Applied Mathematics & Information Sciences
An International Journal

http://dx.doi.org/10.18576/amis/140412

Global Stability of a Secondary Dengue Viral Infection Model

A. A. Raezah[1,2], *A. M. Elaiw*[1,*] *and A. S. Alofi*[1]

[1]Department of Mathematics, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia
[2]Department of Mathematics, Faculty of Science, King Khalid University, P.O. Box 25145, Abha 61466, Saudi Arabia

Received: 3 Jan. 2020, Revised: 3 April 2020, Accepted: 4 Apr. 2020
Published online: 1 Jul. 2020

Abstract: This paper proposes and analyzes a secondary dengue viral infection model with two antibodies, namely heterologous antibody and homologous antibody. The well-posedness of the model is established by showing that the solutions of the model are nonnegative and bounded. We have shown that the model has four steady states, namely: infection-free steady state S_0, infected steady state with inactive antibody immune response S_1, infected steady state with only active heterologous antibody S_2, and infected steady state with only active homologous antibody S_3. We derive three bifurcation parameters: the basic infection reproduction number $\mathscr{R}_0$, the heterologous antibody immune response activation number $\mathscr{R}_1$, and the homologous antibody immune response activation number $\mathscr{R}_2$. These parameters define the existence and global stability of the steady states of the model. We prove the global asymptotic stability of all steady states utilizing Lyapunov function and LaSalle's invariance principle. We illustrate the theoretical results via numerical simulations.

Keywords: Dengue, DENV, Steady state, Global stability, Antibody immune response.

1 Introduction

Dengue is one of the dangerous vector-borne diseases caused by dengue virus (DENV). Throughout the world, around 50-100 million peoples are infected by DENV and approximately 12500 die annually. Southeast Asia and Sub-Saharan Africa are the most affected regions [1]. Aedes aegypti and Aedes albopictus female mosquitoes transmit DENV to humans. A healthy person gets infected when he/she is bitten by DENV-infected mosquitoes. The symptoms involve joint pains, headache, high fever, vomiting, nausea, and pain behind the eyes [2]. Four serologically distinct dengue viruses (DENV-1, DENV-2, DENV-3 and DENV-4) can infect the human body [3]. The target cells of the DENV include monocytes, dendritic cells, macrophages and hepatocytes [4]-[6]. When DENV enters the human body for the first time, the immune response is enhanced [7]. Antibody and Cytotoxic T Lymphocytes (CTLs) immune responses are two arms of the adaptive immune response to fight viruses. Antibodies are produced from the B cells to attach virus antigens and remove it from the body. CTLs kill the DENV-infected cells.

Recently, mathematical modeling of within-host dengue viral infection has witnessed a significant development. Mathematical models of primary within-host dengue viral infection have been introduced in some previous pieces of literature (see e.g. [8]-[16]). These models have been constructed on the basis of the basic viral infection model presented in [17]. It has been reported [18] that when a human is infected by one serotype, he/she will have lifelong immunity against that serotype, but only temporary and partial cross-immunity to the other three serotypes. Mathematical models of within-host dengue dynamics pertaining to secondary dengue infection with another serotype have been proposed in [19]-[25]. We observe that the global stability of the models presented in [19]-[25] is not extensively investigated.

Stability analysis has become one of the most important and fundamental approaches for understanding the within-host virus dynamics. In the present paper, we address the global stability analysis of a secondary dengue viral infection model with two types of antibodies. The well-posedness of the model is investigated by establishing that the solutions of the

* Corresponding author e-mail: a_m_elaiw@yahoo.com.

model are nonnegative and bounded. We derive three threshold parameters which define the existence and stability of the four steady states. Global stability of all steady states is proven by formulating Lyapunov functions and utilizing LaSalle's invariance principle. We perform some numerical simulations to illustrate the theoretical results.

2 Mathematical DENV dynamics model

We formulate a DENV dynamics model with secondary infection and two types of antibodies. The model describes the within-host dynamics of five compartments as:

$$\dot{x} = \varpi - \phi xv - \xi x, \tag{1}$$
$$\dot{y} = \phi xv - \rho y, \tag{2}$$
$$\dot{v} = \tau y - \eta v - \psi_1 vz - \psi_2 vw, \tag{3}$$
$$\dot{z} = \rho_1 vz - \mu_1 z, \tag{4}$$
$$\dot{w} = \rho_2 vw - \mu_2 w, \tag{5}$$

where the variables $x = x(t)$, $y = y(t)$, $v = v(t)$, $z = z(t)$ and $w = w(t)$ are the concentrations of healthy cells, infected cells, DENV particles, heterologous antibody previously formed on primary infection and homologous antibody against the new virus serotype of the secondary infection at time t, respectively. The healthy cells are created at rate ϖ, die at rate ξx and become infected by DENV at rate ϕxv. The DENV-infected cells die at rate ρy and produce DENV particles at rate τy. The DENV particles die at rate ηv. The terms $\psi_1 vz$ and $\psi_2 vw$ represent the neutralization rates of the DENV by heterologous and homologous antibodies, respectively. The heterologous and homologous antibodies are activated at rates $\rho_1 vz$ and $\rho_2 vw$, respectively. The terms $\mu_1 z$ and $\mu_2 w$ are the decay rates of the heterologous and homologous antibodies, respectively.

3 Properties of solutions and steady states

Let $\kappa_i > 0$, $i = 1,2,3,4$, and define the compact set

$$\Delta = \left\{(x,y,v,z,w) \in \mathbb{R}^5_{\geq 0} : 0 \leq x,y \leq \kappa_1, 0 \leq v \leq \kappa_2, \right.$$
$$\left. 0 \leq z \leq \kappa_3, 0 \leq w \leq \kappa_4 \right\}.$$

Theorem 3.1. The set Δ is positively invariant with respect to system (1)-(5).

Proof. We have

$$\begin{aligned} \dot{x}\,|_{x=0} &= \varpi > 0, \\ \dot{y}\,|_{y=0} &= \phi xv \geq 0 \quad \text{for } x,v \geq 0, \\ \dot{v}\,|_{v=0} &= \tau y \geq 0 \quad \text{for } y \geq 0, \\ \dot{z}\,|_{z=0} &= 0, \\ \dot{w}\,|_{w=0} &= 0. \end{aligned}$$

