psi_1\psi_2 F_1 F_2.$$

Next, let's define a function $\mathscr{Z}(V) = \ell_1 V^3 + \ell_2 V^2 + \ell_3 V + \ell_4$, then we find

$$\mathscr{Z}(0) = -\delta\rho\left(\beta_2\gamma_2\psi_1 + \beta_1\gamma_1\psi_2 + \rho\psi_1\psi_2\right)\left(\frac{\eta\kappa\phi F_1 F_2}{\delta\rho\rho\left(\frac{\beta_1\gamma_1}{\psi_1\rho} + \frac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)} - 1\right),$$

$$\mathscr{Z}\left(\frac{\psi_1}{\lambda_1}\right) = \frac{\delta\beta_1\gamma_1\lambda_2\left(\rho\lambda_1 + \kappa\psi_1\right)}{\lambda_1}\left(\frac{\psi_2}{\lambda_2} - \frac{\psi_1}{\lambda_1}\right),$$

$$\mathscr{Z}\left(\frac{\psi_2}{\lambda_2}\right) = \frac{\delta\beta_2\gamma_2\lambda_1\left(\rho\lambda_2 + \kappa\psi_2\right)}{\lambda_2}\left(\frac{\psi_1}{\lambda_1} - \frac{\psi_2}{\lambda_2}\right),$$

$$\lim_{V\to\infty}\mathscr{Z}(V) = \infty.$$

We have $\mathscr{Z}(0) < 0$ if the following condition is satisfied

$$\frac{\eta\kappa\phi F_1 F_2}{\delta\rho\rho\left(\frac{\beta_1\gamma_1}{\psi_1\rho} + \frac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)} > 1. \tag{20}$$

Observe that

$$\frac{\psi_2}{\lambda_2} > \frac{\psi_1}{\lambda_1} \Longrightarrow \mathscr{Z}\left(\frac{\psi_1}{\lambda_1}\right) > 0 \text{ and } \mathscr{Z}\left(\frac{\psi_2}{\lambda_2}\right) < 0,$$

$$\frac{\psi_2}{\lambda_2} < \frac{\psi_1}{\lambda_1} \Longrightarrow \mathscr{Z}\left(\frac{\psi_1}{\lambda_1}\right) < 0 \text{ and } \mathscr{Z}\left(\frac{\psi_2}{\lambda_2}\right) > 0.$$

Hence,

$$\mathscr{Z}\left(\min\left\{\frac{\psi_1}{\lambda_1}, \frac{\psi_2}{\lambda_2}\right\}\right) > 0 \text{ and } \mathscr{Z}\left(\max\left\{\frac{\psi_1}{\lambda_1}, \frac{\psi_2}{\lambda_2}\right\}\right) < 0.$$

If condition (20) holds, then Eq. (19) has three positive roots

$$V_1 \in \left(0, \min\left\{\frac{\psi_1}{\lambda_1}, \frac{\psi_2}{\lambda_2}\right\}\right),$$

$$\bar{V} \in \left(\min\left\{ \frac{\psi_1}{\lambda_1}, \frac{\psi_2}{\lambda_2} \right\}, \max\left\{ \frac{\psi_1}{\lambda_1}, \frac{\psi_2}{\lambda_2} \right\} \right),$$

$$\hat{V} \in \left(\max\left\{ \frac{\psi_1}{\lambda_1}, \frac{\psi_2}{\lambda_2} \right\}, \infty \right).$$

It is evident from Eq. (17) that the solution $\bar{V}$ gives $W_1^N < 0$ or $W_1^S < 0$; moreover, $\hat{V}$ yields $W_1^N < 0$ and $W_1^S < 0$. Thus, the only valid solution is V_1, which results in

$$M_1 = \frac{\phi}{\rho + \kappa V_1} > 0, \qquad E_1 = \frac{\kappa \phi F_1 V_1}{\delta(\rho + \kappa V_1)} > 0,$$

$$W_1^N = \frac{\gamma_1}{\psi_1 - \lambda_1 V_1} > 0, \qquad W_1^S = \frac{\gamma_2}{\psi_2 - \lambda_2 V_1} > 0.$$

Then we can define the basic reproductive number, R_0, as:

$$R_0 = \frac{\eta \kappa \phi F_1 F_2}{\delta \rho \rho \left(\frac{\beta_1 \gamma_1}{\psi_1 \rho} + \frac{\beta_2 \gamma_2}{\psi_2 \rho} + 1 \right)}.$$

The endemic equilibrium $\mathscr{E}\mathscr{P}_1 = \left(M_1, E_1, V_1, W_1^N, W_1^S\right)$ is present when $R_0 > 1$. In this context, R_0 denotes the average number of new infections generated by a single infected cell at the initial stage of infection [42]. □

2.2 *Global stability*

In this section, we examine the global stability of all equilibria for the model (6)-(10). A suitable Lyapunov function is constructed [43, 44], and LaSalle's invariance theorem [45], is applied. Define $\mathscr{L}(u) = u - 1 - \ln u$, and let $\mathscr{Q}_j'$ represent the largest invariant subset of

$$\mathscr{Q}_j = \left\{ \left(M, E, V, W^N, W^S\right) : \frac{d\Theta_j}{dt} = 0 \right\}, \; j = 0, 1,$$

where Θ_j is a Lyapunov function candidate.

Theorem 1 The model described by Equations (6)-(10) exhibits global asymptotic stability at the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ when $R_0 \leq 1$. However, if $R_0 > 1$, the equilibrium $\mathscr{E}\mathscr{P}_0$ becomes unstable.

Proof. Define $\Theta_0(M, E, V, W^N, W^S)$ as:

$$\Theta_0 = M^0 \mathscr{L}\left(\frac{M}{M_0}\right) + \frac{1}{F_1} E + \frac{\delta}{\eta F_1 F_2} V + \frac{\delta \beta_1}{\eta \lambda_1 F_1 F_2} W_0^N \mathscr{L}\left(\frac{W^N}{W_0^N}\right) + \frac{\delta \beta_2}{\eta \lambda_2 F_1 F_2} W_0^S \mathscr{L}\left(\frac{W^S}{W_0^S}\right)$$

$$+ \frac{\kappa}{F_1} \int_0^{h_1} \Lambda_1(\tau) \int_{t-\tau}^{t} M(\theta) V(\theta) d\theta d\tau + \frac{\delta}{F_1 F_2} \int_0^{h_2} \Lambda_2(\tau) \int_{t-\tau}^{t} E(\theta) d\theta d\tau.$$

We note that $\Theta_0\left(M,\, E,\, V,\, W^N,\, W^S\right) > 0$ for any $\left(M,\, E,\, V,\, W^N,\, W^S\right) > 0$ and $\Theta_0\left(M_0,\, 0,\, 0,\, W_0^N,\, W_0^S\right) = 0$. Calculating $\dfrac{d\Theta_0}{dt}$ along the solutions of (6)-(10) as:

$$\frac{d\Theta_0}{dt} = \left(1-\frac{M_0}{M}\right)\frac{dM}{dt} + \frac{1}{F_1}\frac{dE}{dt} + \frac{\delta}{\eta F_1 F_2}\frac{dV}{dt} + \frac{\delta\beta_1}{\eta\lambda_1 F_1 F_2}\left(1-\frac{W_0^N}{W^N}\right)\frac{dW^N}{dt} + \frac{\delta\beta_2}{\eta\lambda_2 F_1 F_2}\left(1-\frac{W_0^S}{W^S}\right)\frac{dW^S}{dt}$$

$$+ \frac{\kappa}{F_1}\int_0^{h_1}\Lambda_1(\tau)\left(MV - M_\tau V_\tau\right)d\tau + \frac{\delta}{F_1 F_2}\int_0^{h_2}\Lambda_2(\tau)\left(E - E_\tau\right)d\tau.$$

From Eqs. (6)-(10) we get

$$\frac{d\Theta_0}{dt} = \left(1-\frac{M_0}{M}\right)(\phi - \rho M - \kappa MV) + \frac{1}{F_1}\left(\kappa\int_0^{h_1}\Lambda_1(\tau)M_\tau V_\tau d\tau - \delta E\right)$$

$$+ \frac{\delta}{\eta F_1 F_2}\left(\eta\int_0^{h_2}\Lambda_2(\tau)E_\tau d\tau - \rho V - \beta_1 V W^N - \beta_2 V W^S\right) + \frac{\delta\beta_1}{\eta\lambda_1 F_1 F_2}\left(1-\frac{W_0^N}{W^N}\right)\left(\gamma_1 + \lambda_1 V W^N - \psi_1 W^N\right)$$

$$+ \frac{\delta\beta_2}{\eta\lambda_2 F_1 F_2}\left(1-\frac{W_0^S}{W^S}\right)\left(\gamma_2 + \lambda_2 V W^S - \psi_2 W^S\right) + \frac{\kappa}{F_1}\int_0^{h_1}\Lambda_1(\tau)\left(MV - M_\tau V_\tau\right)d\tau$$

$$+ \frac{\delta}{F_1 F_2}\int_0^{h_2}\Lambda_2(\tau)\left(E - E_\tau\right)d\tau.$$

Collecting terms and using $\phi = \rho M_0,\ \gamma_1 = \psi_1 W_0^N$, and $\gamma_2 = \psi_2 W_0^S$, we obtain

$$\frac{d\Theta_0}{dt} = -\frac{\rho\left(M - M_0\right)^2}{M} - \frac{\delta\beta_1\psi_1}{\eta\lambda_1 F_1 F_2}\frac{\left(W^N - W_0^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2}{\eta\lambda_2 F_1 F_2}\frac{\left(W^S - W_0^S\right)^2}{W^S} + \kappa M_0 V - \frac{\delta\rho}{\eta F_1 F_2}V$$

$$- \frac{\delta\beta_1}{\eta F_1 F_2}W_0^N V - \frac{\delta\beta_2}{\eta F_1 F_2}W_0^S V.$$

It follows that

$$\frac{d\Theta_0}{dt} = -\frac{\rho\left(M - M_0\right)^2}{M} - \frac{\delta\beta_1\psi_1}{\eta\lambda_1 F_1 F_2}\frac{\left(W^N - W_0^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2}{\eta\lambda_2 F_1 F_2}\frac{\left(W^S - W_0^S\right)^2}{W^S}$$

$$+ \left[\kappa M_0 - \frac{\delta\beta_1}{\eta F_1 F_2}W_0^N - \frac{\delta\beta_2}{\eta F_1 F_2}W_0^S - \frac{\delta\rho}{\eta F_1 F_2}\right]V$$

$$= -\frac{\rho\left(M - M_0\right)^2}{M} - \frac{\delta\beta_1\psi_1}{\eta\lambda_1 F_1 F_2}\frac{\left(W^N - W_0^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2}{\eta\lambda_2 F_1 F_2}\frac{\left(W^S - W_0^S\right)^2}{W^S}$$

$$+\left[\frac{\kappa\phi}{\rho}-\frac{\delta\rho}{\eta F_1F_2}\left(\frac{\beta_1\gamma_1}{\psi_1\rho}+\frac{\beta_2\gamma_2}{\psi_2\rho}+1\right)\right]V.$$

Finally, we obtain

$$\frac{d\Theta_0}{dt}=-\frac{\rho\,(M-M_0)^2}{M}-\frac{\delta\beta_1\psi_1}{\eta\lambda_1F_1F_2}\frac{\left(W^N-W_0^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2}{\eta\lambda_2F_1F_2}\frac{\left(W^S-W_0^S\right)^2}{W^S}$$

$$+\frac{\delta\rho}{\eta F_1F_2}\left(\frac{\beta_1\gamma_1}{\psi_1\rho}+\frac{\beta_2\gamma_2}{\psi_2\rho}+1\right)[R_0-1]\,V.$$

When $R_0\leq 1$, then $\frac{d\Theta_0}{dt}\leq 0$. Furthermore, $\frac{d\Theta_0}{dt}=0$ when $M=M_0$, $W^N=W_0^N$, $W^S=W_0^S$, and $(R_0-1)V=0$. The solutions of the system defined by (6)-(10) tend toward the set $\mathscr{Q}_0'$, as established in [40]. Every element within $\mathscr{Q}_0'$ satisfies $M=M_0$, $W^N=W_0^N$, $W^S=W_0^S$, and

$$(R_0-1)V=0. \tag{21}$$

The analysis can be divided into two distinct cases:
Case (A) $R_0=1$, then from Eq. (6)

$$0=\frac{dM}{dt}=\phi-\rho M_0-\kappa M_0V \quad\Longrightarrow\quad V(t)=0 \quad \text{for any } t. \tag{22}$$

From Eq. (8) we have

$$0=\frac{dV}{dt}=\eta\int_0^{h_2}\Lambda_2(\tau)E_\tau d\tau \quad\Longrightarrow\quad E(t)=0 \quad \text{for any } t. \tag{23}$$

Then $\mathscr{Q}_0'=\{\mathscr{E}\mathscr{P}_0\}$.
Case (B) $R_0<1$, then Eq. (21) leads to $V=0$ and Eq. (23) results in $E=0$. Therefore, the set $\mathscr{Q}_0'$ reduces to the singleton $\{\mathscr{E}\mathscr{P}_0\}$.
LaSalle's Invariance Theorem (LIT) [45], gives that $\mathscr{E}\mathscr{P}_0$ is Globally Asymptotically Stable (GAS).
The characteristic equation corresponding to the model (6)-(10) evaluated at the equilibrium point $\mathscr{E}\mathscr{P}_0$ can be expressed as follows:

$$(x+\rho)(x+\psi_1)(x+\psi_2)\mathscr{N}(x)=0, \tag{24}$$

where x is the eigenvalue, $\mathscr{N}(x)=\omega_2x^2+\omega_1x+\omega_0$ and

$$\omega_2=\rho\,\psi_1\psi_2,$$

$$\omega_1 = \beta_2\gamma_2\rho\psi_1 + \beta_1\gamma_1\rho\psi_2 + \delta\rho\psi_1\psi_2 + \rho\rho\psi_1\psi_2,$$

$$\omega_0 = \beta_2\gamma_2\delta\rho\psi_1 + \beta_1\gamma_1\delta\rho\psi_2 + \delta\rho\rho\psi_1\psi_2 - \eta\kappa\phi\psi_1\psi_2\bar{F}_1\bar{F}_2,$$

where $\bar{F}_j = \int_0^{\varkappa_j} f_j(\tau)e^{-(x+m_j)\tau}d\tau,\ j = 1,\ 2$. Obviously, $\mathscr{N}(0) = \delta\rho\left(\beta_2\gamma_2\psi_1 + \beta_1\gamma_1\psi_2 + \rho\psi_1\psi_2\right)(1 - R_0) < 0$ if $R_0 > 1$ and $\lim_{x\to\infty}\mathscr{N}(x) = \infty$. This implies that Eq. (24) has a positive real root, which means that $\mathscr{E}\mathscr{P}_0$ is unstable. □

Theorem 2 The model (6)-(10) is GAS around an endemic equilibrium $\mathscr{E}\mathscr{P}_1$ if $R_0 > 1$.

Proof. Construct $\Theta_1(M,\ E,\ V,\ W^N,\ W^S)$ as:

$$\Theta_1 = M_1\mathscr{L}\left(\frac{M}{M_1}\right) + \frac{1}{F_1}E_1\mathscr{L}\left(\frac{E}{E_1}\right) + \frac{\delta}{\eta F_1F_2}V_1\mathscr{L}\left(\frac{V}{V_1}\right) + \frac{\delta\beta_1}{\eta\lambda_1F_1F_2}W_1^N\mathscr{L}\left(\frac{W^N}{W_1^N}\right) + \frac{\delta\beta_2}{\eta\lambda_2F_1F_2}W_1^S\mathscr{L}\left(\frac{W^S}{W_1^S}\right)$$

$$+ \frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\int_{t-\tau}^{t}\mathscr{L}\left(\frac{M(\theta)V(\theta)}{M_1V_1}\right)d\theta d\tau + \frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\int_{t-\tau}^{t}\mathscr{L}\left(\frac{E(\theta)}{E_1}\right)d\theta d\tau.$$

Differentiating Θ_1 along the trajectories of the system defined by (6)-(10) yields:

$$\frac{d\Theta_1}{dt} = \left(1 - \frac{M_1}{M}\right)(\phi - \rho M - \kappa MV) + \frac{1}{F_1}\left(1 - \frac{E_1}{E}\right)\left(\kappa\int_0^{h_1}\Lambda_1(\tau)M_\tau V_\tau d\tau - \delta E\right)$$

$$+ \frac{\delta}{\eta F_1F_2}\left(1 - \frac{V_1}{V}\right)\left(\eta\int_0^{h_2}\Lambda_2(\tau)E_\tau d\tau - \rho V - \beta_1VW^N - \beta_2VW^S\right)$$

$$+ \frac{\delta\beta_1}{\eta\lambda_1F_1F_2}\left(1 - \frac{W_1^N}{W^N}\right)\left(\gamma_1 + \lambda_1VW^N - \psi_1W^N\right) + \frac{\delta\beta_2}{\eta\lambda_2F_1F_2}\left(1 - \frac{W_1^S}{W^S}\right)\left(\gamma_2 + \lambda_2VW^S - \psi_2W^S\right)$$

$$+ \frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\frac{MV}{M_1V_1} - \frac{M_\tau V_\tau}{M_1V_1} + \ln\left(\frac{M_\tau V_\tau}{MV}\right)\right]d\tau + \frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\left[\frac{E}{E_1} - \frac{E_\tau}{E_1} + \ln\left(\frac{E_\tau}{E}\right)\right]d\tau.$$

Summing the terms, we obtain

$$\frac{d\Theta_1}{dt} = \left(1 - \frac{M_1}{M}\right)(\phi - \rho M) + \kappa M_1V - \frac{\kappa}{F_1}\int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1}{E}d\tau + \frac{\delta}{F_1}E_1 - \frac{\delta\rho}{\eta F_1F_2}V$$

$$- \frac{\delta}{F_1F_2}\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau V_1}{V}d\tau + \frac{\delta\rho}{\eta F_1F_2}V_1 + \frac{\delta\beta_1}{\eta F_1F_2}V_1W^N + \frac{\delta\beta_2}{\eta F_1F_2}V_1W^S$$

$$+ \frac{\delta\beta_1}{\eta\lambda_1F_1F_2}\left(1 - \frac{W_1^N}{W^N}\right)\left(\gamma_1 - \psi_1W^N\right) - \frac{\delta\beta_1}{\eta F_1F_2}W_1^NV + \frac{\delta\beta_2}{\eta\lambda_2F_1F_2}\left(1 - \frac{W_1^S}{W^S}\right)\left(\gamma_2 - \psi_2W^S\right)$$

$$- \frac{\delta\beta_2}{\eta F_1F_2}W_1^SV + \frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\ln\left(\frac{W_\tau V_\tau}{WV}\right)d\tau + \frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\ln\left(\frac{E_\tau}{E}\right)d\tau.$$