Hence, all solutions of system (1)-(5) with initial $(x(0),y(0),v(0),z(0),w(0)) \in \mathbb{R}^5_{\geq 0}$ are nonnegative. Let

$$T = x + y + \frac{\rho}{2\tau}v + \frac{\rho\psi_1}{2\tau\rho_1}z + \frac{\rho\psi_2}{2\tau\rho_2}w,$$

then

$$\dot{T} = \varpi - \xi x - \frac{\rho}{2}y - \frac{\rho\eta}{2\tau}v - \frac{\rho\psi_1\mu_1}{2\tau\rho_1}z - \frac{\rho\psi_2\mu_2}{2\tau\rho_2}w$$
$$\leq \varpi - \sigma\left(x + y + \frac{\rho}{2\tau}v + \frac{\rho\psi_1}{2\tau\rho_1}z + \frac{\rho\psi_2}{2\tau\rho_2}w\right) = \varpi - \sigma T,$$

where $\sigma = \min\{\xi, \frac{1}{2}\rho, \eta, \mu_1, \mu_2\}$. Hence, $T(t) \leq \kappa_1$, if $T(0) \leq \kappa_1$, where $\kappa_1 = \dfrac{\varpi}{\sigma}$. The nonnegativity of the variables implies $0 \leq x(t),y(t) \leq \kappa_1$, $0 \leq v(t) \leq \kappa_2$, $0 \leq z(t) \leq \kappa_3$ and $0 \leq w(t) \leq \kappa_4$ if $0 \leq x(0) + y(0) + \frac{\rho}{2\tau}v(0) + \frac{\rho\psi_1}{2\tau\rho_1}z(0) + \frac{\rho\psi_2}{2\tau\rho_2}w(0) \leq \kappa_1$, where $\kappa_2 = \frac{2\tau}{\rho}\kappa_1$, $\kappa_3 = \frac{2\tau\rho_1}{\rho\psi_1}\kappa_1$ and $\kappa_4 = \frac{2\tau\rho_2}{\rho\psi_2}\kappa_1$. □

Theorem 3.2. There exist three bifurcation parameters $\mathscr{R}_0$, $\mathscr{R}_1$ and $\mathscr{R}_2$ with $\mathscr{R}_0 > \mathscr{R}_1$ and $\mathscr{R}_0 > \mathscr{R}_2$ such that

(i) if $\mathscr{R}_0 \leq 1$, then the system has only one steady state $S_0 \in \Delta$,

(ii) if $\mathscr{R}_1 \leq 1 < \mathscr{R}_0$ and $\mathscr{R}_2 \leq 1 < \mathscr{R}_0$, then the system has only two steady states $S_0 \in \Delta$ and $S_1 \in \mathring{\Delta}$, where $\mathring{\Delta}$ is the interior of Δ,

(iii) if $\mathscr{R}_1 > 1, \mathscr{R}_2 < 1$, then the system has three steady states $S_0 \in \Delta$, $S_1 \in \mathring{\Delta}$ and $S_2 \in \mathring{\Delta}$.

(iv) if $\mathscr{R}_2 > 1, \mathscr{R}_1 < 1$, then the system has three steady states $S_0 \in \Delta$, $S_1 \in \mathring{\Delta}$ and $S_3 \in \mathring{\Delta}$.

(v) if $\mathscr{R}_2 > 1, \mathscr{R}_1 > 1$, then the system has four steady states $S_0 \in \Delta$, $S_1 \in \mathring{\Delta}$, $S_2 \in \mathring{\Delta}$ and $S_3 \in \mathring{\Delta}$.

Proof. Let the R.H.S. of Eqs. (1)-(5) be zero

$$0 = \varpi - \phi xv - \xi x, \tag{6}$$
$$0 = \phi xv - \rho y, \tag{7}$$
$$0 = \tau y - \eta v - \psi_1 vz - \psi_2 vw, \tag{8}$$
$$0 = \rho_1 vz - \mu_1 z, \tag{9}$$
$$0 = \rho_2 vw - \mu_2 w. \tag{10}$$

Then, solving the system of algebric equations (6)-(10) we get four steady states, as the following:

(i) infection-free steady state $S_0(x_0,0,0,0,0,0)$, where $x_0 = \frac{\varpi}{\xi}$,

(ii) infected steady state with inactive immune antibody response $S_1(x_1,y_1,v_1,0,0)$, where

$$x_1 = \frac{x_0}{\mathscr{R}_0}, \quad y_1 = \frac{\eta\xi}{\tau\phi}(\mathscr{R}_0 - 1), \quad v_1 = \frac{\xi}{\phi}(\mathscr{R}_0 - 1),$$

(iii) infected steady state with only active heterologous antibody $S_2(x_2,y_2,v_2,z_2,0)$, where

$$x_2 = \frac{\rho_1\varpi}{\xi\rho_1 + \phi\mu_1}, \quad y_2 = \frac{\phi\varpi\mu_1}{\rho(\xi\rho_1 + \phi\mu_1)}, \quad v_2 = \frac{\mu_1}{\rho_1},$$
$$z_2 = \frac{\eta}{\psi_1}(\mathscr{R}_1 - 1),$$

(iv) infected steady state with only active homologous antibody $S_3(x_3,y_3,v_3,0,w_3)$, where

$$x_3=\frac{\rho_2\varpi}{\xi\rho_2+\phi\mu_2},\ y_3=\frac{\phi\varpi\mu_2}{\rho(\xi\rho_2+\phi\mu_2)},\ v_3=\frac{\mu_2}{\rho_2},$$
$$w_3=\frac{\eta}{\psi_2}(\mathscr{R}_2-1),$$

where

$$\mathscr{R}_0=\frac{x_0\tau\phi}{\rho\eta},\qquad \mathscr{R}_1=\frac{\mathscr{R}_0}{1+\frac{\phi\mu_1}{\xi\rho_1}},\qquad \mathscr{R}_2=\frac{\mathscr{R}_0}{1+\frac{\phi\mu_2}{\xi\rho_2}}.$$

Clearly $\mathscr{R}_0>\mathscr{R}_1$ and $\mathscr{R}_0>\mathscr{R}_2$.

(v) It is clear from (iii) and (iv) that if $\mathscr{R}_1>1$ and $\mathscr{R}_2>1$, S_0, S_1, S_2 and S_3 all exist.

Here, $\mathscr{R}_0$ represents the basic infection reproduction number, $\mathscr{R}_1$ represents the heterologous antibody immune response activation numbers and $\mathscr{R}_2$ is the homologous antibody immune response activation number.

Now, we show that $S_0\in\Delta$ and $S_1,S_2,S_3\in\mathring{\Delta}$. It is clear that $S_0\in\Delta$. Let $\mathscr{R}_0>1$, then S_1 exists and

$$\xi x_1+\rho y_1=\varpi.$$

It follows that

$$x_1<\frac{\varpi}{\xi}\le\kappa_1,\ y_1<\frac{\varpi}{\rho}<\frac{\varpi}{\frac{1}{2}\rho}\le\kappa_1.$$

Moreover, we have, $\eta v_1=\tau y_1$, then

$$v_1=\frac{\tau}{\eta}y_1<\frac{2\tau}{\rho}\frac{\varpi}{\eta}\le\frac{2\tau}{\rho}\kappa_1=\kappa_2.$$

We have $z_1=w_1=0$ then, $S_1\in\mathring{\Delta}$.
It is clear that $0<x_2,y_2<\kappa_1$. Next, we show that $0<v_2<\kappa_2$ and $0<z_2<\kappa_3$ when $\mathscr{R}_1>1$. From the steady state conditions of S_2, we have

$$\eta v_2+\psi_1 v_2 z_2=\tau y_2.$$

Then if $\mathscr{R}_1>1$ we get

$$\eta v_2<\tau y_2\Rightarrow 0<v_2<\frac{2\tau}{\rho}\frac{\varpi}{\eta}\le\frac{2\tau}{\rho}\kappa_1=\kappa_2.$$

Finally we have

$$z_2<\frac{\tau y_2}{\psi_1 v_2}<\frac{2\tau\rho_1}{\rho\psi_1}\kappa_1=\kappa_3$$

Then, $S_2\in\mathring{\Delta}$. Similarly, one can show that $S_3\in\mathring{\Delta}$. □

4 Global stability

This section is devoted to prove the global stability of the four steady states by of system (1)-(5). The proofs are based on the method of Lyapunov function presented [26]-[32]. Define a function $g(x)=x-1-\ln x$.

Theorem 4.1. Suppose that $\mathscr{R}_0\le 1$, then S_0 is globally asymptotically stable (G.A.S) in Δ.

Proof. Define

$$W_0(x,y,v,z,w)=x_0 g\left(\frac{x}{x_0}\right)+y+\frac{\rho}{\tau}v+\frac{\rho\psi_1}{\tau\rho_1}z+\frac{\rho\psi_2}{\tau\rho_2}w. \tag{11}$$

Observe that $W_0(x,y,v,z,w)>0$ for all $(x,y,v,z,w)>0$ and $W_0(x_0,0,0,0,0)=0$. Calculating $\frac{dW_0}{dt}$ along the solutions of (1)-(5) as:

$$\begin{aligned}\frac{dW_0}{dt}&=\left(1-\frac{x_0}{x}\right)(\varpi-\xi x-\phi xv)+\phi xv-\rho y\\&+\frac{\rho}{\tau}(\tau y-\eta v-\psi_1 vz-\psi_2 vw)+\frac{\rho\psi_1}{\tau\rho_1}(\rho_1 vz-\mu_1 z)\\&+\frac{\rho\psi_2}{\tau\rho_2}(\rho_2 vw-\mu_2 w).\end{aligned} \tag{12}$$

Collecting terms of Eq. (12) we obtain

$$\begin{aligned}\frac{dW_0}{dt}&=-\frac{\xi(x-x_0)^2}{x}+\left(\phi x_0-\frac{\rho\eta}{\tau}\right)v-\frac{\rho\psi_1\mu_1}{\tau\rho_1}z-\frac{\rho\psi_2\mu_2}{\tau\rho_2}w\\&=-\frac{\xi(x-x_0)^2}{x}+\frac{\rho\eta}{\tau}(\mathscr{R}_0-1)v-\frac{\rho\psi_1\mu_1}{\tau\rho_1}z-\frac{\rho\psi_2\mu_2}{\tau\rho_2}w.\end{aligned}$$

Therefore, if $\mathscr{R}_0\le 1$, then $\frac{dW_0}{dt}\le 0$ for $x,v,z,w\in(0,\infty)$. Moreover, $\frac{dW_0}{dt}=0$ when $x(t)=x_0$ and $v(t)=z(t)=w(t)=0$ for all t. Let $\Gamma=\left\{(x,y,v,z,w):\frac{dW_0}{dt}=0\right\}$ and Γ_0 be the largest invariant subset of Γ. We note that the solutions of system (1)-(5) converge to Γ_0 [33]. The set Γ_0 is invariant and contains elements which satisfy $v(t)=z(t)=w(t)=0$. It follows from Eq. (3) that

$$0=\dot{v}(t)=\tau y(t).$$

This yields $y(t)=0$. Hence Γ_0 is the singleton $\{S_0\}$. LaSalle's invariance principle provides that S_0 is G.A.S [33]. □

Theorem 4.2. Suppose that $\mathscr{R}_1\le 1<\mathscr{R}_0$ and $\mathscr{R}_2\le 1$, then S_1 is G.A.S in $\mathring{\Delta}$.

Proof. We define a function $W_1(x,y,v,z,w)$ as:

$$W_1=x_1 g\left(\frac{x}{x_1}\right)+y_1 g\left(\frac{y}{y_1}\right)+\frac{\rho}{\tau}v_1 g\left(\frac{v}{v_1}\right)+\frac{\rho\psi_1}{\tau\rho_1}z+\frac{\rho\psi_2}{\tau\rho_2}w.$$

Calculating $\frac{dW_1}{dt}$ along the trajectories of (1)-(5):

$$\begin{aligned}\frac{dW_1}{dt} &= \left(1-\frac{x_1}{x}\right)(\varpi-\xi x-\ \phi xv)+\left(1-\frac{y_1}{y}\right)\left(\phi xv\right.\\ &\left.-\rho y\right)+\frac{\rho}{\tau}\left(1-\frac{v_1}{v}\right)(\tau y-\eta v-\psi_1 vz-\psi_2 vw)\\ &+\frac{\rho\psi_1}{\tau\rho_1}(\rho_1 vz-\mu_1 z)+\frac{\rho\psi_2}{\tau\rho_2}(\rho_2 vw-\mu_2 w)\\ &=\left(1-\frac{x_1}{x}\right)(\varpi-\xi x)+\phi x_1 v-\frac{\phi xvy_1}{y}+\rho y_1\\ &-\frac{\rho\eta}{\tau}v-\rho\frac{v_1 y}{v}+\frac{\rho\eta}{\tau}v_1+\frac{\rho\psi_1}{\tau}v_1 z+\frac{\rho\psi_2}{\tau}v_1 w\\ &-\frac{\rho\psi_1\mu_1}{\tau\rho_1}z-\frac{\rho\psi_2\mu_2}{\tau\rho_2}w. \end{aligned}\tag{13}$$

Collecting terms of Eq. (13) and applying the steady state conditions

$$\begin{aligned}\varpi &= \xi x_1+\phi x_1 v_1,\\ \rho y_1 &= \phi x_1 v_1,\\ \tau y_1 &= \eta v_1,\end{aligned}$$

we get $\phi x_1 v-\frac{\rho\eta}{\tau}v=0$ and

$$\begin{aligned}\frac{dW_1}{dt} &= -\frac{\xi(x-x_1)^2}{x}+\rho y_1\left(1-\frac{x_1}{x}\right)-\rho y_1\frac{xvy_1}{x_1v_1y}\\ &+2\rho y_1-\rho y_1\frac{v_1y}{vy_1}+\frac{\rho\psi_1}{\tau}\left(v_1-\frac{\mu_1}{\rho_1}\right)z\\ &+\frac{\rho\psi_2}{\tau}\left(v_1-\frac{\mu_2}{\rho_2}\right)w\\ &=-\frac{\xi(x-x_1)^2}{x}+\rho y_1\left[3-\frac{x_1}{x}-\frac{xvy_1}{x_1v_1y}-\frac{v_1y}{vy_1}\right]\\ &+\frac{\rho\psi_1(\xi\rho_1+\phi\mu_1)}{\tau\rho_1\phi}(\mathscr{R}_1-1)z\\ &+\frac{\rho\psi_2(\xi\rho_2+\phi\mu_2)}{\tau\rho_2\phi}(\mathscr{R}_2-1)w.\end{aligned}$$