Using the equilibrium conditions of $\mathscr{E}\mathscr{P}_1$:

$$\begin{cases} \phi = \rho M_1 + \kappa M_1 V_1, \\ \kappa F_1 M_1 V_1 = \delta E_1, \\ \eta F_2 E_1 = \rho V_1 + \beta_1 V_1 W_1^N + \beta_2 V_1 W_1^S, \\ \gamma_1 = -\lambda_1 V_1 W_1^N + \psi_1 W_1^N, \\ \gamma_2 = -\lambda_2 V_1 W_1^S + \psi_2 W_1^S, \end{cases}$$

we obtain

$$\begin{aligned} \frac{d\Theta_1}{dt} = & -\frac{\rho\left(M-M_1\right)^2}{M} - \frac{\delta\beta_1\psi_1}{\eta\lambda_1 F_1 F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2}{\eta\lambda_2 F_1 F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S} + \left(1-\frac{M_1}{M}\right)\kappa M_1 V_1 \\ & - \frac{\delta\beta_1}{\eta F_1 F_2}\left(1-\frac{W_1^N}{W^N}\right)V_1 W_1^N - \frac{\delta\beta_2}{\eta F_1 F_2}\left(1-\frac{W_1^S}{W^S}\right)V_1 W_1^S + \kappa M_1 V - \frac{\kappa}{F_1}M_1 V_1 \int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1}{M_1 V_1 E}d\tau \\ & + \frac{\delta}{F_1}E_1 - \frac{\delta\rho}{\eta F_1 F_2}V - \frac{\delta}{F_1 F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau V_1}{E_1 V}d\tau + \frac{\delta\rho}{\eta F_1 F_2}V_1 + \frac{\delta\beta_1}{\eta F_1 F_2}V_1 W^N + \frac{\delta\beta_2}{\eta F_1 F_2}V_1 W^S \\ & - \frac{\delta\beta_1}{\eta F_1 F_2}W_1^N V - \frac{\delta\beta_2}{\eta F_1 F_2}W_1^S V + \frac{\kappa}{F_1}M_1 V_1\int_0^{h_1}\Lambda_1(\tau)\ln\left(\frac{W_\tau V_\tau}{WV}\right)d\tau + \frac{\delta}{F_1 F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\ln\left(\frac{E_\tau}{E}\right)d\tau. \end{aligned}$$

To prove this theorems, we will use following equalities:

$$\ln\left(\frac{M_\tau V_\tau}{MV}\right) = \ln\left(\frac{M_\tau V_\tau E_1}{M_1 V_1 E}\right) + \ln\left(\frac{M_1}{M}\right) + \ln\left(\frac{V_1 E}{V E_1}\right),$$

$$\ln\left(\frac{E_\tau}{E}\right) = \ln\left(\frac{E_\tau V_1}{E_1 V}\right) + \ln\left(\frac{E_1 V}{E V_1}\right),$$

which leads to

$$\begin{aligned} \frac{d\Theta_1}{dt} = & -\frac{\rho\left(M-M_1\right)^2}{M} - \frac{\delta\beta_1\psi_1}{\eta\lambda_1 F_1 F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2}{\eta\lambda_2 F_1 F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S} + \left(1-\frac{M_1}{M}\right)\kappa M_1 V_1 \\ & - \frac{\delta\beta_1}{\eta F_1 F_2}\left(1-\frac{W_1^N}{W^N}-\frac{W^N}{W_1^N}\right)V_1 W_1^N - \frac{\delta\beta_2}{\eta F_1 F_2}\left(1-\frac{W_1^S}{W^S}-\frac{W^S}{W_1^S}\right)V_1 W_1^S \end{aligned}$$

$$+\left(\kappa M_1V_1-\frac{\delta\beta_1}{\eta F_1F_2}V_1W_1^N-\frac{\delta\beta_2}{\eta F_1F_2}V_1W_1^S-\frac{\delta\rho}{\eta F_1F_2}V_1\right)\frac{V}{V_1}-\frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1}{M_1V_1E}d\tau+\frac{\delta}{F_1}E_1$$

$$-\frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau V_1}{E_1V}d\tau+\frac{\delta\rho}{\eta F_1F_2}V_1+\frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\ln\left(\frac{M_\tau V_\tau E_1}{M_1V_1E}\right)+\ln\left(\frac{M_1}{M}\right)+\ln\left(\frac{V_1E}{VE_1}\right)\right]d\tau$$

$$+\frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\left[\ln\left(\frac{E_\tau V_1}{E_1V}\right)+\ln\left(\frac{E_1V}{EV_1}\right)\right]d\tau-\frac{\delta\beta_1}{\eta F_1F_2}V_1W_1^N+\frac{\delta\beta_1}{\eta F_1F_2}V_1W_1^N$$

$$-\frac{\delta\beta_2}{\eta F_1F_2}V_1W_1^S+\frac{\delta\beta_2}{\eta F_1F_2}V_1W_1^S.$$

Obviously, we can see that

$$\left(\kappa M_1V_1-\frac{\delta\beta_1}{\eta F_1F_2}V_1W_1^N-\frac{\delta\beta_2}{\eta F_1F_2}V_1W_1^S-\frac{\delta\rho}{\eta F_1F_2}V_1\right)\frac{V}{V_1}=0.$$

Hence, we get

$$\frac{d\Theta_1}{dt}=-\frac{\rho\left(M-M_1\right)^2}{M}-\frac{\delta\beta_1\psi_1}{\eta\lambda_1F_1F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2}{\eta\lambda_2F_1F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}+\frac{\delta\beta_1}{\eta F_1F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}V_1$$

$$+\frac{\delta\beta_2}{\eta F_1F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}V_1-\kappa M_1V_1\left(\frac{M_1}{M}-1-\ln\left(\frac{M_1}{M}\right)\right)-\frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1}{M_1V_1E}d\tau+\frac{\delta}{F_1}E_1$$

$$-\frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau V_1}{E_1V}d\tau+\kappa M_1V_1+\frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\ln\left(\frac{M_\tau V_\tau E_1}{M_1V_1E}\right)+\ln\left(\frac{V_1E}{VE_1}\right)\right]d\tau$$

$$+\frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\left[\ln\left(\frac{E_\tau V_1}{E_1V}\right)+\ln\left(\frac{E_1V}{EV_1}\right)\right]d\tau.$$

Then

$$\frac{d\Theta_1}{dt}=-\frac{\rho\left(M-M_1\right)^2}{M}-\frac{\delta\beta_1\psi_1}{\eta\lambda_1F_1F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2}{\eta\lambda_2F_1F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}+\frac{\delta\beta_1}{\eta F_1F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}V_1$$

$$+\frac{\delta\beta_2}{\eta F_1F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}V_1-\kappa M_1V_1\left(\frac{M_1}{M}-1-\ln\left(\frac{M_1}{M}\right)\right)$$

$$-\frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\frac{M_\tau V_\tau E_1}{M_1V_1E}-1-\ln\left(\frac{M_\tau V_\tau E_1}{M_1V_1E}\right)\right]d\tau$$

$$-\frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\left[\frac{E_\tau V_1}{E_1V}-1-\ln\left(\frac{E_\tau V_1}{E_1V}\right)\right]d\tau.$$

From the equilibrium conditions, we have $V_1-\frac{\psi_1}{\lambda_1}=-\frac{\gamma_1}{\lambda_1W_1^N}$ and $V_1-\frac{\psi_2}{\lambda_2}=-\frac{\gamma_2}{\lambda_2W_1^S}$. It follows that

$$\frac{d\Theta_1}{dt}=-\frac{\rho\,(M-M_1)^2}{M}-\frac{\delta\beta_1\gamma_1}{\eta\lambda_1F_1F_2}\frac{\left(W^N-W_1^N\right)^2}{W^NW_1^N}-\frac{\delta\beta_2\gamma_2}{\eta\lambda_2F_1F_2}\frac{\left(W^S-W_1^S\right)^2}{W^SW_1^S}-\kappa M_1V_1\mathscr{L}\left(\frac{M_1}{M}\right)$$

$$-\frac{\kappa}{F_1}M_1V_1\int_0^{h_1}\Lambda_1(\tau)\mathscr{L}\left(\frac{M_\tau V_\tau E_1}{M_1V_1E}\right)d\tau-\frac{\delta}{F_1F_2}E_1\int_0^{h_2}\Lambda_2(\tau)\mathscr{L}\left(\frac{E_\tau V_1}{E_1V}\right)d\tau.$$

Thus, $\frac{d\Theta_1}{dt}\le 0$ for any $(M,\,E,\,V,\,W^N,\,W^S)>0$. Furthermore, $\frac{d\Theta_1}{dt}=0$ when $\left(M,\,W^N,\,W^S\right)=\left(M_1,\,W_1^N,\,W_1^S\right)$ and $\frac{M_\tau V_\tau E_1}{M_1V_1E}=\frac{E_\tau V_1}{E_1V}=1$. Then, solution of model converge to $\mathscr{Q}_1'$. Any element in $\mathscr{Q}_1'$, we have $M=M_1$, $W^N=W_1^N$, and $W^S=W_1^S$. Then $\frac{dM}{dt}=\frac{dW^N}{dt}=\frac{dW^S}{dt}=0$ and from Eqs. (6) and (8), we get

$$0=\frac{dM}{dt}=\rho-\sigma M_1-\alpha M_1V\quad\Longrightarrow\quad V(t)=V_1\quad\text{for any } t,$$

and then

$$0=\frac{dV}{dt}=\eta\int_0^{h_2}\Lambda_2(\tau)E_\tau d\tau-\rho V_1-\beta_1V_1W_1^N-\beta_2V_1W_1^S\quad\Longrightarrow\quad E(t)=E_1\text{ for any }t.$$

Consequently, $\mathscr{Q}_1'=\{\mathscr{E}\mathscr{P}_1\}$. LIT implies that $\mathscr{E}\mathscr{P}_1$ is GAS.

3. Model with latent reservoirs

The objective of this section is to expand on the model (6)-(10) presented in section 2 by including the effect of latently infected cells. These cells contain virions but do not release them until they are activated. We propose our model by considering the factors (A1)-(A7) outlined in section 2, along with the additional factors:

(A8) There are two classes of infected monocytes, latently DENV-infected monocytes, E^L, and actively DENV-infected monocytes, E^A. These compartment die at rates φE^L and δE^A, respectively. A portion $\xi\in[0,\,1]$, of target cells becomes active, while the rest of the portion $1-\xi$ remain latent. The activation rates of latently DENV-infected monocytes by μE^L (see Eqs. (26) and (27)).

(A9) We add two more types of time delays:

(I) The formation delay of latently DENV-infected monocytes. The likelihood that uninfected monocytes contacted by free DENV at time $t-\tau$ survived τ time units and become latently DENV-infected monocytes at time t is represented by $g_1(\tau)e^{-n_1\tau}$, where $1/n_1$, represents the mean lifespan of monocytes throughout the phase in which they become latently infected.

(II) The activation delay of latently DENV-infected monocytes. The probability that latently DENV-infected monocytes persist for a duration τ before activating at time t is represented by $g_2(\tau)e^{-n_2\tau}$, where $1/n_2$ denotes the average lifespan of monocytes during the activation phase.

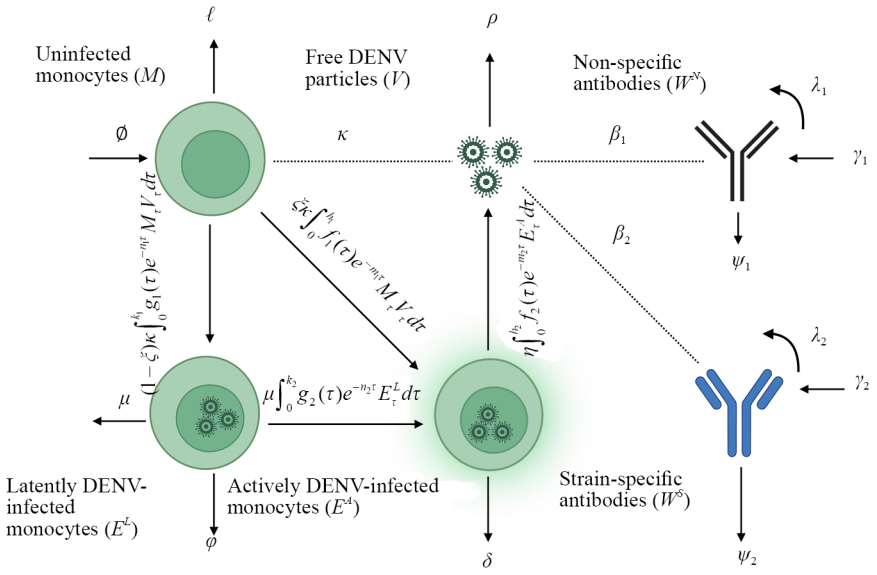


Figure 2. The diagram illustrates the dynamics of secondary DENV infection latent reservoirs

Figure 2 presents a schematic representation depicting the dynamics involved in secondary DENV infection. The above assumptions allow us to formulate the following model:

$$\frac{dM}{dt} = \phi - \rho M - \kappa MV, \tag{25}$$

$$\frac{dE^L}{dt} = (1-\xi)\kappa \int_0^{k_1} g_1(\tau) e^{-n_1\tau} M_\tau V_\tau d\tau - (\mu+\varphi)E^L, \tag{26}$$

$$\frac{dE^A}{dt} = \xi\kappa \int_0^{h_1} f_1(\tau) e^{-m_1\tau} M_\tau V_\tau d\tau + \mu \int_0^{k_2} g_2(\tau) e^{-n_2\tau} E_\tau^L d\tau - \delta E^A, \tag{27}$$

$$\frac{dV}{dt} = \eta \int_0^{h_2} f_2(\tau) e^{-m_2\tau} E_\tau^A d\tau - \rho V - \beta_1 V W^N - \beta_2 V W^S, \tag{28}$$

$$\frac{dW^N}{dt} = \gamma_1 + \lambda_1 V W^N - \psi_1 W^N, \tag{29}$$

$$\frac{dW^S}{dt} = \gamma_2 + \lambda_2 V W^S - \psi_2 W^S. \tag{30}$$

The starting conditions for the system described by Equations (25)-(30) are given as follows:

$$(M,\ E^L,\ E^A,\ V,\ W^N,\ W^S)(\theta) = (\varepsilon_1,\ \varepsilon_2,\ \varepsilon_3,\ \varepsilon_4,\ \varepsilon_5,\ \varepsilon_6)(\theta), \tag{31}$$

$$\varepsilon_j(\theta) \geq 0,\ \theta \in [-\tau^*,\ 0],\ \varepsilon_j(\theta) \in \mathscr{C}([-\tau^*,\ 0],\ \mathbb{R}_{\geq 0}),\ j = 1,\ 2,\ \cdots,\ 6,$$

where $\tau^* = \max\{h_1,\ h_2,\ k_1,\ k_2\}$. We define $\Pi_j(\tau) = g_j(\tau)e^{-n_j\tau}$ and $\Upsilon_j = \int_0^{k_j} \Pi_j(\tau)d\tau$, $j = 1,\ 2$, which ensures that $0 < \Upsilon_j \leq 1$.

3.1 *Preliminary results*

We start by showing that the model (25)-(30) is well-posed, guaranteeing that the solutions remain both nonnegative and bounded. Next, we identify all potential equilibria and determine the basic reproductive number that affect the existence and stability of these equilibria.

Lemma 3 The solutions to the system given by (25)-(30), together with the initial conditions (31), remain non-negative and are eventually bounded over time.

Proof. Let us demonstrate the non-negativity of the solutions for the model (25)-(30). It is evident that the Eqs. (25), (29), and (30) imply that

$$\frac{dM}{dt}|_{M=0} = \phi > 0,\ \ \frac{dW^N}{dt}|_{W^N=0} = \gamma_1 > 0,\ \ \frac{dW^S}{dt}|_{W^S=0} = \gamma_2 > 0.$$

Hence, for all $t \geq 0$, $M(t) > 0$, $W^N(t) > 0$, and $W^S(t) > 0$. Moreover, we have

$$E^L(t) = e^{-(\mu+\varphi)t}\varepsilon_2(0) + (1-\xi)\kappa\int_0^t e^{-(\mu+\varphi)(t-\theta)}\int_0^{k_1}\Pi_1(\tau)M(\theta-\tau)V(\theta-\tau)d\tau d\theta \geq 0,$$

$$E^A(t) = e^{-\delta t}\varepsilon_3(0) + \int_0^t e^{-\delta(t-\theta)}\left[\xi\kappa\int_0^{h_1}\Lambda_1(\tau)M(\theta-\tau)V(\theta-\tau)d\tau + \mu\int_0^{k_2}\Pi_2(\tau)E^L(\theta-\tau)d\tau\right]d\theta \geq 0,$$

$$V(t) = e^{-\int_0^t\left(\rho+\beta_1W^N(x)+\beta_2W^S(x)\right)dx}\varepsilon_4(0) + \eta\int_0^t e^{-\int_\theta^t\left(\rho+\beta_1W^N(x)+\beta_2W^S(x)\right)dx}\int_0^{h_2}\Lambda_2(\tau)E^A(\theta-\tau)d\tau d\theta \geq 0.$$

for all $t \in [0,\ \tau^*]$. Therefore, through recursive reasoning, we conclude that $(E^L,\ E^A,\ V)(t) \geq 0$ for all $t \geq 0$. Consequently, M, E^L, E^A, V, W^N, and W^S are nonnegative.