Since the the geometrical mean is less than or equal the arithmetical mean, then

$$3\le\frac{x_1}{x}+\frac{xvy_1}{x_1v_1y}+\frac{v_1y}{vy_1}.$$

It follows that for all $x,y,v,z,w>0$, we have $\frac{dW_1}{dt}\le 0$ and $\frac{dW_1}{dt}=0$ when $x=x_1$, $y=y_1$, $v=v_1$ and $z=w=0$. Therefore, the largest invariant subset of $\left\{(x,y,v,z,w):\frac{dW_1}{dt}=0\right\}$ is the singleton $\{S_1\}$. By LaSalle's invariance principle, S_1 is G.A.S. □

Theorem 4.3. Let $\mathscr{R}_1>1$ and $\mathscr{R}_2\le\mathscr{R}_1$, then S_2 is G.A.S in $\overset{\circ}{\Delta}$.

Proof. Define a function $W_2(x,y,v,z,w)$ as:

$$\begin{aligned}W_2 &= x_2 g\left(\frac{x}{x_2}\right)+y_2 g\left(\frac{y}{y_2}\right)+\frac{\rho}{\tau}v_2 g\left(\frac{v}{v_2}\right)\\ &+\frac{\rho\psi_1}{\tau\rho_1}z_2 g\left(\frac{z}{z_2}\right)+\frac{\rho\psi_2}{\tau\rho_2}w.\end{aligned}$$

Calculating $\frac{dW_2}{dt}$ along the solutions of model (1)-(5), we get

$$\begin{aligned}\frac{dW_2}{dt} &= \left(1-\frac{x_2}{x}\right)(\varpi-\xi x-\phi xv)+\left(1-\frac{y_2}{y}\right)(\phi xv-\rho y)\\ &+\frac{\rho}{\tau}\left(1-\frac{v_2}{v}\right)(\tau y-\eta v-\psi_1 vz-\psi_2 vw)\\ &+\frac{\rho\psi_1}{\tau\rho_1}\left(1-\frac{z_2}{z}\right)(\rho_1 vz-\mu_1 z)+\frac{\rho\psi_2}{\tau\rho_2}(\rho_2 vw-\mu_2 w).\end{aligned}\tag{14}$$

Collecting terms of Eq. (14), we get

$$\begin{aligned}\frac{dW_2}{dt} &= \left(1-\frac{x_2}{x}\right)(\varpi-\xi x)+\phi x_2 v-\frac{\phi xvy_2}{y}+\rho y_2-\frac{\rho\eta}{\tau}v\\ &-\rho\frac{v_2y}{v}+\frac{\rho\eta}{\tau}v_2+\frac{\rho\psi_1}{\tau}v_2z+\frac{\rho\psi_2}{\tau}v_2w-\frac{\rho\psi_1\mu_1}{\tau\rho_1}z\\ &-\frac{\rho\psi_1}{\tau}z_2v+\frac{\rho\psi_1\mu_1}{\tau\rho_1}z_2-\frac{\rho\psi_2\mu_2}{\tau\rho_2}w\\ &=\left(1-\frac{x_2}{x}\right)(\varpi-\xi x)+(\phi\ x_2-\frac{\rho\eta}{\tau}-\frac{\rho\psi_1}{\tau}z_2)v\\ &-\frac{\phi xvy_2}{y}+\rho y_2-\rho\frac{v_2y}{v}+\frac{\rho\eta}{\tau}v_2+\frac{\rho\psi_2}{\tau}v_2w\\ &+\frac{\rho\psi_1\mu_1}{\tau\rho_1}z_2-\frac{\rho\psi_2\mu_2}{\tau\rho_2}w.\end{aligned}$$

Applying the steady state conditions:

$$\begin{aligned}\varpi &= \xi x_2+\phi x_2 v_2,\\ \rho y_2 &= \phi x_2 v_2,\\ \tau y_2 &= \eta v_2+\psi_1 v_2 z_2,\end{aligned}$$

we get

$$\begin{aligned}\frac{dW_2}{dt} &= -\frac{\xi(x-x_2)^2}{x}+\rho y_2\left(1-\frac{x_2}{x}\right)\\ &-\rho y_2\frac{xvy_2}{x_2v_2y}-\rho y_2\frac{v_2y}{vy_2}+2\rho y_2+\frac{\rho\psi_2}{\tau}(v_2-v_3)w\\ &=-\frac{\xi(x-x_2)^2}{x}+\rho y_2\left[3-\frac{x_2}{x}-\frac{xvy_2}{x_2v_2y}-\frac{v_2y}{vy_2}\right]\\ &+\frac{\rho\psi_2(\xi\rho_2+\phi\mu_2)}{\tau\phi\rho_2\mathscr{R}_1}(\mathscr{R}_2-\mathscr{R}_1)w.\end{aligned}$$

The relation between the arithmetical and geometrical means implies

$$3\le\frac{x_2}{x}+\frac{xvy_2}{x_2v_2y}+\frac{v_2y}{vy_2}.$$

Since $\mathscr{R}_2\le\mathscr{R}_1$, then $\frac{dW_2}{dt}\le 0$ for all $(x,y,v,z,w)>0$. We have $\frac{dW_2}{dt}$ when $x=x_2$, $y=y_2$, $v=v_2$ and $w=0$. Let $\hat{\Gamma}=\left\{(x,y,v,z,w):\frac{dW_2}{dt}=0\right\}$ and $\hat{\Gamma}_0$ be the largest invariant subset of $\hat{\Gamma}$. We note that, the solutions of system (1)-(5) converge to $\hat{\Gamma}_0$. The set $\hat{\Gamma}_0$ is invariant and

contains elements which satisfy $y(t) = y_2$, $v(t) = v_2$ and $w = 0$. It follows from Eq. (3) that

$$0 = \dot{v} = \tau y_2 - \eta v_2 - \psi_1 v_2 z,$$

which gives $z(t) = z_2$. Hence, $\hat{\Gamma}_0$ is the singleton $\{S_2\}$. By LaSalle's invariance principle, S_2 is G.A.S. □

Theorem 4.4. Let $\mathscr{R}_2 > 1$ and $\mathscr{R}_1 \leq \mathscr{R}_2$, then S_3 is G.A.S in $\overset{\circ}{\Delta}$.

Proof. Define a function $W_3(x,y,v,z,w)$ as:

$$W_3 = x_3 g\left(\frac{x}{x_3}\right) + y_3 g\left(\frac{y}{y_3}\right) + \frac{\rho}{\tau} v_3 g\left(\frac{v}{v_3}\right) + \frac{\rho\psi_1}{\tau\rho_1} z + \frac{\rho\psi_2}{\tau\rho_2} w_2 g\left(\frac{w}{w_2}\right).$$

Calculating $\frac{dW_3}{dt}$ along the solutions of model (1)-(5), we get

$$\begin{aligned}\frac{dW_3}{dt} &= \left(1 - \frac{x_3}{x}\right)(\varpi - \xi x - \phi x v) + \left(1 - \frac{y_3}{y}\right)(\phi x v - \rho y) \\ &+ \frac{\rho}{\tau}\left(1 - \frac{v_3}{v}\right)(\tau y - \eta v - \psi_1 v z - \psi_2 v w) \\ &+ \frac{\rho\psi_1}{\tau\rho_1}(\rho_1 v z - \mu_1 z) + \frac{\rho\psi_2}{\tau\rho_2}\left(1 - \frac{w_3}{w}\right)(\rho_2 v w - \mu_2 w).\end{aligned}$$

Collecting terms of the aforementioned equation, we get

$$\begin{aligned}\frac{dW_3}{dt} &= \left(1 - \frac{x_3}{x}\right)(\varpi - \xi x) + \phi x_3 v - \frac{\phi x v y_3}{y} + \rho y_3 - \frac{\rho\eta}{\tau} v \\ &- \rho\frac{v_3 y}{v} + \frac{\rho\eta}{\tau} v_3 + \frac{\rho\psi_1}{\tau} v_3 z + \frac{\rho\psi_2}{\tau} v_3 w - \frac{\rho\psi_1\mu_1}{\tau\rho_1} z \\ &- \frac{\rho\psi_2\mu_2}{\tau\rho_2} w - \frac{\rho\psi_2}{\tau} w_3 v + \frac{\rho\psi_2\mu_2}{\tau\rho_2} w_3.\end{aligned}$$

Applying the steady state conditions:

$$\begin{aligned}\varpi &= \xi x_3 + \phi x_3 v_3, \\ \rho y_3 &= \phi x_3 v_3, \\ \tau y_3 &= \eta v_3 + \psi_2 v_3 w_3,\end{aligned}$$

we get

$$\begin{aligned}\frac{dW_3}{dt} &= -\frac{\xi(x - x_3)^2}{x} + \rho y_3\left(1 - \frac{x_3}{x}\right) - \rho y_3 \frac{x v y_3}{x_3 v_3 y} \\ &- \rho y_3 \frac{v_3 y}{v y_3} + 2\rho y_3 + \frac{\rho\psi_1}{\tau}(v_3 - v_2) z \\ &= -\frac{\xi(x - x_3)^2}{x} + \rho y_3\left[3 - \frac{x_3}{x} - \frac{x v y_3}{x_3 v_3 y} - \frac{v_3 y}{v y_3}\right] \\ &+ \frac{\rho\psi_1(\xi\rho_2 + \phi\mu_2)}{\tau\phi\rho_2\mathscr{R}_1}(\mathscr{R}_1 - \mathscr{R}_2) z.\end{aligned}$$

Clearly, $\frac{dW_3}{dt} \leq 0$ for all $(x,y,v,z,w) > 0$ and $\frac{dW_3}{dt} = 0$ when $x = x_3$, $y = y_3$, $v = v_3$ and $z = 0$. Let $\tilde{\Gamma} = \left\{(x,y,v,z,w) : \frac{dW_3}{dt} = 0\right\}$ and $\tilde{\Gamma}_0$ be the largest invariant subset of $\tilde{\Gamma}$. We note that the solutions of system (1)-(5) converge to $\tilde{\Gamma}_0$. The set $\tilde{\Gamma}_0$ is invariant and contains elements which satisfy $y(t) = y_3$, $v(t) = v_3$ and $w(t) = 0$. It follows that from Eq. (3) that

$$0 = \dot{v} = \tau y_3 - \eta v_3 - \psi_2 v_3 w,$$

which gives $w(t) = w_3$. Hence $\tilde{\Gamma}_0$ is the singleton $\{S_3\}$. By LaSalle's invariance principle S_3 is G.A.S. □

5 Numerical simulations

We solve system (1)-(5) numerically with different initial values:

IV1: $(x(0),y(0),v(0),z(0),w(0)) = (700,5,4,3,2)$,
IV2: $(x(0),y(0),v(0),z(0),w(0)) = (600,8,7,4,3)$,
IV3: $(x(0),y(0),v(0),z(0),w(0)) = (450,12,10,5,4)$,
IV4: $(x(0),y(0),v(0),z(0),w(0)) = (350,20,13,6,6)$,

and with parameters values given in Table 1. The parameters ϕ, ρ_1 and ρ_2 will be selected in four cases:

Case (I): In this case, we choose $\phi = 0.00005, \rho_1 = 0.0005$ and $\rho_2 = 0.001$ which give $\mathscr{R}_0 = 0.2778 < 1$, $\mathscr{R}_1 = 0.1389 < 1$ and $\mathscr{R}_2 = 0.1852$. Theorems 3.2 and 4.1 state that the system has a single steady state, S_0 and it is G.A.S. Figure 1 shows that the concentrations of infected cells, DENV particles, heterologous antibody and homologous antibody are decreasing w.r.t. time and finally tend to zero. In the mean time, the concentration of the healthy cells is increasing and tends to its healthy value $x_0 = 1000$. In this case, the DENV is cleared from the body.

Case (II): By taking $\phi = 0.0005, \rho_1 = 0.0005$ and $\rho_2 = 0.001$, we get $\mathscr{R}_0 = 2.7778 > 1$, $\mathscr{R}_1 = 0.2525 < 1$ and $\mathscr{R}_2 = 0.4630 < 1$. Consequently, based on Theorems 3.2 and 4.2, the antibody-inactive infection steady state S_1 exists and it is G.A.S. Figure 2 displays the numerical solutions of the system with IV1-IV4. The results illustrate the theoretical results presented in Theorem 4.2. It is noticeable that, the solutions of the system eventually converge to the steady state $S_1 = (360, 21.3333, 35.5556, 0, 0)$. In this case, the patient has no antibody immune response to DENV infection.

Case (III): $\phi = 0.0005, \rho_1 = 0.005$ and $\rho_2 = 0.001$. Then, we calculate $\mathscr{R}_0 = 2.7778 > 1$ and $\mathscr{R}_1 = 1.3889 > 1$ and $\mathscr{R}_2 = 0.4630 < \mathscr{R}_1$. Theorems 3.2 and 4.3 state that the infected steady state with only active heterologous antibody $S_2 = (500, 16.6667, 20, 3.8889, 0)$ exists and it is G.A.S. Figure 3 displays the numerical solutions of the system with IV1-IV4. The results support the theoretical results presented in Theorem 4.3. In this case the patient has only active heterologous antibody immune response to DENV infection.