Let's demonstrate that the solution $(M,\ E^L,\ E^A,\ V,\ W^N,\ W^S)$ is ultimately bounded. Eq. (25) gives

$$\limsup_{t\to\infty} M(t) \leq \frac{\phi}{\rho} = \bar{\Omega}_1.$$

To establish the ultimate boundedness of $E^L(t)$, we define

$$\mathscr{O}_1 = (1-\xi)\int_0^{k_1}\Pi_1(\tau)M_\tau d\tau + E^L.$$

Then, we obtain

$$\frac{d\mathscr{O}_1}{dt} = (1-\xi)\int_0^{k_1}\Pi_1(\tau)\frac{dM_\tau}{dt}d\tau + \frac{dE^L}{dt}$$

$$= (1-\xi)\int_0^{k_1}\Pi_1(\tau)\left(\phi - \rho M_\tau - \kappa M_\tau V_\tau\right)d\tau + (1-\xi)\kappa\int_0^{k_1}\Pi_1(\tau)M_\tau V_\tau d\tau - (\mu+\varphi)E^L$$

$$= (1-\xi)\phi\int_0^{k_1}\Pi_1(\tau)d\tau - (1-\xi)\rho\int_0^{k_1}\Pi_1(\tau)M_\tau d\tau - (\mu+\varphi)E^L$$

$$\leq (1-\xi)\phi\Upsilon_1 - \nu_1\left[(1-\xi)\int_0^{k_1}\Pi_1(\tau)M_\tau d\tau + E^L\right]$$

$$= (1-\xi)\phi - \nu_1\mathscr{O}_1,$$

where $\nu_1 = \min\{\rho,\ \mu+\varphi\}$. It follows that, $\limsup_{t\to\infty}\mathscr{O}_1(t) \leq \bar{\Omega}_2$, and then $\limsup_{t\to\infty}E^L(t) \leq \bar{\Omega}_2$, where $\bar{\Omega}_2 = \dfrac{(1-\xi)\phi}{\nu_1}$. Define

$$\mathscr{O}_2 = \xi\int_0^{h_1}\Lambda_1(\tau)M_\tau d\tau + E^A.$$

Then, we get

$$\frac{d\mathscr{O}_2}{dt} = \xi\int_0^{h_1}\Lambda_1(\tau)\left(\phi - \rho M_\tau - \kappa M_\tau V_\tau\right)d\tau + \xi\kappa\int_0^{h_1}\Lambda_1(\tau)M_\tau V_\tau d\tau + \mu\int_0^{k_2}\Pi_2(\tau)E^L_\tau d\tau - \delta E^A$$

$$= \xi\phi\int_0^{h_1}\Lambda_1(\tau)d\tau - \rho\xi\int_0^{h_1}\Lambda_1(\tau)M_\tau d\tau + \mu\int_0^{k_2}\Pi_2(\tau)E^L_\tau d\tau - \delta E^A$$

$$\leq \xi\phi\digamma_1 + \mu\Upsilon_2\bar{\Omega}_2 - \nu_2\left[\xi\int_0^{h_1}\Lambda_1(\tau)M_\tau d\tau + E^A\right]$$

$$\leq \xi\phi + \mu\bar{\Omega}_2 - \nu_2\mathscr{O}_2,$$

where $\nu_2 = \min\{\rho,\ \delta\}$. It follows that $\limsup_{t\to\infty}\mathscr{O}_2(t) \leq \bar{\Omega}_3$, where $\bar{\Omega}_3 = \dfrac{\xi\phi + \mu\bar{\Omega}_2}{\nu_2}$, then $\limsup_{t\to\infty}E^A(t) \leq \bar{\Omega}_3$. Now, let us define

$$\mathscr{O}_3 = V + \frac{\beta_1}{\lambda_1}W^N + \frac{\beta_2}{\lambda_2}W^S.$$

Then, we get

$$\frac{d\mathscr{O}_3}{dt} = \frac{dV}{dt} + \frac{\beta_1}{\lambda_1}\frac{dW^N}{dt} + \frac{\beta_2}{\lambda_2}\frac{dW^S}{dt}$$

$$= \eta \int_0^{h_2} \Lambda_2(\tau) E_\tau^A d\tau - \rho V - \beta_1 V W^N - \beta_2 V W^S + \frac{\beta_1}{\lambda_1}\left(\gamma_1 + \lambda_1 V W^N - \psi_1 W^N\right)$$

$$+ \frac{\beta_2}{\lambda_2}\left(\gamma_2 + \lambda_2 V W^S - \psi_2 W^S\right)$$

$$= \eta \int_0^{h_2} \Lambda_2(\tau) E_\tau^A d\tau + \frac{\beta_1\gamma_1}{\lambda_1} + \frac{\beta_2\gamma_2}{\lambda_2} - \rho V - \frac{\beta_1\psi_1}{\lambda_1} W^N - \frac{\beta_2\psi_2}{\lambda_2} W^S$$

$$\leq \eta \digamma_2 \bar{\Omega}_3 + \frac{\beta_1\gamma_1}{\lambda_1} + \frac{\beta_2\gamma_2}{\lambda_2} - \nu_3 \left[V + \frac{\beta_1}{\lambda_1} W^N + \frac{\beta_2}{\lambda_2} W^S\right]$$

$$\leq \eta \bar{\Omega}_3 + \frac{\beta_1\gamma_1}{\lambda_1} + \frac{\beta_2\gamma_2}{\lambda_2} - \nu_3 \mathscr{O}_3,$$

where $\nu_3 = \min\{\rho,\ \psi_1,\ \psi_2\}$. It follows that $\lim\limits_{t\to\infty} \sup \mathscr{O}_3(t) \leq \bar{\Omega}_4$, where $\bar{\Omega}_4 = \dfrac{\eta\bar{\Omega}_2}{\nu_3} + \dfrac{\beta_1\gamma_1}{\lambda_1\nu_3} + \dfrac{\beta_2\gamma_2}{\lambda_2\nu_3}$, then $\lim\limits_{t\to\infty} \sup V(t) \leq \bar{\Omega}_4$, $\lim\limits_{t\to\infty} \sup W^N(t) \leq \bar{\Omega}_5$, and $\lim\limits_{t\to\infty} \sup W^S(t) \leq \bar{\Omega}_6$, where $\bar{\Omega}_5 = \dfrac{\lambda_1\bar{\Omega}_4}{\beta_1}$, $\bar{\Omega}_6 = \dfrac{\lambda_2\bar{\Omega}_4}{\beta_2}$. □

As a result of Lemma 3, the set

$$\bar{\Gamma} = \left\{\left(M,\ E^L,\ E^A V,\ W^N,\ W^S\right) \in \mathscr{C}^6_{\geq 0} : \|M\| \leq \bar{\Omega}_1,\ \|E^L\| \leq \bar{\Omega}_2,\ \|E^A\| \leq \bar{\Omega}_3,\ \|V\| \leq \bar{\Omega}_4,\ \|W^N\| \leq \bar{\Omega}_5,\ \|W^S\| \leq \bar{\Omega}_6\right\}$$

is positively invariant for the system described by Equations (25)-(30).

Lemma 4 Let $\bar{R}_0$ represents the basic reproductive number for system (25)-(30). Then, the following holds:
(I) If $\bar{R}_0 \leq 1$, there is a unique infection-free equilibrium $\mathscr{E}\mathscr{P}_0$.
(II) If $\bar{R}_0 > 1$, an endemic equilibrium $\mathscr{E}\mathscr{P}_1$ exists in addition to $\mathscr{E}\mathscr{P}_0$.

Proof. Let the R.H.S. of Eqs. (25)-(30) be zero

$$0 = \phi - \rho M - \kappa M V, \tag{32}$$

$$0 = (1-\xi)\kappa\Upsilon_1 M V - (\mu + \varphi) E^L, \tag{33}$$

$$0 = \xi\kappa\digamma_1 M V + \mu\Upsilon_2 E^L - \delta E^A, \tag{34}$$

$$0 = \eta\digamma_2 E^A - \rho V - \beta_1 V W^N - \beta_2 V W^S, \tag{35}$$

$$0 = \gamma_1 + \lambda_1 V W^N - \psi_1 W^N, \tag{36}$$

$$0 = \gamma_2 + \lambda_2 V W^S - \psi_2 W^S. \tag{37}$$

From Eqs. (32), (33), (35)-(37), we have

$$\begin{aligned} M &= \frac{\phi}{\rho + \kappa V}, \qquad E^L = \frac{(1-\xi)\kappa\phi\Upsilon_1 V}{(\mu+\varphi)(\rho+\kappa V)}, \\ E^A &= \frac{\phi\kappa\mathscr{P}V}{\delta(\mu+\varphi)(\rho+\kappa V)}, \quad W^N = \frac{\gamma_1}{\psi_1 - \lambda_1 V}, \quad W^S = \frac{\gamma_2}{\psi_2 - \lambda_2 V}, \end{aligned} \tag{38}$$

where $\mathscr{P} = \mu(1-\xi)\Upsilon_1\Upsilon_2 + \xi(\mu+\varphi)F_1$. By substituting in Eq. (34), we obtain:

$$\left(-\rho + \frac{\eta\kappa\phi F_2\mathscr{P}}{\delta(\mu+\varphi)(\rho+\kappa V)} + \frac{\beta_1\gamma_1}{\lambda_1 V - \psi_1} + \frac{\beta_2\gamma_2}{\lambda_2 V - \psi_2}\right) V = 0. \tag{39}$$

Eq. (39) outlines two possible scenarios. The first scenario is when $V = 0$, which corresponds to the infection-free equilibrium $\mathscr{E}\mathscr{P}_0 = \left(M_0,\ 0,\ 0,\ 0,\ W_0^N,\ W_0^S\right)$. The second scenario occurs when $V \neq 0$, in this case

$$-\rho + \frac{\eta\kappa\phi F_2\mathscr{P}}{\delta(\mu+\varphi)(\rho+\kappa V)} + \frac{\beta_1\gamma_1}{\lambda_1 V - \psi_1} + \frac{\beta_2\gamma_2}{\lambda_2 V - \psi_2} = 0,$$

which gives

$$\frac{\bar{\ell}_1 V^3 + \bar{\ell}_2 V^2 + \bar{\ell}_3 V + \bar{\ell}_4}{\delta(\mu+\varphi)(\rho+\kappa V)(\lambda_1 V - \psi_1)(\lambda_2 V - \psi_2)} = 0, \tag{40}$$

where

$$\bar{\ell}_1 = \delta\rho\lambda_1\lambda_2\kappa(\mu+\varphi),$$

$$\begin{aligned} \bar{\ell}_2 = {} & \delta\rho\rho\lambda_1\lambda_2(\mu+\varphi) - \eta\lambda_1\lambda_2\kappa\phi\mathscr{P}F_2 - \delta\lambda_2\beta_1\kappa\gamma_1(\mu+\varphi) - \delta\lambda_1\beta_2\kappa\gamma_2(\mu+\varphi) \\ & - \delta\rho\lambda_2\kappa\psi_1(\mu+\varphi) - \delta\rho\lambda_1\kappa\psi_2(\mu+\varphi), \end{aligned}$$

$$\begin{aligned} \bar{\ell}_3 = {} & -\delta\rho\lambda_2\beta_1\gamma_1(\mu+\varphi) - \delta\rho\lambda_1\beta_2\gamma_2(\mu+\varphi) - \delta\rho\rho\lambda_2\psi_1(\mu+\varphi) + \eta\lambda_2\kappa\phi\psi_1\mathscr{P}F_2 + \delta\beta_2\kappa\gamma_2\psi_1(\mu+\varphi) \\ & - \delta\rho\rho\lambda_1\psi_2(\mu+\varphi) + \eta\lambda_1\kappa\phi\psi_2\mathscr{P}F_2 + \delta\beta_1\kappa\gamma_1\psi_2(\mu+\varphi) + \delta\rho\kappa\psi_1\psi_2(\mu+\varphi), \end{aligned}$$

$$\bar{\ell}_4 = \delta\rho\beta_2\gamma_2\psi_1(\mu+\varphi) + \delta\rho\beta_1\gamma_1\psi_2(\mu+\varphi) + \delta\rho\rho\psi_1\psi_2(\mu+\varphi) - \eta\kappa\phi\psi_1\psi_2\mathscr{P}F_2.$$

Next, let's define a function $\mathscr{Z}(V) = \bar{\ell}_1 V^3 + \bar{\ell}_2 V^2 + \bar{\ell}_3 V + \bar{\ell}_4$, then we find

$$\mathscr{Z}(0) = -\delta\rho(\mu+\varphi)\left(\beta_2\gamma_2\psi_1 + \beta_1\gamma_1\psi_2 + \rho\psi_1\psi_2\right)\left(\frac{\eta\kappa\phi\mathscr{P}F_2}{\delta\rho\rho(\mu+\varphi)\left(\beta_1\gamma_1\psi_1\rho + \frac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)} - 1\right),$$

$$\mathscr{Z}\left(\frac{\psi_1}{\lambda_1}\right) = \frac{\delta\beta_1\gamma_1\lambda_2(\mu+\varphi)\left(\rho\lambda_1 + \kappa\psi_1\right)}{\lambda_1}\left(\frac{\psi_2}{\lambda_2} - \frac{\psi_1}{\lambda_1}\right),$$

$$\mathscr{Z}\left(\frac{\psi_2}{\lambda_2}\right) = \frac{\delta\beta_2\gamma_2\lambda_1(\mu+\varphi)\left(\rho\lambda_2 + \kappa\psi_2\right)}{\lambda_2}\left(\frac{\psi_1}{\lambda_1} - \frac{\psi_2}{\lambda_2}\right),$$

$$\lim_{v\to\infty}\mathscr{Z}(V) = \infty.$$

Hence, $\mathscr{Z}(0) < 0$ holds true provided that the following condition is met.

$$\frac{\eta\kappa\phi\mathscr{P}F_2}{\delta\rho\rho(\mu+\varphi)\left(\frac{\beta_1\gamma_1}{\psi_1\rho} + \frac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)} > 1. \tag{41}$$

Analogous to the argument presented in Lemma 2, it can be shown that there exists $E_1 \in \left(0, \min\left\{\frac{\psi_1}{\lambda_1}, \frac{\psi_2}{\lambda_2}\right\}\right)$ satisfies Eq. (40). It follows that

$$M_1 = \frac{\phi}{\rho + \kappa V_1} > 0, \qquad E_1^L = \frac{(1-\xi)\kappa\phi\Upsilon_1 V_1}{(\mu+\varphi)(\rho+\kappa V_1)} > 0,$$

$$E_1^A = \frac{\phi\kappa\mathscr{P}V_1}{\delta(\mu+\varphi)(\rho+\kappa V_1)} > 0, \quad W_1^N = \frac{\gamma_1}{\psi_1 - \lambda_1 V_1} > 0, \quad W_1^S = \frac{\gamma_2}{\psi_2 - \lambda_2 V_1} > 0.$$

The basic reproductive number, $\bar{R}_0$, can therefore be defined as:

$$\bar{R}_0 = \frac{\eta\kappa\phi\mathscr{P}F_2}{\delta\rho\rho(\mu+\varphi)\left(\frac{\beta_1\gamma_1}{\psi_1\rho} + \frac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)}.$$

The endemic equilibrium $\mathscr{E}\mathscr{P}_1 = \left(M_1,\, E^L{}_1,\, E^A{}_1,\, V_1,\, W_1^N,\, W_1^S\right)$ is present when $\bar{R}_0 > 1$.

3.2 *Global stability*

Let $\bar{\Theta}$ be the potential Lyapunov function and Φ_j' be the largest invariant set of

$$\Phi_j = \left\{ \left(M,\, E^L,\, E^A,\, V,\, W^N,\, W^S\right) : \frac{d\bar{\Theta}_j}{dt} = 0 \right\},\ j = 0,\ 1.$$

Theorem 3 The system described by Equations (25)-(30) exhibits global asymptotic stability at the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ when $\bar{R}_0 \leq 1$. However, if $\bar{R}_0 > 1$, this equilibrium loses stability.

Proof. Define $\bar{\Theta}_0(M,\, E^L,\, E^A,\, V,\, W^N,\, W^S)$ as:

$$\begin{aligned}
\bar{\Theta}_0 = {} & \mathscr{P}M^0\mathscr{L}\left(\frac{M}{M_0}\right) + \mu\Upsilon_2 E^L + (\mu+\varphi)E^A + \frac{\delta(\mu+\varphi)}{\eta F_2}V + \frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1 F_2}W_0^N\mathscr{L}\left(\frac{W^N}{W_0^N}\right) \\
& + \frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2 F_2}W_0^S\mathscr{L}\left(\frac{W^S}{W_0^S}\right) + \mu\kappa(1-\xi)\Upsilon_2\int_0^{k_1}\Pi_1(\tau)\int_{t-\tau}^{t}M(\theta)V(\theta)d\theta d\tau \\
& + \xi\kappa(\mu+\varphi)\int_0^{h_1}\Lambda_1(\tau)\int_{t-\tau}^{t}M(\theta)V(\theta)d\theta d\tau + \mu(\mu+\varphi)\int_0^{k_2}\Pi_2(\tau)\int_{t-\tau}^{t}E^L(\theta)d\theta d\tau \\
& + \frac{\delta(\mu+\varphi)}{F_2}\int_0^{h_2}\Lambda_2(\tau)\int_{t-\tau}^{t}E^A(\theta)d\theta d\tau.
\end{aligned}$$

We note that $\bar{\Theta}_0\left(M,\, E^L,\, E^A,\, V,\, W^N,\, W^S\right) > 0$ for any $\left(M,\, E^L,\, E^A,\, V,\, W^N a,\, W^S\right) > 0$ and $\bar{\Theta}_0(M_0,\, 0,\, 0,\, 0,\, W_0^N,\, W_0^S) = 0$. Calculating $\dfrac{d\bar{\Theta}_0}{dt}$ along the solutions of (25)-(30) as:

$$\begin{aligned}
\frac{d\bar{\Theta}_0}{dt} = {} & \mathscr{P}\left(1-\frac{M_0}{M}\right)\frac{dM}{dt} + \mu\Upsilon_2\frac{dE^L}{dt} + (\mu+\varphi)\frac{dE^A}{dt} + \frac{\delta(\mu+\varphi)}{\eta F_2}\frac{dV}{dt} + \frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1 F_2}\left(1-\frac{W_0^N}{W^N}\right)\frac{dW^N}{dt} \\
& + \frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2 F_2}\left(1-\frac{W_0^S}{W^S}\right)\frac{dW^S}{dt} + \mu\kappa(1-\xi)\Upsilon_2\int_0^{k_1}\Pi_1(\tau)\left(MV - M_\tau V_\tau\right)d\tau \\
& + \xi\kappa(\mu+\varphi)\int_0^{h_1}\Lambda_1(\tau)\left(MV - M_\tau V_\tau\right)d\tau + (\mu+\varphi)\mu\int_0^{k_2}\Pi_2(\tau)\left(E^L - E_\tau^L\right)d\tau \\
& + \frac{\delta(\mu+\varphi)}{F_2}\int_0^{h_2}\Lambda_2(\tau)\left(E^A - E_\tau^A\right)d\tau.
\end{aligned}$$

From Eqs. (25)-(30) we get

$$\begin{aligned}
\frac{d\bar{\Theta}_0}{dt} = {} & \mathscr{P}\left(1-\frac{M_0}{M}\right)(\phi - \rho M - \kappa MV) + \mu\Upsilon_2\left((1-\xi)\kappa\int_0^{k_1}\Pi_1(\tau)M_\tau V_\tau d\tau - (\mu+\varphi)E^L\right) \\
& + (\mu+\varphi)\left(\xi\kappa\int_0^{h_1}\Lambda_1(\tau)M_\tau V_\tau d\tau + \mu\int_0^{k_2}\Pi_2(\tau)E_\tau^L d\tau - \delta E^A\right)
\end{aligned}$$

$$+\frac{\delta(\mu+\varphi)}{\eta F_2}\left(\eta\int_0^{h_2}\Lambda_2(\tau)E_\tau^A d\tau-\rho V-\beta_1 VW^N-\beta_2 VW^S\right)$$

$$+\frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1 F_2}\left(1-\frac{W_0^N}{W^N}\right)\left(\gamma_1+\lambda_1 VW^N-\psi_1 W^N\right)+\frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2 F_2}\left(1-\frac{W_0^S}{W^S}\right)\left(\gamma_2+\lambda_2 VW^S-\psi_2 W^S\right)$$

$$+\mu\kappa(1-\xi)\Upsilon_2\int_0^{k_1}\Pi_1(\tau)\left(MV-M_\tau V_\tau\right)d\tau+\xi\kappa(\mu+\varphi)\int_0^{h_1}\Lambda_1(\tau)\left(MV-M_\tau V_\tau\right)d\tau$$

$$+(\mu+\varphi)\mu\int_0^{k_2}\Pi_2(\tau)\left(E^L-E_\tau^L\right)d\tau+\frac{\delta(\mu+\varphi)}{F_2}\int_0^{h_2}\Lambda_2(\tau)\left(E^A-E_\tau^A\right)d\tau.$$