Case (IV): $\phi = 0.0005, \rho_1 = 0.01$ and $\rho_2 = 0.02$. Then, we calculate $\mathscr{R}_0 = 2.7778 > 1$ and $\mathscr{R}_1 = 1.8519 > 1$ and $\mathscr{R}_2 = 2.2222 > \mathscr{R}_1$. According to Theorems 3.2 and 4.4, the infected steady state with only active homologous antibody $S_3 = (800, 6.6667, 5, 0, 36.6667)$ exists and it is G.A.S.

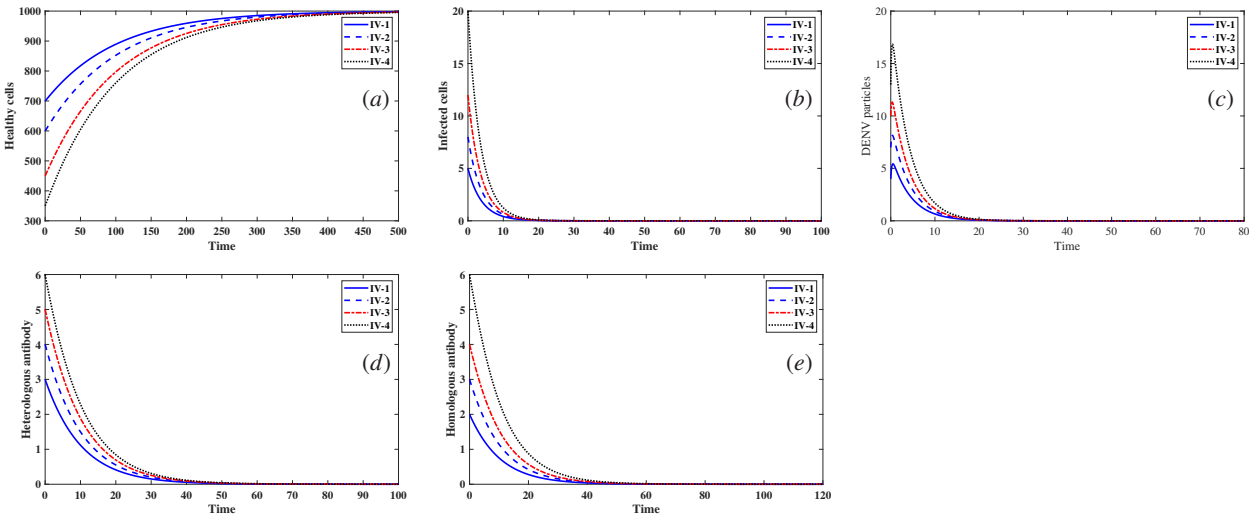

Fig. 1: Solutions of system (1)-(5) with different initial conditions for Case (I).

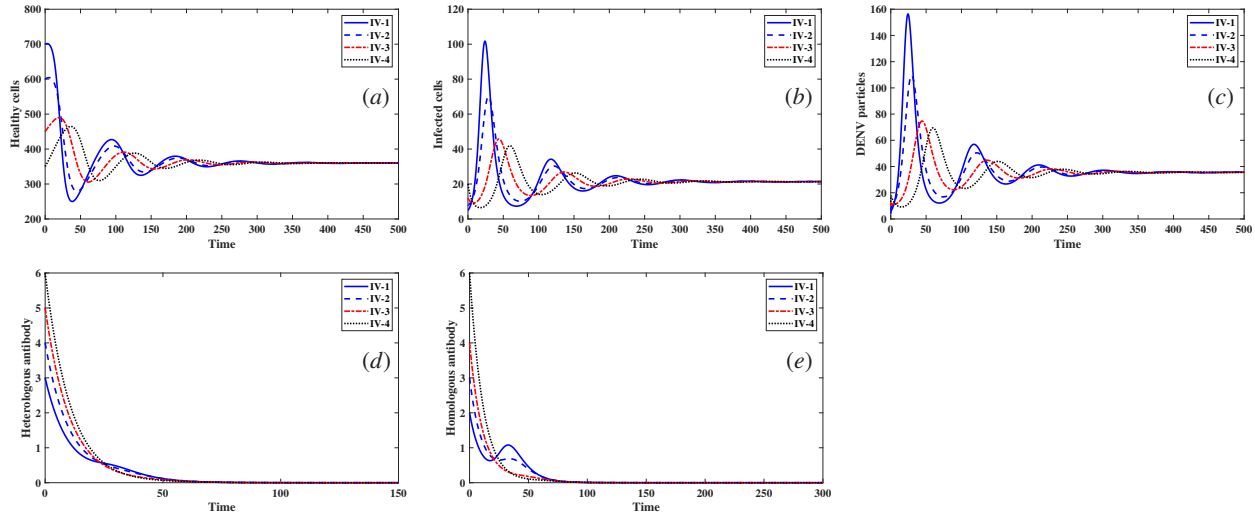

Fig. 2: Solutions of system (1)-(5) with different initial conditions for Case (II).

Figure 4 illustrates and supports the results of Theorem 4.4. In this case, the patient has only active homologous antibody immune response to DENV infection.

Table 1: The values of the parameters of system (1)-(5).

Parameter	Value	Parameter	Value	Parameter	Value
λ	10	τ	5	ρ_1	Varied
ξ	0.01	η	3	μ_1	0.1
ϕ	Varied	ψ_1	0.3	ρ_2	Varied
ρ	0.3	ψ_2	0.1	μ_2	0.1

Second, we calculate the Jacobian matrix $J = J(x,y,v,z,w)$ of system (1)-(5) as:

$$J = \begin{pmatrix} -\xi - \phi v & 0 & -\phi x & 0 & 0 \\ \phi v & -\rho & \phi x & 0 & 0 \\ 0 & \tau & -\eta - \psi_2 w - \psi_1 z & -\psi_1 v & -\psi_2 v \\ 0 & 0 & \rho_1 z & \rho_1 v - \mu_1 & 0 \\ 0 & 0 & \rho_2 w & 0 & \rho_2 v - \mu_2 \end{pmatrix}.$$