Collecting terms we get

$$\frac{d\bar{\Theta}_0}{dt}=\mathscr{P}\left(1-\frac{M_0}{M}\right)(\phi-\rho M)+\frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1 F_2}\left(1-\frac{W_0^N}{W^N}\right)\left(\gamma_1^N-\psi_1 W^N\right)+\frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2 F_2}\left(1-\frac{W_0^S}{W^S}\right)\left(\gamma_2-\psi_2 W^S\right)$$

$$+\kappa\mathscr{P}M_0V-\frac{\delta\rho(\mu+\varphi)}{\eta F_2}V-\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}W_0^N V-\frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}W_0^S V.$$

Using $\phi=\rho M_0,\ \gamma_1=\psi_1 W_0^N$, and $\gamma_2=\psi_2 W_0^S$, we obtain

$$\frac{d\bar{\Theta}_0}{dt}=-\frac{\rho\mathscr{P}(M-M_0)^2}{M}-\frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1 F_2}\frac{\left(W^N-W_0^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2 F_2}\frac{\left(W^S-W_0^S\right)^2}{W^S}+\kappa\mathscr{P}M_0V-\frac{\delta\rho(\mu+\varphi)}{\eta F_2}V$$

$$-\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}W_0^N V-\frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}W_0^S V.$$

It follows that

$$\frac{d\bar{\Theta}_0}{dt}=-\frac{\rho\mathscr{P}(M-M_0)^2}{M}-\frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1 F_2}\frac{\left(W^N-W_0^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2 F_2}\frac{\left(W^S-W_0^S\right)^2}{W^S}$$

$$+\left[\kappa\mathscr{P}M_0-\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}W_0^N-\frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}W_0^S-\frac{\delta\rho(\mu+\varphi)}{\eta F_2}\right]V$$

$$=-\frac{\rho\mathscr{P}(M-M_0)^2}{M}-\frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1 F_2}\frac{\left(W^N-W_0^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2 F_2}\frac{\left(W^S-W_0^S\right)^2}{W^S}$$

$$+\left[\frac{\kappa\phi\mathscr{P}}{\rho}-\frac{\delta\rho(\mu+\varphi)}{\eta F_2}\left(\frac{\beta_1\gamma_1}{\psi_1\rho}+\frac{\beta_2\gamma_2}{\psi_2\rho}+1\right)\right]V.$$

Finally, from the definition of $\bar{R}_0$, we obtain

$$\frac{d\bar{\Theta}_0}{dt} = -\frac{\rho\mathscr{P}(M-M_0)^2}{M} - \frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1 F_2}\frac{\left(W^N-W_0^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2 F_2}\frac{\left(W^S-W_0^S\right)^2}{W^S}$$

$$+\frac{\delta\rho(\mu+\varphi)}{\eta F_2}\left(\frac{\beta_1\gamma_1}{\psi_1\rho}+\frac{\beta_2\gamma_2}{\psi_2\rho}+1\right)[\bar{R}_0-1]V.$$

Since $\bar{R}_0 \leq 1$, then $\frac{d\bar{\Theta}_0}{dt} \leq 0$. Furthermore, $\frac{d\bar{\Theta}_0}{dt} = 0$ when $M = M_0$, $W^N = W_0^N$, $W^S = W_0^S$, and $(\bar{R}_0-1)V = 0$. The solutions of system (6)-(10) tend toward the set Φ_0' as time progresses [40]. Every element within Φ_0' satisfies $M = M_0$, $W^N = W_0^N$, $W^S = W_0^S$, and

$$(\bar{R}_0-1)V = 0. \tag{42}$$

The analysis can be divided into two distinct scenarios:

S-1. $\bar{R}_0 = 1$, then from Eq. (25)

$$0 = \frac{dM}{dt} = \phi - \rho M_0 - \kappa M_0 V \quad \Longrightarrow \quad V(t) = 0 \quad \text{for any } t. \tag{43}$$

From Eq. (28) we have

$$0 = \frac{dV}{dt} = \eta\int_0^{h_2}\Lambda_2(\tau)E_\tau^A d\tau \quad \Longrightarrow \quad E^A(t) = 0 \quad \text{for any } t. \tag{44}$$

Eq. (27) implies that

$$0 = \frac{dE^A}{dt} = \mu\int_0^{k_2}\Pi_2(\tau)E^L d\tau \quad \Longrightarrow \quad E^L(t) = 0 \quad \text{for any } t. \tag{45}$$

Then $\Phi_0' = \{\mathscr{E}\mathscr{P}_0\}$.

S-2. $\bar{R}_0 < 1$, Eq. (42) leads to $V = 0$ and from Eqs. (44)-(45), it follows that $E^A = E^L = 0$. Therefore, the set Φ_0' reduces to the infection-free equilibrium $\{\mathscr{E}\mathscr{P}_0\}$.

Applying LIT, we obtain that $\mathscr{E}\mathscr{P}_0$ is GAS.

The characteristic equation corresponding to $\mathscr{E}\mathscr{P}_0$ is given by:

$$(x+\rho)(x+\psi_1)(x+\psi_2)\bar{\mathscr{N}}(x) = 0, \tag{46}$$

where x is the eigenvalue, $\bar{\mathscr{N}}(x) = \vartheta_3 x^3 + \vartheta_2 x^2 + \vartheta_1 x + \vartheta_0$ and

$$\vartheta_3 = \rho\psi_1\psi_2,$$

$$\vartheta_2 = \beta_2\gamma_2\rho\psi_1 + \beta_1\gamma_1\rho\psi_2 + \delta\rho\psi_1\psi_2 + \rho\rho\psi_1\psi_2 + \rho\psi_1\psi_2(\mu+\varphi),$$

$$\vartheta_1 = \beta_2\gamma_2\delta\rho\psi_1 + \beta_2\gamma_2\rho\psi_1(\mu+\varphi) + \beta_1\gamma_1\delta\rho\psi_2 + \beta_1\gamma_1\rho\psi_2(\mu+\varphi) + \delta\rho\rho\psi_1\psi_2$$
$$+ \delta\rho\psi_1\psi_2(\mu+\varphi) + \rho\rho\psi_1\psi_2(\mu+\varphi) - \eta\kappa\phi\psi_1\psi_2\xi\bar{F}_1\bar{F}_2,$$

$$\vartheta_0 = \beta_2\gamma_2\delta\rho\psi_1(\mu+\varphi) + \beta_1\gamma_1\delta\rho\psi_2(\mu+\varphi) + \delta\rho\rho\psi_1\psi_2(\mu+\varphi)$$
$$- \eta\kappa\phi\mu\psi_1\psi_2(1-\xi)\bar{\Upsilon}_1\bar{\Upsilon}_2\bar{F}_2 - \eta\kappa\phi\xi\psi_1\psi_2(\mu+\phi)\bar{F}_1\bar{F}_2,$$

where $\bar{F}_j = \int_0^{h_j} f_j(\tau)e^{-(x+m_j)\tau_j}d\tau$ and $\bar{\Upsilon}_j = \int_0^{k_j} g_j(\tau)e^{-(x+n_j)\tau_j}d\tau$, $j = 1, 2$. Clearly, if $\bar{R}_0 > 1$, then

$$\bar{N}(0) = \delta\rho\left(\beta_2\gamma_2\psi_1 + \beta_1\gamma_1\psi_2 + \rho\psi_1\psi_2\right)(1-\bar{R}_0) < 0.$$

Moreover, $\lim_{x\to\infty}\bar{N}(x) = \infty$. This indicates that Eq. (46) has a positive real root when $\bar{R}_0 > 1$. Consequently, if $\bar{R}_0 > 1$, the equilibrium point $\mathscr{E}\mathscr{P}_0$ becomes unstable. □

Theorem 4 The endemic equilibrium $\mathscr{E}\mathscr{P}_1$ of model (25)-(30) is GAS when $\bar{R}_0 > 1$.

Proof. Construct $\bar{\Theta}_1\left(M,\, E^L,\, E^A,\, V,\, W^N,\, W^S\right)$ as:

$$\bar{\Theta}_1 = \mathscr{P}M_1\mathscr{L}\left(\frac{M}{M_1}\right) + \mu\Upsilon_2E_1^L\mathscr{L}\left(\frac{E^L}{E_1^L}\right) + (\mu+\varphi)E_1^A\mathscr{L}\left(\frac{E^A}{E_1^A}\right) + \frac{\delta(\mu+\varphi)}{\eta F_2}V_1\mathscr{L}\left(\frac{V}{V_1}\right) + \frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1F_2}W_1^N\mathscr{L}\left(\frac{W^N}{W_1^N}\right)$$
$$+ \frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2F_2}W_1^S\mathscr{L}\left(\frac{W^S}{W_1^S}\right) + \mu\kappa(1-\xi)\Upsilon_2M_1V_1\int_0^{k_1}\Pi_1(\tau)\int_{t-\tau}^{t}\mathscr{L}\left(\frac{M(\theta)V(\theta)}{M_1V_1}\right)d\theta d\tau$$
$$+ \xi\kappa(\mu+\varphi)M_1V_1\int_0^{h_1}\Lambda_1(\tau)\int_{t-\tau}^{t}\mathscr{L}\left(\frac{M(\theta)V(\theta)}{M_1V_1}\right)d\theta d\tau + \mu(\mu+\varphi)E_1^L\int_0^{k_2}\Pi_2(\tau)\int_{t-\tau}^{t}\mathscr{L}\left(\frac{E^L(\theta)}{E_1^L}\right)d\theta d\tau$$
$$+ \frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\int_{t-\tau}^{t}\mathscr{L}\left(\frac{E^A(\theta)}{E_1^A}\right)d\theta d\tau.$$

The derivative of $\bar{\Theta}_1$ is given as:

$$\frac{d\bar{\Theta}_1}{dt} = \mathscr{P}\left(1-\frac{M_1}{M}\right)\frac{dM}{dt} + \mu\Upsilon_2\left(1-\frac{E_1^L}{E^L}\right)\frac{dE^L}{dt} + (\mu+\varphi)\left(1-\frac{E_1^A}{E^A}\right)\frac{dE^A}{dt} + \frac{\delta(\mu+\varphi)}{\eta F_2}\left(1-\frac{V_1}{V}\right)\frac{dV}{dt}$$

$$+\frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1 F_2}\left(1-\frac{W_1^N}{W^N}\right)\frac{dW^N}{dt}+\frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2 F_2}\left(1-\frac{W_1^S}{W^S}\right)\frac{dW^S}{dt}$$

$$+\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\left[\frac{MV}{M_1V_1}-\frac{M_\tau V_\tau}{M_1V_1}+\ln\left(\frac{M_\tau V_\tau}{MV}\right)\right]d\tau$$

$$+(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\frac{MV}{M_1V_1}-\frac{M_\tau V_\tau}{M_1V_1}+\ln\left(\frac{M_\tau V_\tau}{MV}\right)\right]d\tau$$

$$+(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\left[\frac{E^L}{E_1^L}-\frac{E_\tau^L}{E_1^L}+\ln\left(\frac{E_\tau^L}{E^L}\right)\right]d\tau+\frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\left[\frac{E^A}{E_1^A}-\frac{E_\tau^A}{E_1^A}+\ln\left(\frac{E_\tau^A}{E^A}\right)\right]d\tau.$$

By substituting the equations from model (25)-(30), we obtain

$$\frac{d\bar{\Theta}_1}{dt}=\mathscr{P}\left(1-\frac{M_1}{M}\right)(\phi-\rho M-\kappa MV)+\mu\Upsilon_2\left(1-\frac{E_1^L}{E^L}\right)\left((1-\xi)\kappa\int_0^{k_1}\Pi_1(\tau)M_\tau V_\tau d\tau-(\mu+\varphi)E^L\right)$$

$$+(\mu+\varphi)\left(1-\frac{E_1^A}{E^A}\right)\left(\xi\kappa\int_0^{h_1}\Lambda_1(\tau)M_\tau V_\tau d\tau+\mu\int_0^{k_2}\Pi_2(\tau)E_\tau^L d\tau-\delta E^A\right)$$

$$+\frac{\delta(\mu+\varphi)}{\eta F_2}\left(1-\frac{V_1}{V}\right)\left(\eta\int_0^{h_2}\Lambda_2(\tau)E_\tau^A d\tau-\rho V-\beta_1VW^N-\beta_2VW^S\right)$$

$$+\frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1F_2}\left(1-\frac{W_1^N}{W^N}\right)(\gamma_1+\lambda_1VW^N-\psi_1W^N)+\frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2F_2}\left(1-\frac{W_1^S}{W^S}\right)(\gamma_2+\lambda_2VW^S-\psi_2W^S)$$

$$+\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\left[\frac{MV}{M_1V_1}-\frac{M_\tau V_\tau}{M_1V_1}+\ln\left(\frac{M_\tau V_\tau}{MV}\right)\right]d\tau$$

$$+(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\frac{MV}{M_1V_1}-\frac{M_\tau V_\tau}{M_1V_1}+\ln\left(\frac{M_\tau V_\tau}{MV}\right)\right]d\tau$$

$$+(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\left[\frac{E^L}{E_1^L}-\frac{E_\tau^L}{E_1^L}+\ln\left(\frac{E_\tau^L}{E^L}\right)\right]d\tau+\frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\left[\frac{E^A}{E_1^A}-\frac{E_\tau^A}{E_1^A}+\ln\left(\frac{E_\tau^A}{E^A}\right)\right]d\tau.$$

Gathering the terms results in the following expression

$$\frac{d\bar{\Theta}_1}{dt}=\mathscr{P}\left(1-\frac{M_1}{M}\right)(\phi-\rho M)+\kappa\mathscr{P}M_1V-\mu(1-\xi)\Upsilon_2\kappa\int_0^{k_1}\Pi_1(\tau)\frac{M_\tau V_\tau E_1^L}{E^L}d\tau+\mu\Upsilon_2(\mu+\varphi)E_1^L$$

$$-(\mu+\varphi)\xi\kappa\int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1^A}{E^A}d\tau-(\mu+\varphi)\mu\int_0^{k_2}\Pi_2(\tau)\frac{E^LE_1^A}{E^A}d\tau+(\mu+\varphi)\delta E_1^A-\frac{\delta\rho(\mu+\varphi)}{\eta F_2}V$$

$$
\begin{aligned}
&-\frac{\delta(\mu+\varphi)}{F_2}\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau^A V_1}{V}d\tau+\frac{\delta\rho(\mu+\varphi)}{\eta F_2}V_1+\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}V_1W^N+\frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}V_1W^S\\
&+\frac{\delta\beta_1(\mu+\varphi)}{\eta\lambda_1 F_2}\left(1-\frac{W_1^N}{W^N}\right)(\gamma_1-\psi_1W^N)-\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}W_1^NV+\frac{\delta\beta_2(\mu+\varphi)}{\eta\lambda_2 F_2}\left(1-\frac{W_1^S}{W^S}\right)(\gamma_2-\psi_2W^S)\\
&-\frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}W_1^SV+\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau\\
&+(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau+(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\ln\left(\frac{E_\tau^L}{E^L}\right)d\tau\\
&+\frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\ln\left(\frac{E_\tau^A}{E^A}\right)d\tau.
\end{aligned}
$$

Using the equilibrium conditions of $\mathscr{E}\mathscr{P}_1$

$$
\begin{cases}
\phi=\rho M_1+\kappa M_1V_1,\\
(1-\xi)\kappa\Upsilon_1M_1V_1=(\mu+\varphi)E_1^L,\\
\xi\kappa_1F_1M_1V_1+\mu\Upsilon_2E_1^L=\delta E_1^A,\\
\eta F_2E_1^A=\rho V_1+\beta_1V_1W_1^N+\beta_2V_1W_1^S,\\
\gamma_1=-\lambda_1V_1W_1^N+\psi_1W_1^N,\\
\gamma_2=-\lambda_2V_1W_1^S+\psi_2W_1^S,
\end{cases}
$$

we get

$$
\begin{aligned}
(\mu+\varphi)\delta E_1^A&=(\mu+\varphi)\xi\kappa F_1M_1V_1+(\mu+\varphi)\mu\Upsilon_2E_1^L\\
&=(\mu+\varphi)\xi\kappa F_1M_1V_1+\mu(1-\xi)\Upsilon_1\Upsilon_2\kappa M_1V_1\\
&=\mathscr{P}\kappa M_1V_1.
\end{aligned}
$$

We then derive

$$\frac{d\bar{\Theta}_1}{dt} = -\frac{\rho\mathscr{P}(M-M_1)^2}{M} - \frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1 F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2 F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S} + \mathscr{P}\left(1-\frac{M_1}{M}\right)\kappa M_1 V_1$$

$$-\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}\left(1-\frac{W_1^N}{W^N}\right)V_1W_1^N - \frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}\left(1-\frac{W_1^S}{W^S}\right)V_1W_1^S + \left(\kappa\mathscr{P}M_1V_1 - \frac{\delta\rho(\mu+\varphi)}{\eta F_2}V_1\right.$$

$$\left.-\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}W_1^NV_1 - \frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}W_1^SV_1\right)\frac{V}{V_1} - \mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}d\tau$$

$$+\mu\Upsilon_2(\mu+\varphi)E_1^L - (\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}d\tau - (\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\frac{E^LE_1^A}{E_1^LE^A}d\tau$$

$$+(\mu+\varphi)\delta E_1^A - \frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau^AV_1}{E_1^AV}d\tau + \frac{\delta\rho(\mu+\varphi)}{\eta F_2}V_1 + \frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}V_1W^N + \frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}V_1W^S$$

$$+\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau + (\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau$$

$$+(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\ln\left(\frac{E_\tau^L}{E^L}\right)d\tau + \frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\ln\left(\frac{E_\tau^A}{E^A}\right)d\tau$$

$$+\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}V_1W_1^N - \frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}V_1W_1^N + \frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}V_1W_1^S - \frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}V_1W_1^S.$$

Clearly, it's evident that

$$\left(\kappa\mathscr{P}M_1V_1 - \frac{\delta\rho(\mu+\varphi)}{\eta F_2}V_1 - \frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}W_1^NV_1 - \frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}W_1^SV_1\right)\frac{V}{V_1} = 0.$$

It follows that

$$\frac{d\bar{\Theta}_1}{dt} = -\frac{\rho\mathscr{P}(M-M_1)^2}{M} - \frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1 F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N} - \frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2 F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S} + \mathscr{P}\left(1-\frac{M_1}{M}\right)\kappa M_1V_1$$

$$-\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}\left(2-\frac{W_1^N}{W^N}-\frac{W^N}{W_1^N}\right)V_1W_1^N - \frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}\left(2-\frac{W_1^S}{W^S}-\frac{W^S}{W_1^S}\right)V_1W_1^S$$

$$-\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}d\tau + \mu\Upsilon_2(\mu+\varphi)E_1^L$$

$$-(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}d\tau-(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\frac{E^LE_1^A}{E_1^LE^A}d\tau$$

$$+(\mu+\varphi)\delta E_1^A-\frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau^AV_1}{E_1^AV}d\tau+(\mu+\varphi)\xi\kappa F_1M_1V_1+\mu(1-\xi)\Upsilon_1\Upsilon_2\kappa M_1V_1$$

$$+\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau+(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\ln\left(\frac{M_\tau V_\tau}{MV}\right)d\tau$$

$$+(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\ln\left(\frac{E_\tau^L}{E^L}\right)d\tau+\frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\ln\left(\frac{E_\tau^A}{E^A}\right)d\tau.$$