Then, we calculate the eigenvalues λ_i, $i = 1,2,...,6$ of the matrix J at each steady state. The examined steady will be locally stable if all its eigenvalues satisfy the following condition:

$$\mathrm{Re}(\lambda_i) < 0,\ i = 1,2,...,6$$

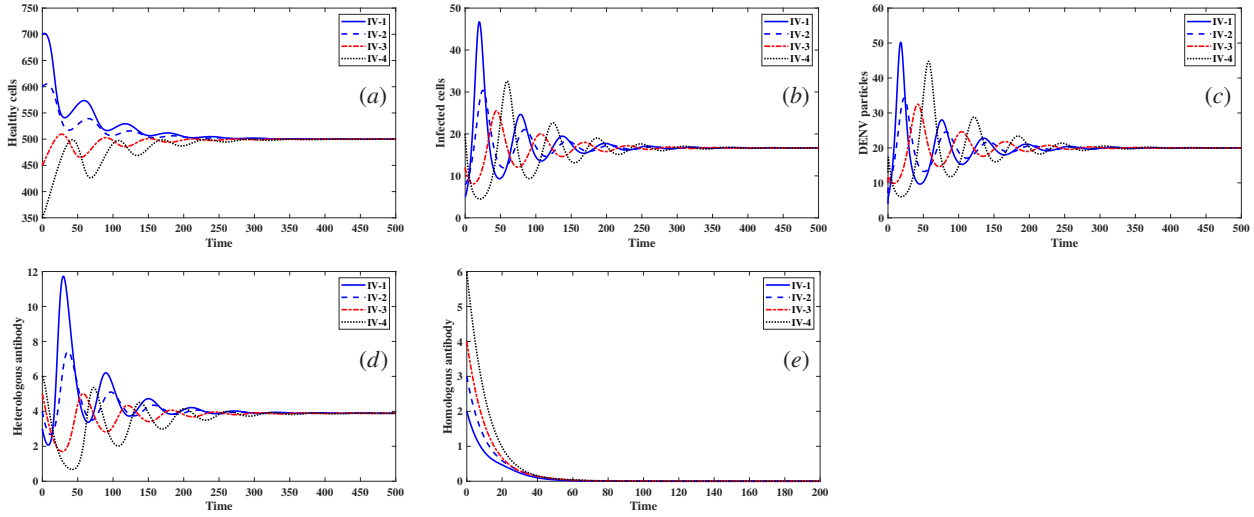

Fig. 3: Solutions of system (1)-(5) with different initial conditions for Case (III).

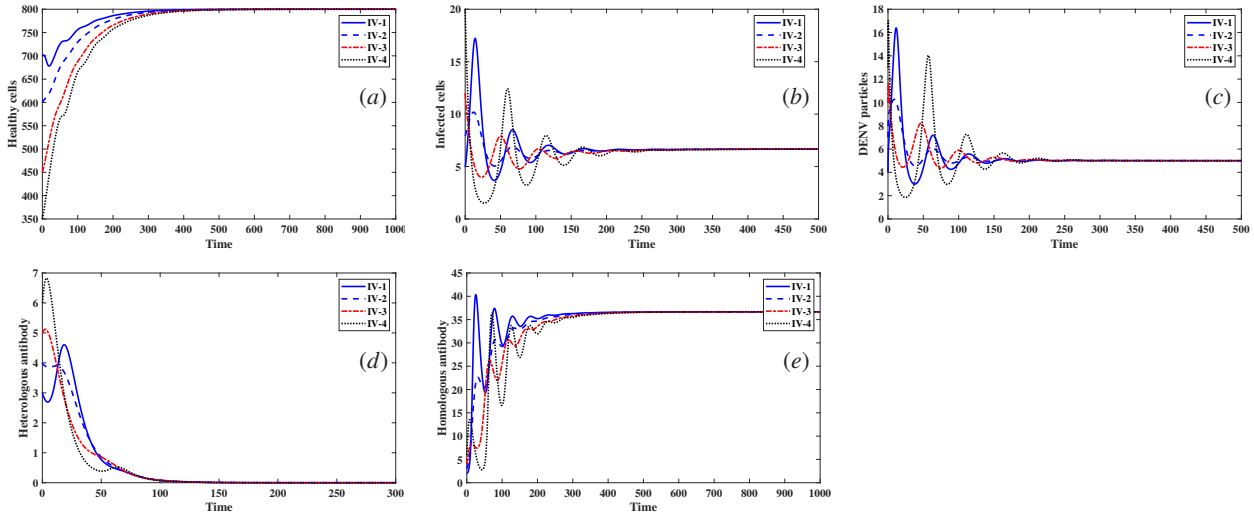

Fig. 4: Solutions of system (1)-(5) with different initial conditions for Case (IV).

We use the values of the parameters ϕ, ρ_1 and ρ_2 given in Cases (I)-(IV) to compute all positive steady states and the corresponding eigenvalues. In Table 2, we present the positive steady states, and the real parts of the eigenvalues, whether the steady state is locally stable or unstable for Cases (I)-(IV).

Acknowledgement

This work was funded by King Abdulaziz City for Science and Technology (KACST), Saudi Arabia, under grant No. (1-17-01-009-0103). Thus, the authors are enormously grateful to KACST for technical and financial support.

Table 2: Local stability of positive steady states for Cases (I)-(IV).

Case	Steady states	$(\mathrm{Re}(\lambda_i), i = 1,2,...,5)$	Stability
(I)	$S_0 = (1000,0,0,0,0)$	$(-3.09,-0.210,-0.1,-0.1,-0.01)$	stable
(II)	$S_0 = (1000,0,0,0,0)$	$(-3.729,0.429,-0.1,-0.1,-0.017)$	unstable
	$S_1 = (360,21.333,35.556,0,0)$	$(-3.301,-0.082,-0.013,-0.013,-0.064)$	stable
(III)	$S_0 = (1000,0,0,0,0)$	$(-3.729,0.429,-0.1,-0.1,-0.01)$	unstable
	$S_1 = (360,21.333,35.556,0,0)$	$(-3.301,0.078,-0.013,-0.013,-0.064)$	unstable
	$S_2 = (500,16.667,20,3.889,0)$	$(-4.443,-0.015,-0.015,-0.08,-0.015)$	stable
(IV)	$S_0 = (1000,0,0,0,0)$	$(-3.729,0.429,-0.1,-0.1,-0.01)$	unstable
	$S_1 = (360,21.333,35.556,0,0)$	$(-3.301,0.611,0.256,-0.013,-0.013)$	unstable
	$S_2 = (666.667,11.111,10,8.519,0)$	$(-5.814,-0.021,-0.021,0.1,-0.013)$	unstable
	$S_3 = (800,6.667,5,0,36.667)$	$(-6.916,-0.026,-0.026,-0.05,-0.012)$	stable

References

[1] WHO, Dengue and dengue haemorrhagic fever. 2013. http://www.who.int/mediacentre/factsheets/fs117/en/

[2] S. B. Halstead, *Dengue,* Lancet, **370** (2007), 1644-1652..

[3] E. Navarro-Sanchez, P. Despres and L. Cedillo-Barreon, *Innate immune responses to dengue virus*, Archchives of Medical Research, **36** (2005) 425-435.

[4] S. Jindadamrongwech, C. Thepparit, D. R. Smith, *Identification of GRP78(BiP)as a liver cell expressed receptor element for dengue virus serotype 2,* Archives of Virology, **149** (2004), 915-927.

[5] S. C. Kliks, A. Nisalak, W. E. Brandt, L. Wahl, D. S. Burke, *Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue haemorrhagic fever*, The American Journal of Tropical Medecine and Hygiene, **40** (1989), 444-451.