To prove this theorem, we will use following equalities:

$$\ln\left(\frac{M_\tau V_\tau}{MV}\right)=\ln\left(\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}\right)+\ln\left(\frac{M_1}{M}\right)+\ln\left(\frac{V_1E^L}{VE_1^L}\right),$$

$$\ln\left(\frac{M_\tau V_\tau}{MV}\right)=\ln\left(\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}\right)+\ln\left(\frac{M_1}{M}\right)+\ln\left(\frac{V_1E^A}{VE_1^A}\right),$$

$$\ln\left(\frac{E^L{}_\tau}{E^L}\right)=\ln\left(\frac{E_\tau^LE_1^A}{E_1^LE^A}\right)+\ln\left(\frac{E_1^LE^A}{E^LE_1^A}\right),$$

$$\ln\left(\frac{E_\tau^A}{E^A}\right)=\ln\left(\frac{E_\tau^AV_1}{E_1^AV}\right)+\ln\left(\frac{E_1^AV}{E^AV_1}\right),$$

which leads to

$$\frac{d\bar{\Theta}_1}{dt}=-\frac{\rho\mathscr{P}(M-M_1)^2}{M}-\frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}+\mathscr{P}\left(1-\frac{M_1}{M}\right)\kappa M_1V_1$$

$$+\frac{\delta\beta_1(\mu+\varphi)}{\eta F_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}V_1+\frac{\delta\beta_2(\mu+\varphi)}{\eta F_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}V_1$$

$$-\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}d\tau+\mu\Upsilon_2(\mu+\varphi)E_1^L$$

$$-(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}d\tau-(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\frac{E^LE_1^A}{E_1^LE^A}d\tau$$

$$+(\mu+\varphi)\delta E_1^A-\frac{\delta(\mu+\varphi)}{F_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\frac{E_\tau^AV_1}{E_1^AV}d\tau+(\mu+\varphi)\xi\kappa F_1M_1V_1+\mu(1-\xi)\Upsilon_1\Upsilon_2\kappa M_1V_1$$

$$+\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\left[\ln\left(\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}\right)+\ln\left(\frac{M_1}{M}\right)+\ln\left(\frac{V_1E^L}{VE_1^L}\right)\right]d\tau$$

$$+(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\ln\left(\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}\right)+\ln\left(\frac{M_1}{M}\right)+\ln\left(\frac{V_1E^A}{VE_1^A}\right)\right]d\tau$$

$$+(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\left[\ln\left(\frac{E_\tau^LE_1^A}{E_1^LE^A}\right)+\ln\left(\frac{E_1^LE^A}{E^LE_1^A}\right)\right]d\tau$$

$$+\frac{\delta(\mu+\varphi)}{\digamma_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\left[\ln\left(\frac{E_\tau^AV_1}{E_1^AV}\right)+\ln\left(\frac{E_1^AV}{E^AV_1}\right)\right]d\tau.$$

Then we obtain

$$\frac{d\bar{\Theta}_1}{dt}=-\frac{\rho\mathscr{P}(M-M_1)^2}{M}-\frac{\delta\beta_1\psi_1(\mu+\varphi)}{\eta\lambda_1\digamma_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}-\frac{\delta\beta_2\psi_2(\mu+\varphi)}{\eta\lambda_2\digamma_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}$$

$$-\mathscr{P}\left(\frac{M_1}{M}-1-\ln\left(\frac{M_1}{M}\right)\right)\kappa M_1V_1+\frac{\delta\beta_1(\mu+\varphi)}{\eta\digamma_2}\frac{\left(W^N-W_1^N\right)^2}{W^N}V_1+\frac{\delta\beta_2(\mu+\varphi)}{\eta\digamma_2}\frac{\left(W^S-W_1^S\right)^2}{W^S}V_1$$

$$-\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\left[\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}-1-\ln\left(\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}\right)\right]d\tau$$

$$-(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\left[\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}-1-\ln\left(\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}\right)\right]d\tau$$

$$-(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\left[\frac{E^LE_1^A}{E_1^LE^A}-1-\ln\left(\frac{E_\tau^LE_1^A}{E_1^LE^A}\right)\right]d\tau$$

$$-\frac{\delta(\mu+\varphi)}{\digamma_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\left[\frac{E_\tau^AV_1}{E_1^AV}-1-\ln\left(\frac{E_\tau^AV_1}{E_1^AV}\right)\right]d\tau$$

$$+\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\ln\left(\frac{V_1E^L}{VE_1^L}\right)d\tau$$

$$+(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\ln\left(\frac{V_1E^A}{VE_1^A}\right)d\tau$$

$$+(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\ln\left(\frac{E_1^LE^A}{E^LE_1^A}\right)d\tau$$

$$+\frac{\delta(\mu+\varphi)}{\digamma_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\ln\left(\frac{E_1^AV}{E^AV_1}\right)d\tau.$$

From the equilibrium conditions, we obtain $V_1-\dfrac{\psi_1}{\lambda_1}=-\dfrac{\gamma_1}{\lambda_1W_1^N}$ and $V_1-\dfrac{\psi_2}{\lambda_2}=-\dfrac{\gamma_2}{\lambda_2W_1^S}$. This leads to the conclusion that

$$\frac{d\bar{\Theta}_1}{dt}=-\frac{\rho\mathscr{P}(M-M_1)^2}{M}-\frac{\delta\beta_1\gamma_1(\mu+\varphi)}{\eta\lambda_1\digamma_2}\frac{\left(W^N-W_1^N\right)^2}{W^NW_1^N}-\frac{\delta\beta_2\gamma_2(\mu+\varphi)}{\eta\lambda_2\digamma_2}\frac{\left(W^S-W_1^S\right)^2}{W^SW_1^S}$$

$$-\mathscr{P}\mathscr{L}\left(\frac{M_1}{M}\right)\kappa M_1V_1-\mu(1-\xi)\Upsilon_2\kappa M_1V_1\int_0^{k_1}\Pi_1(\tau)\mathscr{L}\left(\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}\right)d\tau$$

$$-(\mu+\varphi)\xi\kappa M_1V_1\int_0^{h_1}\Lambda_1(\tau)\mathscr{L}\left(\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}\right)d\tau-(\mu+\varphi)\mu E_1^L\int_0^{k_2}\Pi_2(\tau)\mathscr{L}\left(\frac{E^LE_1^A}{E_1^LE^A}\right)d\tau$$

$$-\frac{\delta(\mu+\varphi)}{\digamma_2}E_1^A\int_0^{h_2}\Lambda_2(\tau)\mathscr{L}\left(\frac{E_\tau^AV_1}{E_1^AV}\right)d\tau.$$

Hence, $\dfrac{d\bar{\Theta}_1}{dt}\leq 0$ for any $(M,\ E^L,\ E^A,\ V,\ W^N,\ W^S)>0$ in addition to $\dfrac{d\bar{\Theta}_1}{dt}=0$ when $\left(M,\ W^N,\ W^S\right)=\left(M_1,\ W_1^N,\ W_1^S\right)$ and

$$\frac{M_\tau V_\tau E_1^L}{M_1V_1E^L}=\frac{M_\tau V_\tau E_1^A}{M_1V_1E^A}=\frac{E^LE_1^A}{E_1^LE^A}=\frac{E_\tau^AV_1}{E_1^AV}=1.$$

Then, solution of model converge to Φ_1', for any element in Φ_1', we find $M=M_1$, $W^N=W_1^N$, and $W^S=W_1^S$. Then $\dfrac{dM}{dt}=\dfrac{dW^N}{dt}=\dfrac{dW^S}{dt}=0$ and from Eqs. (25), (27), (28), we get

$$0=\frac{dM}{dt}=\rho-\sigma M_1-\alpha M_1V\quad\Longrightarrow\quad V(t)=V_1\ \text{ for any } t,$$

$$0=\frac{dV}{dt}=\eta\int_0^{h_2}\Lambda_2(\tau)E_\tau^Ad\tau-\rho V_1-\beta_1V_1W_1^N-\beta_2V_1W_1^S\quad\Longrightarrow\quad E^A(t)=E_1^A\ \text{ for any } t.$$

$$0=\frac{dE^A}{dt}=\xi\kappa\digamma_1M_1V_1+\mu\int_0^{k_2}\Pi_2(\tau)E_\tau^Ld\tau-\delta E_1^A\quad\Longrightarrow\quad E^L(t)=E_1^L\ \text{ for any } t.$$

Consequently, $\Phi_1'=\{\mathscr{E}\mathscr{P}_1\}$. LIT implies that $\mathscr{E}\mathscr{P}_1$ is GAS.

4. Effect of latent reservoirs and time delays on the DENV dynamics

An analysis of the dynamics of DENV in the presence of latent reservoirs and time delays (L, D) is presented. Consider antiviral drug therapy with drug efficacy $\chi \in [0,\ 1]$, aimed at blocking virus production [2]. The model (25)-(30) under the influence of RTI is as follows:

$$\begin{aligned}
\frac{dM}{dt} &= \phi - \rho M - \kappa MV,\\
\frac{dE^L}{dt} &= (1-\xi)\kappa \int_0^{k_1} \Pi_1(\tau) M_\tau V_\tau d\tau - (\mu+\varphi)E^L,\\
\frac{dE^A}{dt} &= \xi\kappa \int_0^{h_1} \Lambda_1(\tau) M_\tau V_\tau d\tau + \mu \int_0^{k_2} \Pi_2(\tau) E^L_\tau d\tau - \delta E^A,\\
\frac{dV}{dt} &= (1-\chi)\eta \int_0^{h_2} \Lambda_2(\tau) E^A_\tau d\tau - \rho V - \beta_1 V W^N - \beta_2 V W^S,\\
\frac{dW^N}{dt} &= \gamma_1 + \lambda_1 V W^N - \psi_1 W^N,\\
\frac{dW^S}{dt} &= \gamma_2 + \lambda_2 V W^S - \psi_2 W^S.
\end{aligned} \tag{47}$$

The basic reproduction number of system (47) is defined as

$$\bar{R}_0^{(\mathrm{L,\ D})}(\chi) = \frac{(1-\chi)\eta\kappa\phi[\mu(1-\xi)\Upsilon_1\Upsilon_2 + \xi(\mu+\varphi)F_1]F_2}{\delta\rho\rho(\mu+\varphi)\left(\dfrac{\beta_1\gamma_1}{\psi_1\rho} + \dfrac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)} = (1-\chi)\bar{R}_0^{(\mathrm{L,\ D})}(0).$$

Here, $\bar{R}_0^{(\mathrm{L,\ D})}(0)$ represents the basic reproductive number of model (25)-(30) in the absence of treatment. Given that $\bar{R}_0^{(\mathrm{L,\ D})}(0) > 1$, the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ for system (25)-(30) loss it stability. Our goal is to determine the range of treatment effectiveness, denoted by χ, that guarantees the stability of the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ in system (47), while satisfying the condition $\bar{R}_0^{(\mathrm{L,\ D})}(\chi) \leq 1$:

$$1 \geq \chi \geq \chi_{\min}^{(\mathrm{L,\ D})} = \frac{\bar{R}_0^{(\mathrm{L,\ D})}(0) - 1}{\bar{R}_0^{(\mathrm{L,\ D})}(0)}. \tag{48}$$

To assess how latent reservoirs and time delays influence the minimum required drug efficacy for achieving stability at the infection-free equilibrium, we examine the system defined by (1)-(5), which assumes no latency and no delay (No Latency, No Delay (NL, ND)), under the effect of treatment as:

$$\frac{dM}{dt} = \phi - \rho M - \kappa MV,$$

$$\frac{dE}{dt} = \kappa MV - \delta E,$$

$$\frac{dV}{dt} = (1-\chi)\eta E - \rho V - \beta_1 V W^N - \beta_2 V W^S, \tag{49}$$

$$\frac{dW^N}{dt} = \gamma_1 + \lambda_1 V W^N - \psi_1 W^N,$$

$$\frac{dW^S}{dt} = \gamma_2 + \lambda_2 V W^S - \psi_2 W^S,$$

and the basic reproduction number of model (49) is provided as:

$$R_0^{(\mathrm{NL,\,ND})}(\chi) = \frac{(1-\chi)\eta\kappa\phi}{\delta\rho\rho\left(\dfrac{\beta_1\gamma_1}{\psi_1\rho} + \dfrac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)} = (1-\chi)R_0^{(\mathrm{NL,\,ND})}(0).$$

Here, $R_0^{(\mathrm{NL,\,ND})}(0)$ represents the basic reproductive number of (49) in the absence of RTI. Let us assume that $R_0^{(\mathrm{NL,\,ND})}(0) > 1$. We determine the value of drug efficacy χ that guarantees $R_0^{(\mathrm{NL,\,ND})}(\chi) \leq 1$, thereby stabilizing the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ of the system described in (49), as outlined below:

$$1 \geq \chi \geq \chi_{\min}^{(\mathrm{NL,\,ND})} = \frac{R_0^{(\mathrm{NL,\,ND})}(0) - 1}{R_0^{(\mathrm{NL,\,ND})}(0)}.$$

Since $F_j,\ \Upsilon_j \leq 1$ for $j = 1,\ 2$, and $\xi \leq 1$, then

$$\bar{R}_0^{(\mathrm{L,\,D})}(0) = \frac{\eta\kappa\phi[\mu(1-\xi)\Upsilon_1\Upsilon_2 + \xi(\mu+\varphi)F_1]F_2}{\delta\rho\rho(\mu+\varphi)\left(\dfrac{\beta_1\gamma_1}{\psi_1\rho} + \dfrac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)}$$

$$\leq \frac{\eta\kappa\phi[\mu(1-\xi) + \xi(\mu+\varphi)]}{\delta\rho\rho(\mu+\varphi)\left(\dfrac{\beta_1\gamma_1}{\psi_1\rho} + \dfrac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)}$$

$$= \frac{\mu + \xi\varphi}{\mu+\varphi}\frac{\eta\kappa\phi}{\delta\rho\rho\left(\dfrac{\beta_1\gamma_1}{\psi_1\rho} + \dfrac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)}$$

$$= \frac{\mu + \xi\varphi}{\mu + \varphi} R_0^{(\mathrm{NL,\ ND})}(0) < R_0^{(\mathrm{NL,\ ND})}(0).$$

In comparison, we find that $\chi_{\min}^{(\mathrm{L,\ D})} < \chi_{\min}^{(\mathrm{NL,\ ND})}$. This indicates that accounting for latently infected cells and time delays will lower the required antiviral drug dosage to stabilize the system at the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ and eliminate the DENV from the body. Latently infected monocytes and time delays contribute to lowering the basic reproductive number. Consequently, disregarding these factors in the DENV infection model may result in prescribing unnecessarily high doses of antiviral drugs.

5. Numerical simulations

In this section, we perform numerical simulations using MATLAB's dde23 solver for the model described by (6)-(10) and the model with effect of latently infected cells described by (25)-(30), in order to complement the theoretical results presented in Theorems 1-2 and Theorems 3-4. The parameter values for the models are listed in Table 1.

Table 1. Model parameters

Parameter	Value	Parameter	Value	Parameter	Value
ϕ	10	β_2	0.1	ξ	0.3
ρ	0.01	γ_1	5	μ	0.4
κ	Varied	γ_2	3	φ	0.1
δ	0.5	λ_1	0.01	n_i	1
η	10	λ_2	0.002	m_i	1
ρ	3	ψ_1	0.1	τ_1	0.1
β_1	0.3	ψ_2	0.1	ω_i	0.1
τ_2	varied				

5.1 *Simulation results for model (6)-(10)*

This subsection presents numerical simulations to validate the global stability of equilibria in the system governed by Equations (6)-(10). For this purpose, the model incorporating distributed time delays is reformulated into a discrete-delay version using a specific probability distribution–namely, the Dirac delta function $D_f(.)$. Specifically, we define

$$f_j(\tau) = D_f(\tau - \tau_j), \quad j = 1,\ 2.$$

When $h_j \to \infty,\ j = 1,\ 2$, it follows that

$$\int_0^\infty f_j(\tau)d\tau = 1 \text{ and } F_j = \int_0^\infty D_f(\tau - \tau_j)e^{-m_j\tau}d\tau = e^{-m_j\tau_j}, \quad j = 1,\ 2.$$

Then,

$$\int_0^\infty D_f(\tau - \tau_1)e^{-m_1\tau}M_\tau V_\tau d\tau = e^{-m_1\tau_1}M_{\tau_1}V_{\tau_1}, \qquad \int_0^\infty D_f(\tau - \tau_2)e^{-m_2\tau}E_\tau d\tau = e^{-m_2\tau_2}E_{\tau_2}.$$

Thus, model (6)-(10) becomes:

$$\begin{cases} \dfrac{dM}{dt} = \phi - \rho M - \kappa MV, \\ \dfrac{dE}{dt} = \kappa e^{-m_1\tau_1} M_{\tau_1} V_{\tau_1} - \delta E, \\ \dfrac{dV}{dt} = \eta e^{-m_2\tau_2} E_{\tau_2} - \rho V - \beta_1 V W^N - \beta_2 V W^S, \\ \dfrac{dW^N}{dt} = \gamma_1 + \lambda_1 V W^N - \psi_1 W^N, \\ \dfrac{dW^S}{dt} = \gamma_2 + \lambda_2 V W^S - \psi_2 W^S. \end{cases} \tag{50}$$

The basic reproductive number of model (50) are defined as follows:

$$R_0 = \frac{\eta\kappa\phi e^{-(m_1\tau_1 + m_2\tau_2)}}{\delta\rho\rho\left(\dfrac{\beta_1\gamma_1}{\psi_1\rho} + \dfrac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)}.$$

5.1.1 *Stability of equilibria*

We perform numerical simulations for the system described in Eqs. (50), utilizing the parameter values listed in Table 1. To evaluate the stability of the equilibrium points in system (50), we fix $\tau_2 = 0.1$ and begin the simulations with different sets of initial points inspired by the research of Song et al. [46]:

$$\begin{pmatrix} M(\theta) \\ E(\theta) \\ V(\theta) \\ W^N(\theta) \\ W^S(\theta) \end{pmatrix} = \begin{pmatrix} 700 + 10\sin(\theta) - 50k \\ 5 + 0.5\sin(\theta) + 1.5k \\ 1 + 0.2\sin(\theta) + 0.3k \\ 30 + 3\sin(\theta) + 7k \\ 20 + 2\sin(\theta) + 3k \end{pmatrix},$$

$$\theta \in [-0.1,\ 0], \quad k = 1,\ 2,\ ...,\ 12.$$

Varying the parameter κ leads to two different scenarios:

Scenario 1: Global stability of the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$: In this case, we consider the parameter value $\kappa = 0.0005$, which results in a basic reproduction number $R_0 = 0.39 < 1$. Under this condition, the disease cannot sustain itself within the host. As illustrated in Figure 3, the trajectories of the system, starting from a wide range of initial conditions, all approach the infection-free equilibrium point $\mathscr{E}\mathscr{P}_0 = (1{,}000,\ 0,\ 0,\ 50,\ 30)$ over time. This observation aligns with the result of Theorem 1, which establishes the global asymptotic stability of $\mathscr{E}\mathscr{P}_0$. Biologically, this implies that the DENV will be completely cleared from the host, allowing the population of uninfected monocytes to recover to its baseline level.

Scenario 2: Persistence of infection and stability of the endemic equilibrium $\mathscr{E}\mathscr{P}_1$: In this scenario, we set the infection parameter $\kappa = 0.005$, yielding a basic reproduction number $R_0 = 3.9 > 1$, which exceeds the epidemic threshold. As depicted in Figure 4, the system's trajectories originating from biologically feasible initial conditions converge to the endemic equilibrium point $\mathscr{E}\mathscr{P}_1 = (360.23,\ 11.58,\ 3.55,\ 77.54,\ 32.29)$. This numerical result is in agreement with Lemma 2 and Theorem 2, which confirm the existence and global asymptotic stability of $\mathscr{E}\mathscr{P}_1$. From a biological perspective, this indicates that the dengue virus persists within the host, leading to a chronic infection state.

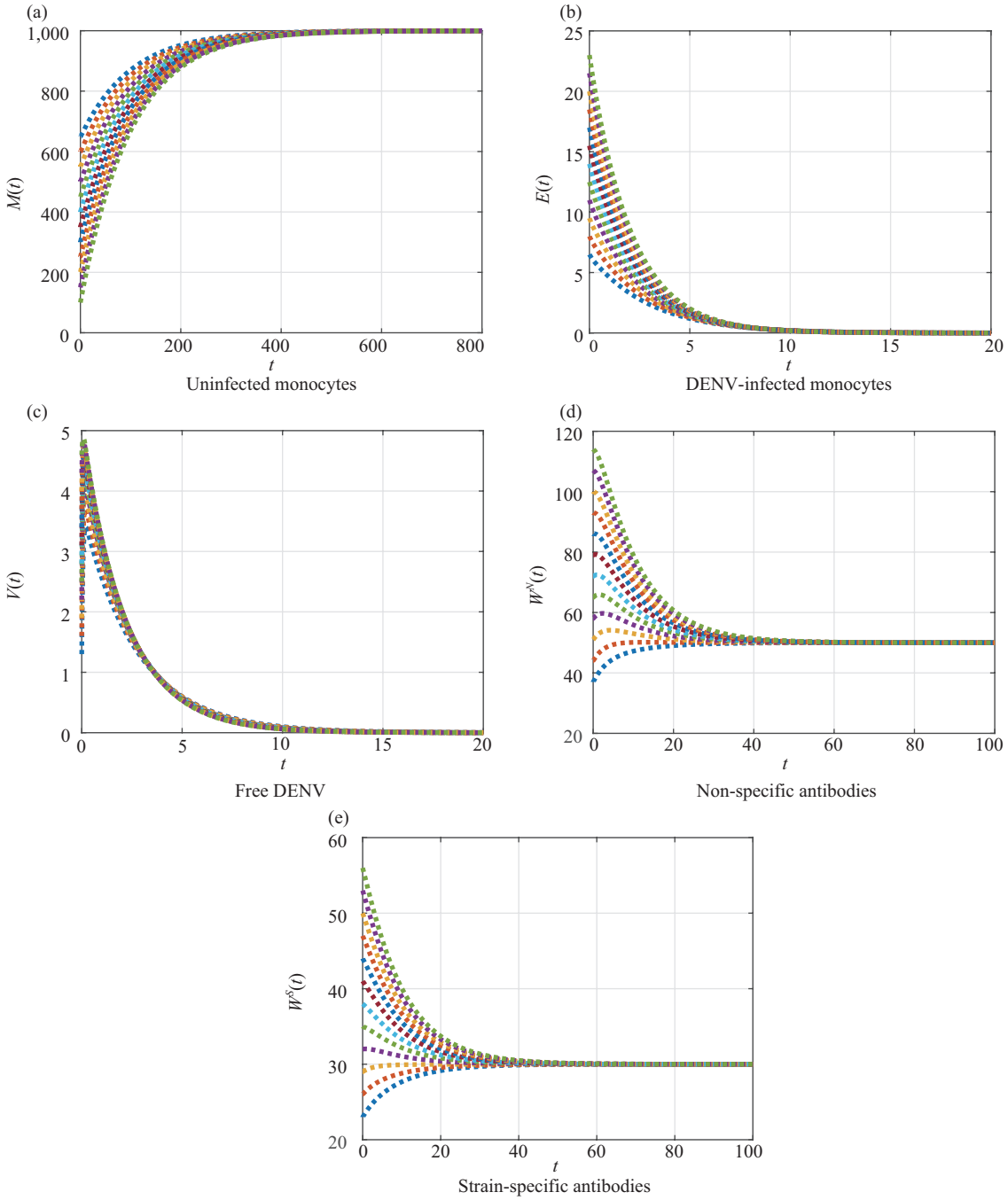


Figure 3. Global asymptotic stability of the infection-free equilibrium point $\mathscr{E}\mathscr{P}_0 = (1{,}000,\ 0,\ 0,\ 50,\ 30)$

Figure 3 showed simulation for Scenario 1 illustrates the global asymptotic stability of the infection-free equilibrium point $\mathscr{E}\mathscr{P}_0 = (1{,}000,\ 0,\ 0,\ 50,\ 30)$. When the basic reproduction number satisfies $R_0 \leq 1$, all trajectories of system (50), initiated from a wide range of biologically feasible initial conditions, converge to $\mathscr{E}\mathscr{P}_0$ as time increases. This behavior confirms that the infection cannot persist in the population under this threshold, regardless of the initial distribution of the state variables.

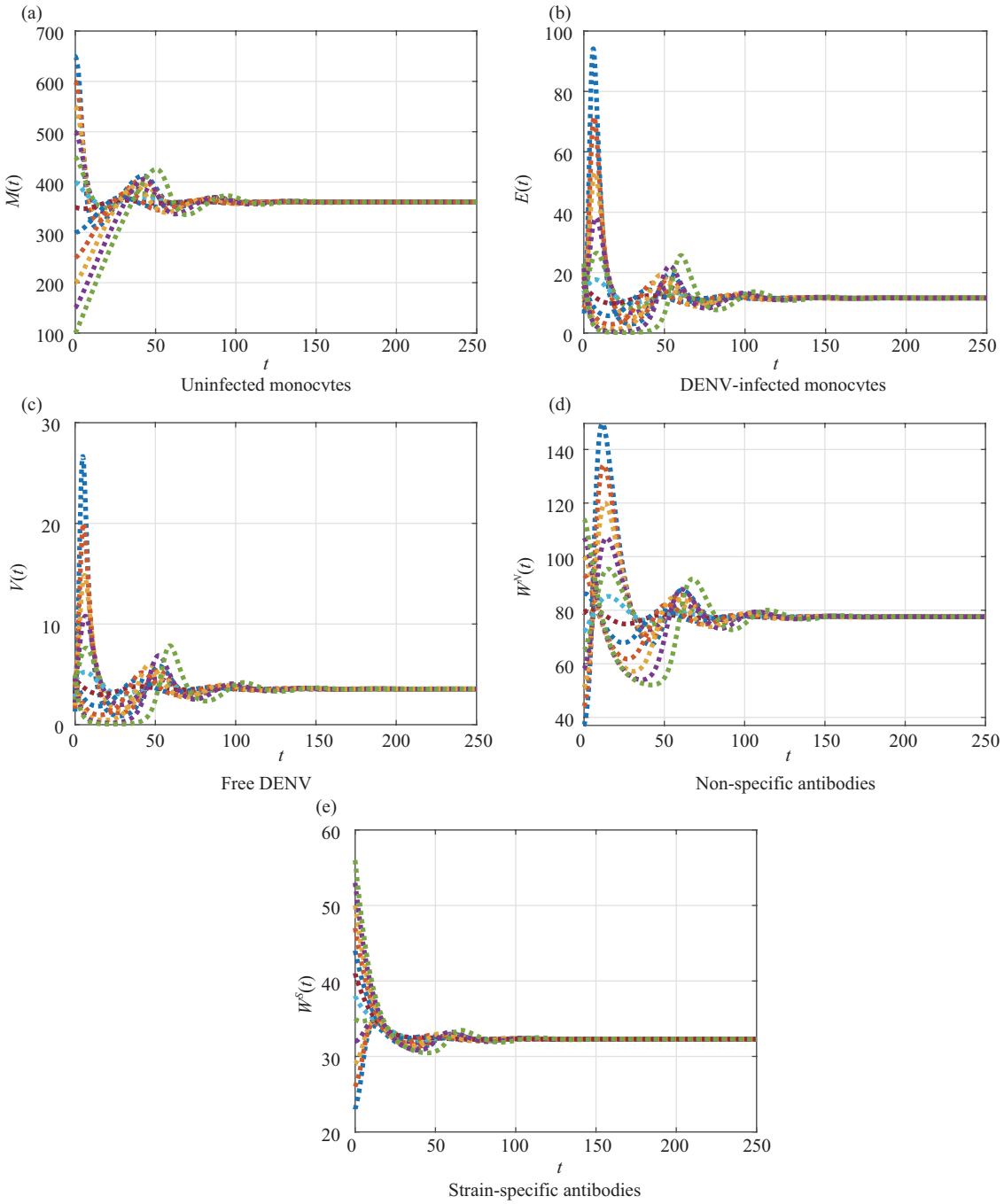


Figure 4. Global asymptotic stability of the endemic equilibrium point

Figure 4 showed the simulation for Scenario 2 demonstrates the global asymptotic stability of the endemic equilibrium point $\mathscr{E}\mathscr{P}_1 = (360.23,\ 11.58,\ 3.55,\ 77.54,\ 32.29)$. When the basic reproduction number satisfies $R_0 > 1$, all solution trajectories of system (50) originating from a broad range of biologically plausible initial conditions converge to $\mathscr{E}\mathscr{P}_1$ over time. This result indicates that the infection persists in the population above this threshold, irrespective of the initial state configuration.

5.2 *Simulation results for model (25)-(30)*

This subsection provides numerical simulations to support the global stability analysis of the equilibria associated with the system given by Equations (25)-(30). Using Dirac delta function $D_g(.)$, the model with distributed-time delay (25)-(30) is converted into a discrete form. Define

$$g_j(\tau) = D_g(\tau - \omega_j),\ \ j = 1,\ 2.$$

In case $k_j \to \infty,\ j = 1,\ 2$, we have

$$\int_0^\infty g_j(\tau)d\tau = 1 \text{ and } \Upsilon_j = \int_0^\infty D_g\left(\tau - \omega_j\right)e^{-n_j\tau}d\tau = e^{-n_j\omega_j},\ j = 1,\ 2.$$

Then,

$$\int_0^\infty D_g(\tau-\omega_1)e^{-n_1\tau}M_\tau V_\tau d\tau = e^{-n_1\omega_1}M_{\omega_1}V_{\omega_1}, \qquad \int_0^\infty D_g(\tau-\omega_2)e^{-n_2\tau}E^L_\tau d\tau = e^{-n_2\omega_2}E^L_{\omega_2}.$$

Thus, model (25)-(30) becomes:

$$\begin{cases} \dfrac{dM}{dt} = \phi - \rho M - \kappa MV, \\ \dfrac{dE^L}{dt} = (1-\xi)\kappa e^{-n_1\omega_1}M_{\omega_1}V_{\omega_1} - (\mu+\varphi)E^L, \\ \dfrac{dE^A}{dt} = \xi\kappa e^{-m_1\tau_1}M_{\tau_1}V_{\tau_1} + \mu e^{-n_2\omega_2}E^L_{\omega_2} - \delta E^A, \\ \dfrac{dV}{dt} = \eta e^{-m_2\tau_2}E^A_{\tau_2} - \rho V - \beta_1 VW^N - \beta_2 VW^S, \\ \dfrac{dW^N}{dt} = \gamma_1 + \lambda_1 VW^N - \psi_1 W^N, \\ \dfrac{dW^S}{dt} = \gamma_2 + \lambda_2 VW^S - \psi_2 W^S. \end{cases} \tag{51}$$

The basic reproductive number for model (51) are outlined as follows:

$$\bar{R}_0 = \frac{\eta\kappa\phi[\mu(1-\xi)e^{-(n_1\omega_1+n_2\omega_2+m_2\tau_2)}+\xi(\mu+\varphi)e^{-(m_1\tau_1+m_2\tau_2)}]}{\delta\rho\rho(\mu+\varphi)\left(\frac{\beta_1\gamma_1}{\psi_1\rho}+\frac{\beta_2\gamma_2}{\psi_2\rho}+1\right)}. \tag{52}$$

5.2.1 *Stability of equilibria*

We fix $\tau_2 = 0.1$ and consider the following set of initials:

$$\begin{pmatrix} M(\theta) \\ E^L(\theta) \\ E^A(\theta) \\ V(\theta) \\ W^N(\theta) \\ W^S(\theta) \end{pmatrix} = \begin{pmatrix} 750+10\sin(\theta)-50k \\ 2+0.5\sin(\theta)+0.8k \\ 3+0.8\sin(\theta)+1.0k \\ 0.5+0.1\sin(\theta)+0.2k \\ 30+3\sin(\theta)+7k \\ 20+2\sin(\theta)+3k \end{pmatrix}, \tag{53}$$

$$\theta \in [-0.1,\ 0],\ k = 1,\ 2,\ ...,\ 12.$$

By selecting various values of κ and applying the parameters from Table 1 along with the initial points outlined above. We observe the following cases:

Figure 5 showed simulation for Scenario 1 illustrates the global asymptotic stability of the infection-free equilibrium point $\mathscr{E}\mathscr{P}_0 = (1{,}000,\ 0,\ 0,\ 0,\ 50,\ 30)$. When the basic reproduction number satisfies $\bar{R}_0 \leq 1$, all trajectories of the system with latent reservoirs (51), initiated from a wide range of biologically feasible initial conditions, converge to $\mathscr{E}\mathscr{P}_0$ as time increases. This behavior confirms that the infection cannot persist in the population under this threshold, regardless of the initial distribution of the state variables.

Figure 6 showed simulation for Scenario 4 demonstrates the global asymptotic stability of the endemic equilibrium point $\mathscr{E}\mathscr{P}_1 = (411.62,\ 7.45,\ 8.59,\ 2.86,\ 70.02,\ 31.82)$. When the basic reproduction number satisfies $\bar{R}_0 > 1$, all solution trajectories of the system with latent reservoirs (51), originating from a broad range of biologically plausible initial conditions, converge to over time. This result indicates that the infection persists in the population above this threshold, regardless of the initial state configuration.

Scenario 3: Global stability of the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ (with latent reservoirs): In this setting, we take $\kappa = 0.0005$, resulting in a basic reproduction number $\bar{R}_0 = 0.31 < 1$, indicating that the infection is not sustainable within the host. As shown in Figure 5, all solution trajectories, initiated from diverse biologically relevant states, converge toward the infection-free equilibrium point $\mathscr{E}\mathscr{P}_0 = (1{,}000,\ 0,\ 0,\ 0,\ 50,\ 30)$. This convergence supports the theoretical result presented in Theorem 3, which guarantees the global asymptotic stability of $\mathscr{E}\mathscr{P}_0$ under this parameter regime. Biologically, this means that both latently and actively infected monocytes, along with free DENV particles, are eventually cleared, and the host returns to a disease-free state.

Scenario 4: Stability of the endemic equilibrium $\mathscr{E}\mathscr{P}_1$ (with latent reservoirs): In this case, we set $\kappa = 0.005$, leading to a basic reproduction number $\bar{R}_0 = 3.15 > 1$, which allows for the persistence of the virus. Figure 6 illustrates that, regardless of the initial conditions, all trajectories of the system converge to the endemic equilibrium $\mathscr{E}\mathscr{P}_1 = (411.62,\ 7.45,\ 8.59,\ 2.86,\ 70.02,\ 31.82)$. This numerical behavior is consistent with Theorem 4, confirming that EP_1 is GAS. In this scenario, both latently and actively infected monocytes, along with circulating DENV particles, persist in the host, characterizing a chronic infection state.

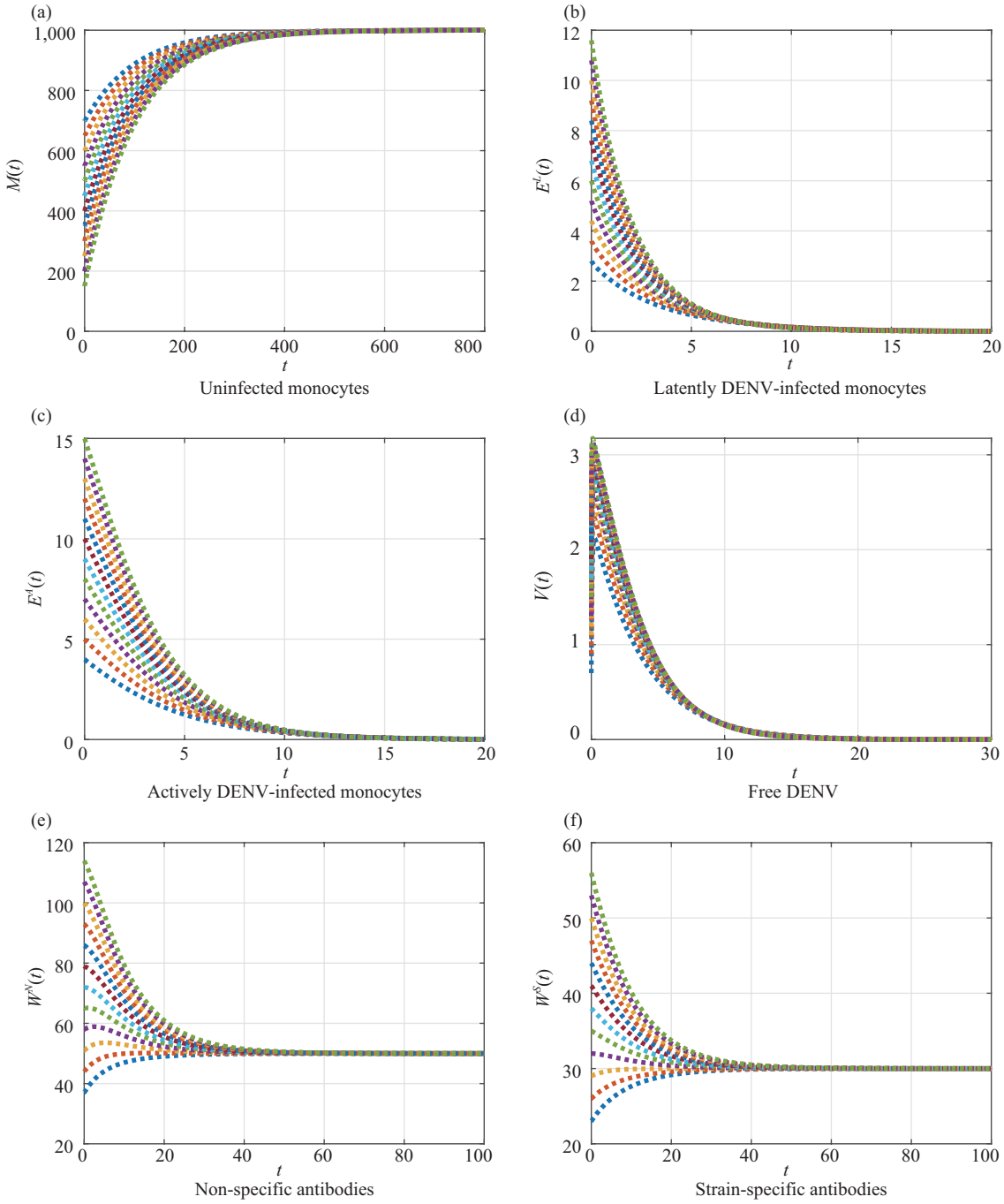


Figure 5. Global asymptotic stability of the infection-free equilibrium point $\mathscr{E}\mathscr{P}_0 = (1,000,\ 0,\ 0,\ 0,\ 50,\ 30)$