[6] J. M. Willey, L. M. Sherwood, C. J. Woolverton, Microbiology, 7th edn. McGraw Hill, New York (2008).

[7] R. V. Gibbons and D. W. Vaughn, *Dengue: an escalating problem*, Br Med J **324** (2002), 1563-1566.

[8] N. Nuraini, H. Tasman, E. Soewono, K.A. Sidarto, *A within host dengue infection model with immune response*, Mathematical and Computer Modelling, **49** (2009), 1148-1155.

[9] H. Ansari, M. Hesaaraki, *A within-host dengue infection model with immune response and Beddington–DeAngelis incidence rate*, Applied Mathematics, **3** (2012), 177-184.

[10] A. Mishra and S. Gakkhar, *A micro-epidemic model for primary dengue infection*, Communications in Nonlinear Science and Numerical Simulation, **47** (2017), 426–437.

[11] B. R. Murphy and S. S. Whitehead, *Immune response to dengue virus and prospects for a vaccine*, Annual Review Immunologym **29** (2011), 587-619.

[12] S. K. Sasmal, Y. Dong, and Y. Takeuchi, *Mathematical modeling on t-cell mediated adaptive immunity in primary dengue infections*. Journal of Theoretical Biology, **429** (2017), 229-240.

[13] S. D. Perera and S. S. N. Perera, *Simulation model for dynamics of dengue with innate and humoral immune responses*, Computational and Mathematical Methods in Medicine, **2018** (2018), Article ID 8798057.

[14] S. Perera and S. S. N. Perera, *Mathematical modeling and analysis of innate and humoral immune responses to dengue infections*, International Journal of Biomathematics, **12**(7) (2019), Article ID 1950077.

[15] J. J. Thibodeaux, D. Nunez and A. Rivera, *A generalized within-host model of dengue infection with a non-constant monocyte production rate*, Journal of Biological Dynamics, **14**(1) (2020), 143-161.

[16] H.E. Clapham, V. Tricou, N. Van Vinh Chau, C.P. Simmons, N.M. Ferguson, *Within-host viral dynamics of dengue serotype 1 infection*, Journal of the Royal Society Interface, **11** (2014), Article ID 20140094.

[17] M. A. Nowak and C. R. M. Bangham. *Population dynamics of immune responses to persistent viruses*, Science, **272** (1996)**,** 74-79.

[18] World Health Organization, "Dengue and dengue hemorrhagic fever. Fact sheet no. 117," 2017, http://www.who.int/meidacentre/factsheets/fs117/en.

[19] T. P. Gujarati and G. Ambika, *Virus antibody dynamics in primary and secondary dengue infections*, Journal of Mathematical Biology, **69** (2014), 1773-1800.

[20] R. Ben-Shachar and K. Koelle, *Minimal within-host dengue models highlight the specific roles of the immune response in primary and secondary dengue infections*. Journal of the Royal Society Interface, **12** (2015), Article ID 20140886.

[21] R. Nikin-Beers and S. M. Ciupe, *Modelling original antigenic sin in dengue viral infection*, Mathematical Medicine and Biology: A Journal of the IMA, **35**(2) (2018), 257-272.

[22] A. Mishra, *A within-host model of dengue viral infection dynamics*, In: Cushing J., Saleem M., Srivastava H., Khan M., Merajuddin M. (eds) Applied Analysis in Biological and Physical Sciences. Springer Proceedings in Mathematics & Statistics, vol 186 (2016) Springer, New Delhi.

[23] M. Ceron Comez and H. M. Yang, *A simple mathematical model to describe antibody-dependent enhancement in heterologous secondary infection in dengue,* Mathematical Medicine and Biology: A Journal of the IMA, **36** (2019), 411-438.

[24] M. Borisov, G. Dimitriu and P. Rashkov, *Modelling the host immune response to mature and immature dengue viruses,* Bulletin of Mathematical Biology, **81** (2019), 4951-4976.

[25] S. K. Sasmal, Y. Takeuchi and S. Nakaoka, *T-Cell me diate d adaptive immunity and antibody-dependent enhancement in secondary dengue infection*, Journal of Theoretical Biology, **470** (2019), 50-63.

[26] A. Korobeinikov, *Global properties of basic virus dynamics models*, Bulletin of Mathematical Biology, **66**(4). (2004), 879-883.

[27] A. M. Elaiw, *Global properties of a class of HIV models*, Nonlinear Analysis: Real World Applications, **11** (2010), 2253-2263.
[28] A. M. Elaiw, E. Kh. Elnahary and A. A. Raezah, *Effect of cellular reservoirs and delays on the global dynamics of HIV*, Advances in Difference Equations, (2018) 2018:85.
[29] A. M. Elaiw, A. A. Raezah and S. A. Azoz, *Stability of delayed HIV dynamics models with two latent reservoirs and immune impairment*, Advances in Difference Equations, (2018) 2018:414.
[30] A. M. Elaiw and A. A. Raezah, *Stability of general virus dynamics models with both cellular and viral infections and delays*, Mathematical Methods in the Applied Sciences, **40**(16) (2017), 5863-5880.
[31] A. M. Elaiw and N. H. AlShamrani, *Global stability of humoral immunity virus dynamics models with nonlinear infection rate and removal*, Nonlinear Analysis: Real World Applications, **26**, (2015), 161-190.
[32] A.M. Elaiw, *Global properties of a class of virus infection models with multitarget cells*, Nonlinear Dynamics, **69**(1-2) (2012), 423-435.
[33] J.K. Hale, and S. V. Lunel, *Introduction to functional differential equations*, Springer-Verlag, New York, (1993).

A. A. Raezah received her MSc degree in Applied Mathematics from King Khalid University in 2008. She received PhD degree from King Abdulaziz University in 2017. Currently she is an assistant professor at the Department of Mathematical at King Khalid University, Abha Saudi Arabia. His research interests include: mathematical modeling, mathematical analysis of viral infections, differential equations (ODE), delay differential equations (DDE) with application on biology.

A. M. Elaiw graduated in mathematics at Sohag University in 1992. He received his Ph.D. degree in stabilization of sampled-data nonlinear systems form Budapest University of Technology and Economics in 2005. Since 2005, he has been with Al-Azhar University, Assiut, Egypt. Currently he is a professor at Department of Mathematics, Faculty of Science, King Abdulaziz University, Saudi Arabia. His research interests include nonlinear control systems, power systems, optimization, mathematical biology and fluid dynamics.

A. S. Alofi received the B.Sc. degree in Mathematics from King Abdulaziz University, Jeddah, KSA. He received the M.Sc. degree and the Ph.D. degree from Durham University, Durham, UK. He was the chairman of Mathematics Department. In the period from 2015 to 2019, he was the Vice-Dean of the Faculty of Sciences. His research interests include nonlinear control systems, dynamics systems, mathematical biology and differential equations.