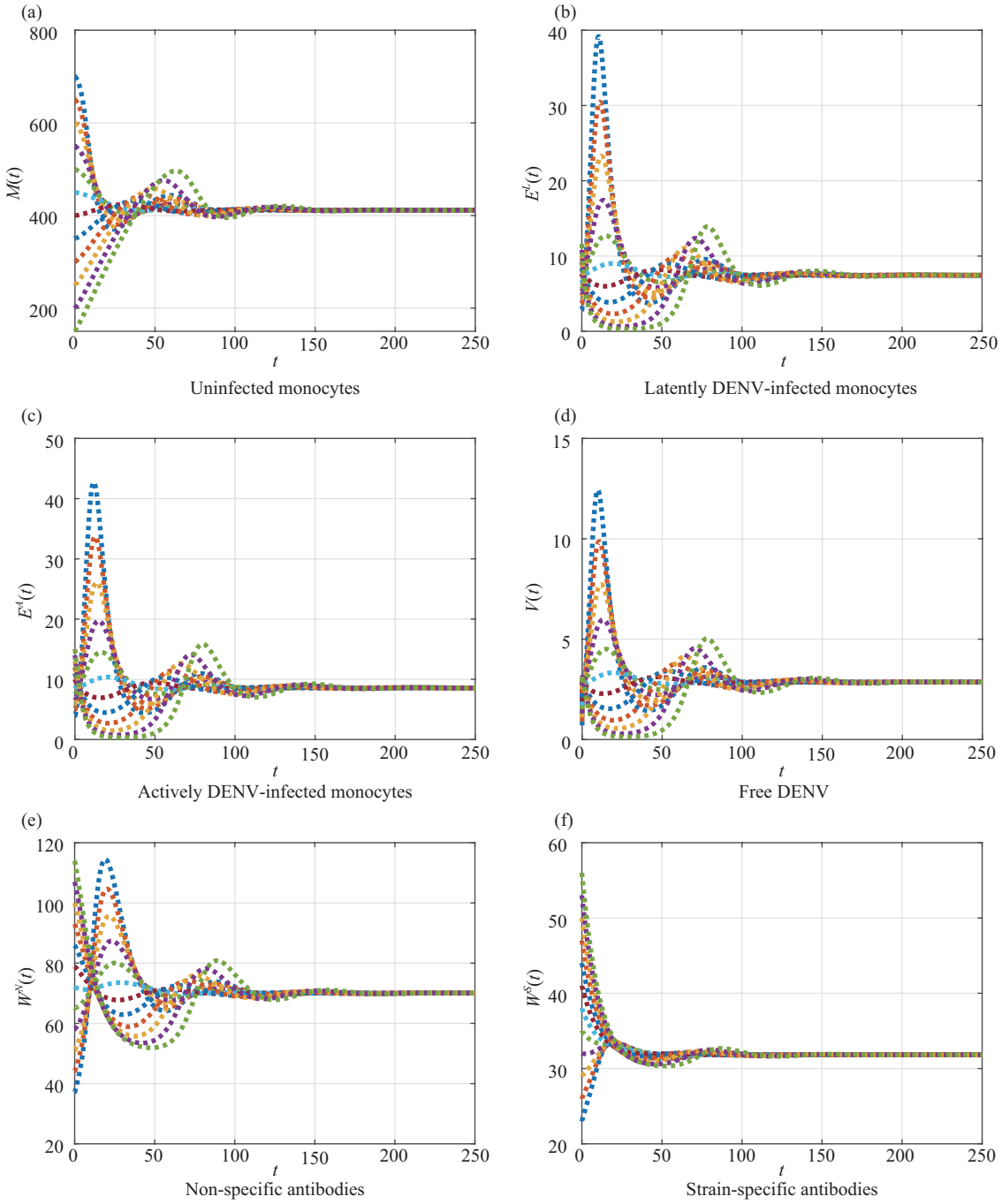


Figure 6. Global asymptotic stability of the endemic equilibrium point $\mathscr{E}\mathscr{P}_1 = (411.62,\ 7.45,\ 8.59,\ 2.86,\ 70.02,\ 31.82)$

5.2.2 *Effect of treatment on the dynamics of DENV infection with latency*

In this section, we investigate how antiviral therapies or immunostimulatory agents influence the progression of DENV infection in the presence of latent reservoirs [2, 21].

Effect of antiviral treatment

To model the effect of antiviral therapy that inhibits viral production, the parameter η is modified to $(1-\chi)\eta$, where $\chi \in [0,\ 1]$ represents the drug efficacy [2]. The resulting system of equations is as follows:

$$\frac{dM}{dt} = \phi - \rho M - \kappa MV, \tag{54}$$

$$\frac{dE^L}{dt} = (1-\xi)\kappa e^{-n_1\omega_1} M_{\omega_1} V_{\omega_1} - (\mu+\varphi)E^L, \tag{55}$$

$$\frac{dE^A}{dt} = \xi\kappa e^{-m_1\tau_1} M_{\tau_1} V_{\tau_1} + \mu e^{-n_2\omega_2} E^L_{\omega_2} - \delta E^A, \tag{56}$$

$$\frac{dV}{dt} = (1-\chi)\eta e^{-m_2\tau_2} E^A_{\tau_2} - \rho V - \beta_1 V W^N - \beta_2 V W^S, \tag{57}$$

$$\frac{dW^N}{dt} = \gamma_1 + \lambda_1 V W^N - \psi_1 W^N, \tag{58}$$

$$\frac{dW^S}{dt} = \gamma_2 + \lambda_2 V W^S - \psi_2 W^S. \tag{59}$$

The basic reproduction number of this model is give by

$$\bar{R}_0(\chi) = \frac{(1-\chi)\eta\kappa\phi[\mu(1-\xi)e^{-(n_1\omega_1+n_2\omega_2+m_2\tau_2)} + \xi(\mu+\varphi)e^{-(m_1\tau_1+m_2\tau_2)}]}{\delta\rho\rho(\mu+\varphi)\left(\frac{\beta_1\gamma_1}{\psi_1\rho} + \frac{\beta_2\gamma_2}{\psi_2\rho} + 1\right)}. \tag{60}$$

Based on Eq. (60), it is clear that increasing the drug efficacy parameter χ, while holding all other parameters constant, leads to a decrease in $\bar{R}_0(\chi)$ (refer to Table 2). As a result, the value of χ can have a notable impact on the stability of the equilibrium point $\mathscr{E}\mathscr{P}_0$. For this study, we set $\kappa = 0.005$ and $\tau_2 = 0.1$, and examine several values of χ: 0.0, 0.1, 0.4, 0.7, and 0.9. We also consider the following initial condition:

$$\begin{pmatrix} M(\theta) \\ E^L(\theta) \\ E^A(\theta) \\ V(\theta) \\ W^N(\theta) \\ W^S(\theta) \end{pmatrix} = \begin{pmatrix} 700 + 10\sin(\theta) \\ 2.8 + 0.5\sin(\theta) \\ 4 + 0.8\sin(\theta) \\ 0.7 + 0.1\sin(\theta) \\ 60 + 3\sin(\theta) \\ 31 + 2\sin(\theta) \end{pmatrix}, \tag{61}$$

$$\theta \in [-\max\{\tau_1,\ \tau_2,\ \omega_1,\ \omega_2\},\ 0].$$

Table 2. The variation of $\bar{R}_0(\chi)$ with respect to drug efficacy parameter χ

χ	$\bar{R}_0(\chi)$
0	3.14513
0.1	2.83062
0.4	1.88708
0.682048	1
0.7	0.943539
0.9	0.314513

Subsequently, we aim to determine the critical value of the drug efficacy parameter, denoted by χ^{cr}, at which a change in the stability of $\mathscr{E}\mathscr{P}_0$, occurs. This transition is governed by the condition $\bar{R}_0(\chi^{cr}) = 1$. When this condition holds, $\mathscr{E}\mathscr{P}_0$ becomes stable, indicating that:

$$\bar{R}_0(\chi) \leq 1 \text{ for all } \chi \geq \chi^{cr}.$$

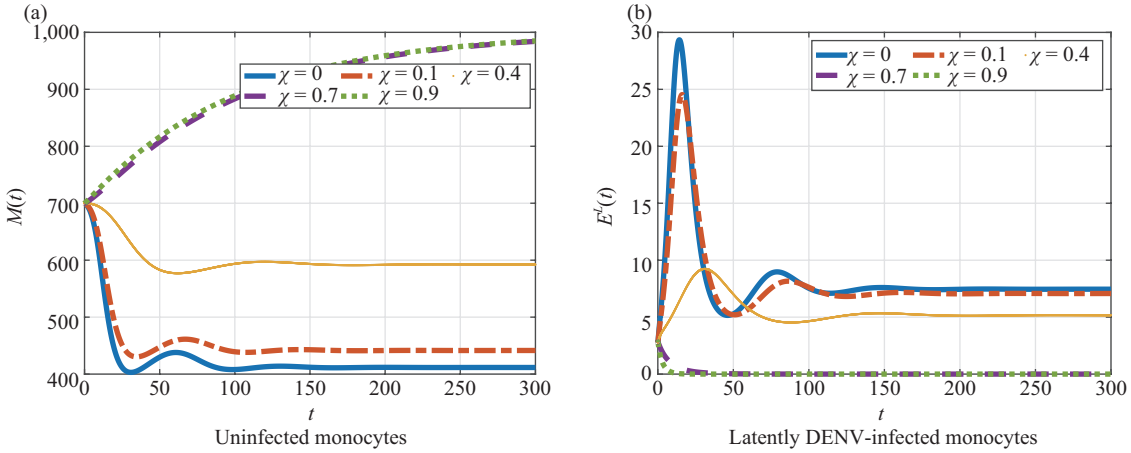
Hence, when χ satisfies $\chi \geq \chi^{cr}$, $\mathscr{E}\mathscr{P}_0$ will be globally stable. Utilizing the parameter values provided in Table 1, we calculate $\chi^{cr} = 0.682048$. Consequently,

(i) When $\chi \geq 0.682048$, the condition $\bar{R}_0(\chi) \leq 1$ is satisfied, guaranteeing that $\mathscr{E}\mathscr{P}_0$ is GAS. This indicates that the DENV infection will be successfully eliminated.

(ii) For values of χ within the interval $0 \leq \chi < 0.682048$, the $\bar{R}_0(\chi)$ satisfies $\bar{R}0(\chi) > 1$, causing $\mathscr{E}\mathscr{P}_0$ to lose stability. As a result, the equilibrium point $\mathscr{E}\mathscr{P}_1$ becomes GAS, indicating the continued persistence of the infection.

Figure 7 depicts the effect of antiviral treatment on the system's trajectories. An increase in χ leads to a rise in the concentration of uninfected monocytes, M, while the concentrations of other compartments such as E^L, E^A, V, W^N, and W^S decline. These results highlight that increasing the antiviral drug dosage plays a significant role in mitigating the progression of DENV infection in patients.

Figure 7 showed solutions of the system described by (54)-(59) are analyzed under the influence of the drug efficacy parameter χ. As χ increases, the concentration of uninfected monocytes rises, while the concentrations of other compartments decrease. For $\chi \leq 0.682048$, the infection remains chronic. When $\chi \geq 0.682048$, the system's solutions converge to the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$, indicating viral clearance.



Uninfected monocytes Latently DENV-infected monocytes

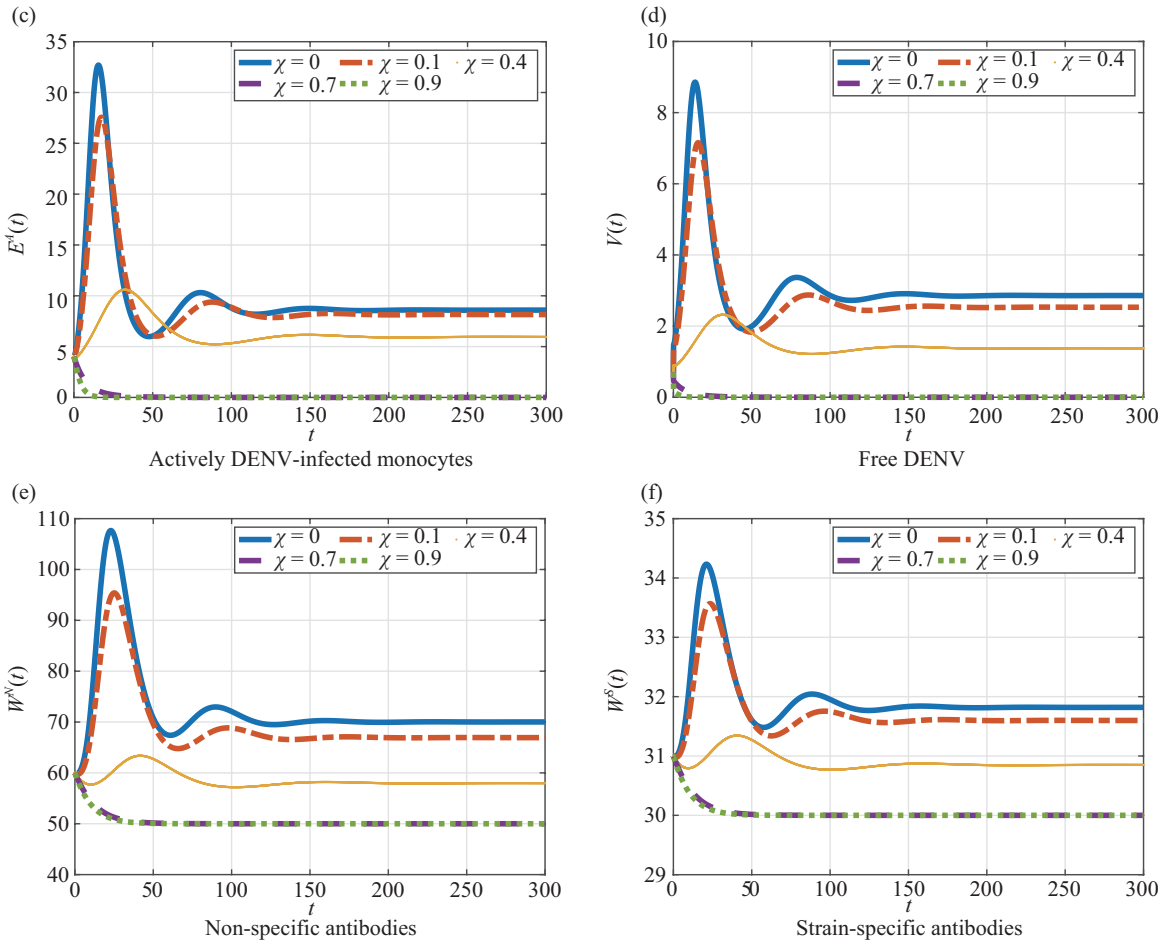


Figure 7. Concentration changes of uninfected monocytes

Effect of immunostimulatory treatments

Immunostimulatory therapies aim to enhance the immune response by increasing its effectiveness and activity [21, 47]. Within this framework, the immune activation rates λ_i for $i = 1,\ 2$, can be amplified by a factor of $(1+\varepsilon)$, where $\varepsilon \in [0,\ \varepsilon^{\max}]$ [21]. The upper bound $\varepsilon^{\max}$ must be carefully chosen to reflect safe and physiologically acceptable levels of immune stimulation [47]. The modified model incorporating the effects of immunostimulatory intervention is expressed as follows:

$$\frac{dM}{dt} = \phi - \rho M - \kappa MV, \tag{62}$$

$$\frac{dE^L}{dt} = (1-\xi)\kappa e^{-n_1\omega_1} M_{\omega_1} V_{\omega_1} - (\mu+\varphi)E^L, \tag{63}$$

$$\frac{dE^A}{dt} = \xi\kappa e^{-m_1\tau_1} M_{\tau_1} V_{\tau_1} + \mu e^{-n_2\omega_2} E^L_{\omega_2} - \delta E^A, \tag{64}$$

$$\frac{dV}{dt} = \eta e^{-m_2\tau_2} E^A_{\tau_2} - \rho V - \beta_1 V W^N - \beta_2 V W^S, \tag{65}$$

$$\frac{dW^N}{dt} = \gamma_1 + (1+\varepsilon)\lambda_1 V W^N - \psi_1 W^N, \tag{66}$$

$$\frac{dW^S}{dt} = \gamma_2 + (1+\varepsilon)\lambda_2 V W^S - \psi_2 W^S. \tag{67}$$

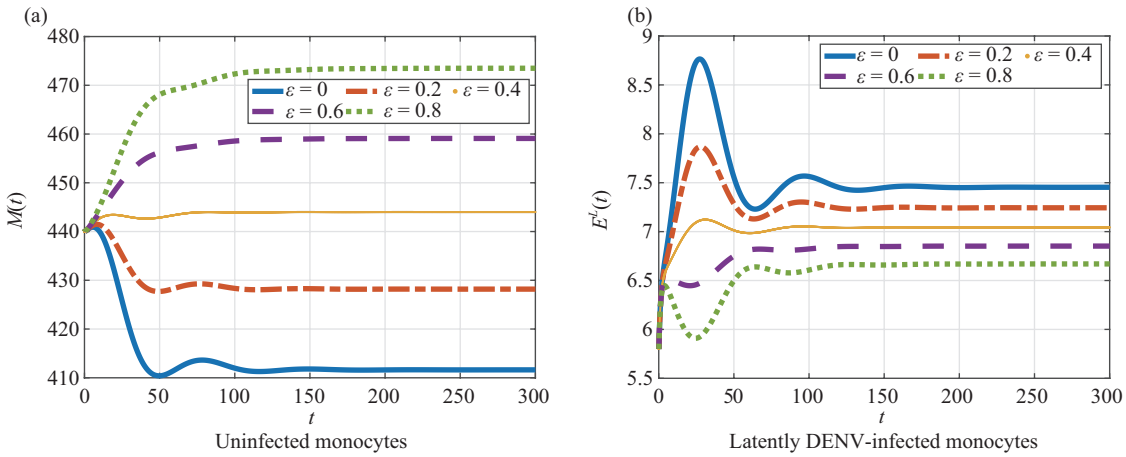
It is important to note that the basic reproduction number for the system defined by Equations (62)-(67) remains unchanged from that given in (52), as $\bar{R}_0$ is independent of the parameters λ_i, for $i = 1,\ 2$. In this case, we fix $\kappa = 0.005$ and $\tau_2 = 0.1$, and evaluate the system dynamics for various values of the immunostimulatory efficacy parameter ε: 0.0, 0.2, 0.4, 0.6, and 0.8. The simulation is conducted using the following initial condition:

$$\begin{pmatrix} M(\theta) \\ E^L(\theta) \\ E^A(\theta) \\ V(\theta) \\ W^N(\theta) \\ W^S(\theta) \end{pmatrix} = \begin{pmatrix} 440 + 10\sin(\theta) \\ 5.8 + 0.5\sin(\theta) \\ 8 + 0.8\sin(\theta) \\ 2.2 + 0.1\sin(\theta) \\ 75 + 3\sin(\theta) \\ 32.2 + 2\sin(\theta) \end{pmatrix},$$

$$\theta \in [-0.1,\ 0].$$

As illustrated in Figure 8, increasing the value of ε leads to higher concentrations of M, W^N, and W^S. Conversely, the concentrations of E^L, E^A, and V decline. These results suggest that immunostimulatory treatments contribute to the control of DENV infection. However, since $\bar{R}_0$ is independent of ε, increasing ε does not facilitate the attainment of the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$. Therefore, while immunostimulatory treatments are effective in suppressing the progression of DENV infection, they are insufficient for complete viral eradication.

Figure 8 showed solutions of the system described by (62)-(67) are analyzed under the influence of the immunostimulatory efficacy parameter ε. As ε increases, the concentrations of uninfected monocytes, non-specific antibodies, and strain-specific antibodies rise, while the concentrations of other compartments decrease.



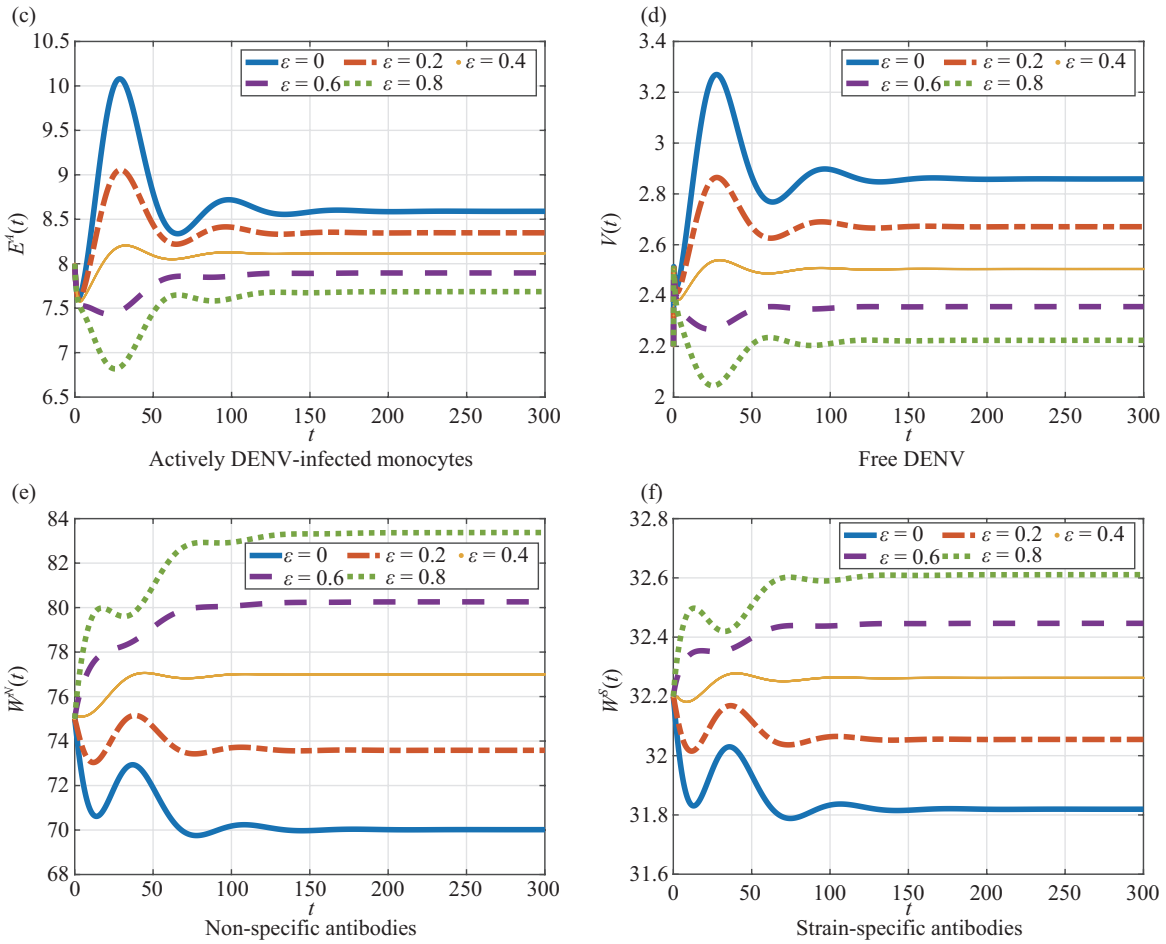


Figure 8. Changes in the concentrations of uninfected monocytes, nonspecific antibodies, and strain-specific antibodies under the influence of the immunostimulatory efficacy parameter ε

5.2.3 *Effect of time delays on the dynamics of DENV infection with latency*

We illustrate the impact of the time delay τ_2 on the system's solutions and the stability of $\mathscr{E}\mathscr{P}_0$. From Eq. (52), it is evident that increasing the delay parameter τ_2, while keeping all other parameters constant, results in a reduction of $\bar{R}_0$ (see Table 3). Consequently, the stability of $\mathscr{E}\mathscr{P}_0$ can be significantly influenced by τ_2. Now, let us set $\kappa = 0.005$, and vary τ_2 as follows: $\tau_2 = 0.0, 0.1, 0.5, 1.4$ and 1.8. Additionally, we take into account the starting condition given by (61):

Table 3. The variation of $\bar{R}_0$ with respect to the delay parameters τ_2

τ_2	$\bar{R}_0$
0	3.47591
0.1	3.14513
0.5	2.10824
1.24586	1
1.4	0.857148
1.8	0.574564

We proceed to determine the critical delay value τ_2^{cr} at which the stability of the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ changes, satisfying the condition $\bar{R}_0(\tau_2^{cr}) = 1$. As a result, the system remains stable, i.e.,

$$\bar{R}_0 \leq 1 \text{ for all } \tau_2 \geq \tau_2^{cr}.$$

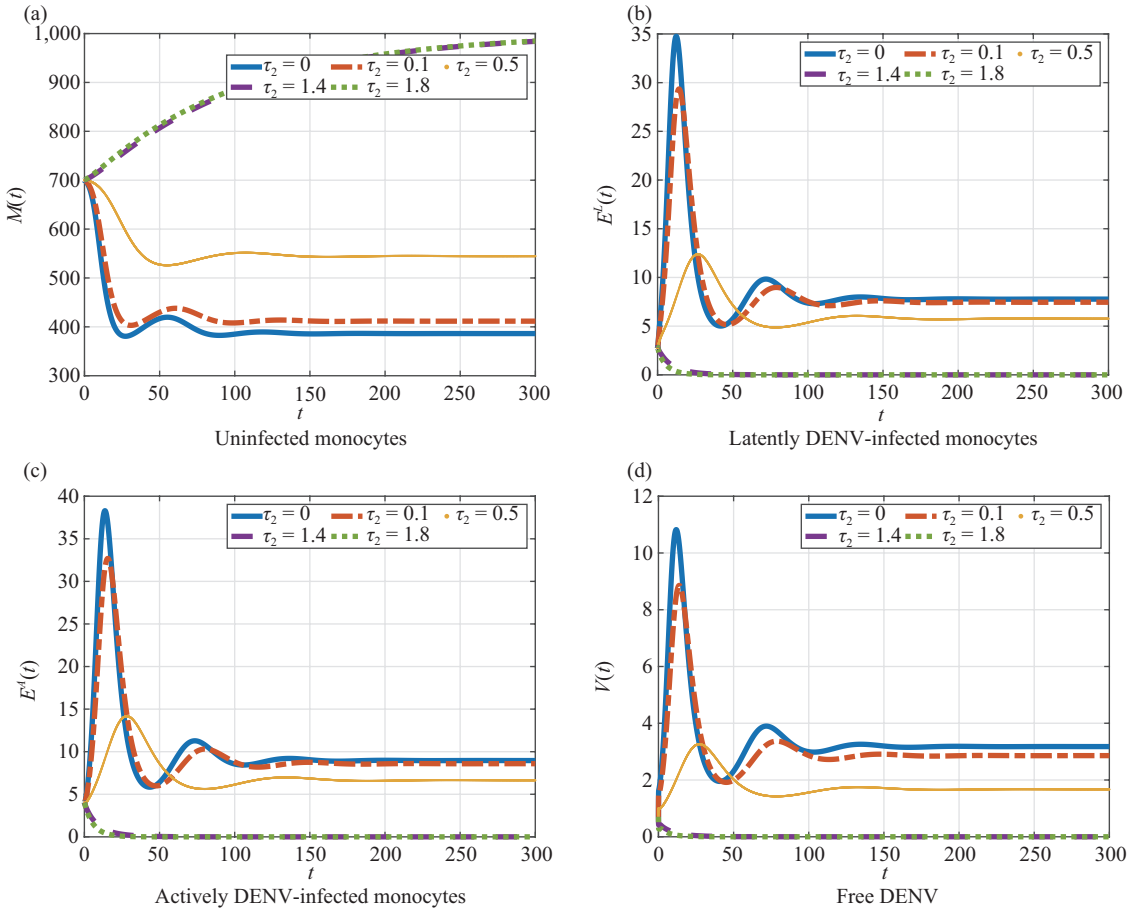
Thus, if $\tau_2 \geq \tau_2^{cr}$, then $\mathscr{E}\mathscr{P}_0$ is GAS. Using the values of parameters given in Table 1, we obtain $\tau_2^{cr} = 1.24586$. Consequently,

(i) If $\tau_2 \geq 1.24586$, then $\bar{R}_0(\tau_2) \leq 1$, and $\mathscr{E}\mathscr{P}_0$ is GAS. This shows that the DENV will be cleared.

(ii) If $0 \leq \tau_2 < 1.24586$, then $\bar{R}_0(\tau_2) > 1$ causing $\mathscr{E}\mathscr{P}_0$ to become unstable. Consequently, $\mathscr{E}\mathscr{P}_1$ will be GAS, leading to the persistence of the infection.

Figure 9 demonstrates how the time delay influences the trajectories of the system. As τ_2 increases, the concentration of uninfected monocytes, M, rise, whereas the concentrations of other compartments such as E^L, E^A, V, W^N, and W^S decline. As the delay period increases, it becomes evident that time delays can contribute to managing DENV progression in patients, demonstrating an effect comparable to drug efficacy. Therefore, incorporating time delays may be vital in designing innovative and effective treatment strategies.

Figure 9 showed solutions of the system described by (51) are analyzed under the influence of the time delay τ_2. As τ_2 increases, the concentration of uninfected monocytes rises, while the concentrations of other compartments decrease. For $\tau_2 < 1.24586$, the infection remains chronic. When $\tau_2 \geq 1.24586$, the system's solutions converge to the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$, indicating viral clearance.



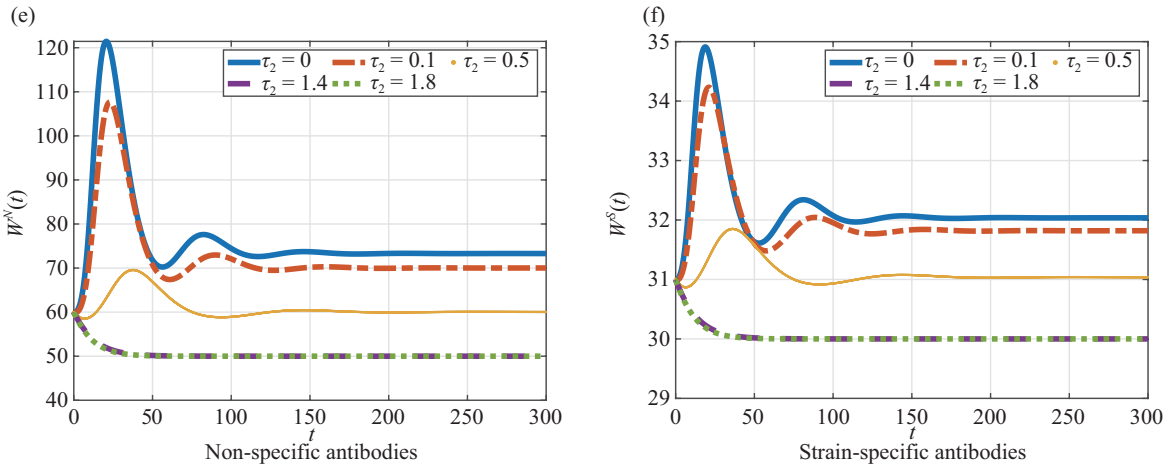


Figure 9. Changes in the concentration of uninfected monocytes under the influence of time delay τ_2

5.2.4 *Sensitivity analysis of* $\bar{R}_0$

Sensitivity analysis plays a crucial role in modeling complex interactions, especially in fields like pathology and epidemiology [48]. By examining sensitivities, we can assess our capacity to manage the spread of diseases. To evaluate the biological effects of parameter variations in a model, several methods can be employed, such as direct differentiation, the Latin hypercube sampling method, or linearizing the system and solving the resulting equations [48].

For our system described by (51), we utilize derivative-based sensitivity analysis, computed analytically using partial derivatives with respect to the model parameters. The normalized forward sensitivity index for $\bar{R}_0$ is typically expressed as:

$$S_\gamma^{\bar{R}_0} = \frac{\partial \bar{R}_0}{\partial \gamma} \cdot \frac{\gamma}{\bar{R}_0}, \tag{68}$$

where γ is a parameter. When setting $\kappa = 0.005$ and $\tau_2 = 0.1$, the sensitivity index for each parameter is presented in Table 4 and Figure 10.

Table 4. Sensitivity index of $\bar{R}_0$

Parameter	$S_\gamma^{\bar{R}_0}$	Parameter	$S_\gamma^{\bar{R}_0}$	Parameter	$S_\gamma^{\bar{R}_0}$
η	1	φ	−0.1256	n_2	−0.0628
κ	1	β_1	−0.7143	m_1	−0.0372
ϕ	1	β_2	−0.1429	m_2	−0.1000
μ	0.1256	γ_1	−0.7143	ω_1	−0.0628
ξ	0.1027	γ_2	−0.1429	τ_1	−0.0372
δ	−1	ψ_1	0.7143	ω_2	−0.0628
ρ	−1	ψ_2	0.1429	τ_2	−0.1000
ρ	−0.1429	n_1	−0.0628		

According on the sign of the indices, we obtain that:

• The parameters η, κ, ϕ, μ, ξ, ψ_1, and ψ_2 all have positive sensitivity indices, indicating they have a positive impact on $\bar{R}_0$. Thus, these parameters play a significant role in the progression of DENV within the body. Among these, η, κ,

and ϕ exhibit the highest positive indices, followed by ψ_1 while ψ_2, μ, and ξ show the lowest positive sensitivity indices. For instance, a 10% increase (or decrease) in ψ_1 will lead to a 7.143% increase (or decrease) in the $\bar{R}_0$ value.

• The parameters δ, ρ, ρ, φ, β_1, β_2, γ_1, γ_2, n_1, n_2, m_1, m_2, ω_1, τ_1, ω_2, and τ_2 are associated with negative indices, indicating that they exert a negative influence on $\bar{R}_0$. That means when the values of these parameters increase (or decrease), the value of $\bar{R}_0$ decreases (or increases). As an example, the sensitivity index of ρ is -0.1429. This means that a 10% increase (or decrease) in ρ will lead to a 1.429% decrease (or increase) in the value of $\bar{R}_0$. It is worth mentioning that δ and ρ have the most negative sensitivity index.

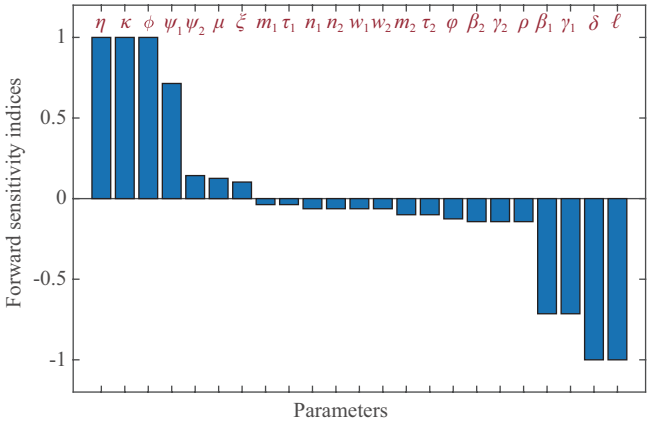


Figure 10. Sensitivity analysis of the basic reproduction number $\bar{R}_0$

Figure 10 showed analysis quantifies the relative influence of key biological parameters on $\bar{R}_0$. Parameters exhibiting higher sensitivity indices significantly impact infection outcomes and are therefore considered primary candidates for therapeutic modulation.

6. Conclusion and discussion

This study develops two models to analyze DENV dynamics. The first model consists of five compartments: uninfected monocytes (M), DENV-infected monocytes (E), free DENV particles (V), non-specific antibodies (W^N), and strain-specific antibodies (W^S). The model includes two forms of distributed time delays: one associated with the development of DENV-infected monocytes and the other representing the maturation process of newly produced virions. The second model expands on the first by incorporating the presence of latently infected cells, and including two additional delays: one for the formation of latently infected monocytes and another for their activation. The solutions derived from these models exhibit key properties of non-negativity and boundedness. Within this framework, two key equilibrium points were identified: the infection-free equilibrium $\mathscr{E}\mathscr{P}_0$ and the endemic equilibrium $\mathscr{E}\mathscr{P}_1$. To evaluate the existence and stability of these equilibrium points over time, we calculated the basic reproductive number for both models. The Lyapunov function and LIT are utilized to analyze the system's long-term behavior by investigating the global asymptotic stability of the equilibrium points. Our investigation on both models revealed two key findings:

(i) The infection-free equilibrium, $\mathscr{E}\mathscr{P}_0$, is always present and remains globally asymptotically stable when the basic reproductive number is less than or equal to one. This indicates that under these conditions, DENV will be eradicated from the system.

(ii) The endemic equilibrium, $\mathscr{E}\mathscr{P}_1$, is present and globally asymptotically stable when the basic reproductive number exceeds one. This suggests that DENV infection will persist within the infected individual.

To verify our theoretical results, we performed numerical simulations, and the outcomes were consistent with the analytical solutions. Furthermore, a sensitivity analysis identified key factors affecting the system's behavior, providing

deeper insights into DENV dynamics. We examined the impact of latently infected monocytes and time delays on secondary DENV infection. Our analysis revealed that these factors play a crucial role in reducing the basic reproductive number. As a result, overlooking them in the DENV infection model could lead to the administration of excessively high antiviral drug doses. Additionally, our findings indicate that prolonging the delay can substantially decrease the basic reproductive number, thereby limiting DENV progression. This insight opens new possibilities for designing treatments that focus on extending the delay period to help control the infection.

Conflict of interest

The authors declare no competing financial interest.

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