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A Mathematical Model for Accessing Dengue Hemorrhagic Fever in Infants

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ABSTRACT. A mathematical model was developed to describe the dynamics of the primary infection of dengue virus in infants who were born to a mother immune to some serotype of the dengue virus. The model is given by a system of nonlinear ordinary differential equations with time-dependent variables for the number of dengue virus antibodies of the infant transferred from their immune, uninfected, and infected monocytes and dengue virus. The mathematical analysis was carried out where the conditions for the existence of the disease-free equilibrium and the endemic equilibrium were established. The numerical simulations were performed considering different scenarios for a basic reproductive number, $\mathscr{R}_0$, illustrating the global convergence of the numerical results for the equilibrium points. The results are in agreement with our derived global stability analysis. It can be concluded that dengue hemorrhagic fever in infants could occur in the peaks observed for the infected monocytes and dengue virus.

Keywords: system of differential equations, global analysis, virus, infant, numerical simulations.

1 INTRODUCTION

The dengue virus (DENV) has four different serotypes (DENV 1-4), and any of these can cause different severities, such as dengue (DF) in the classic form and dengue hemorrhagic fever (DHF) in the severe form.

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DENV is the most important arbovirus that affects man. Currently, DHF affects most Latin American and Asian countries as well as regions of tropical and subtropical climates, and has become a major cause of hospitalization and death among children and adults in these regions [18].

In the first infection with a serotype, the individual acquires antibodies specific to that serotype. In the second heterologous infection, DHF can develop. Secondary infections can cause 40 times more DHF cases than primary infections [5]. The humoral immune response that controls the viral infection and dissemination is the cellular immune response required for eliminating an established infection.

With respect to the immunological aspects of the disease, an individual's recovery from infection by one of the serotypes provides lifelong immunity after primary infection by the homologous serotype and short immunity by the heterologous serotype. However, immunity or cross-protection for individuals recovering from a primary infection who become susceptible to other serotypes is only partial and temporary. [18]. Subsequent infections with other serotypes substantially increase the risk of contracting DHF [13]. The mechanisms responsible for the severity of secondary dengue infections are not completely understood.

One hypothesis postulates that cross-reactive antibodies are responsible for enhancing the infection in a mechanism called antibody-dependent enhancement (ADE) [2]. The ADE makes vaccination difficult, as failure to immunize against all strains exposes the population to the risk of more severe infections [12]. In adults and children, the ADE process works as follows: the susceptible individual is first infected with one of the DENV serotypes and produces neutralizing antibodies specific to that serotype.

Following the elimination of the primary infection, specific antibodies persist in the body and, if another infection occurs with a second distinct serotype, the primary infection antibodies bind to this second serotype and do not neutralize it, facilitating the penetration of the viral particles from the new serotype and causing an increase in the number of infected cells and free virus.

Although the main form of transmission of the disease is caused by the bite of an infected female mosquito, there are reports of vertical transmission of dengue [9]. Vertical transmission of DENV and anti-DENV immunoglobulins (Ig) are pointed out as being responsible for the pathogenesis and its manifestations in infants [7, 13].

In particular, DHF may occur in infants upon primary infection with one of the serotypes due to the vertical transfer of specific antibodies from their DENV-immune mother [7]. These specific antibodies play an important role in the infants? lives, protecting during the first months of life, but then, as their serum levels decrease, the chance of infection may increase through the ADE [12]. The number of severe cases of DHF occurring in infants (< 1 year old) born to dengue-immune mothers is increasing [6, 7, 13].

The studies involving the concepts of immunology in the problem of DHF in infants are far from ideal. Furthermore, in terms of mathematical modeling, it is not commonly studied. The construction of a compartmental mathematical model can be an important tool, as well as analyzing

and understanding the behavior of these immunological aspects associated with the problem of DHF in infants. The main objectives of the work presented here are to propose and study a mathematical model that mimics dengue disease in infants, considering passive immunity.

The paper is organized as follows: in Section 2, we begin by discussing the immunological mathematical model, taking into account passive immunity and also presenting the global stability analysis. In Section 3 we present the numerical simulations, as illustrations to the mathematical analysis and to understand the dynamics of dengue hemorrhagic fever in infants. Finally, in Section 4 we present concluding remarks.

2 MATHEMATICAL MODEL

The main hypothesis considered in the mathematical modeling is infant passive immunity, which is acquired by transferring specific antibodies from their immune mother. The mathematical model, based on [1], is described by a system of nonlinear ordinary differential equations. Table 1 shows the state variables for the mathematical model.

Table 1: The state variables.

Variable	Description	Unit
A	number of antibodies of the infants	[molecules] $[\text{ml}]^{-1}$
X	number of uninfected monocytes	[cells] $[\text{ml}]^{-1}$
Y	number of infected monocytes	[cells] $[\text{ml}]^{-1}$
V	number of free immature DENV	[RNA copies] $[\text{ml}]^{-1}$

In this paper, passive immunity is modeled considering the variable A, where $\alpha_A A$ is the natural decay at the rate of $\alpha_A > 0$ and ηAV is the antibody neutralization, consumed at a rate $\eta > 0$, due to their contact with DENV.

The dynamics of the uninfected monocytes, X, is modeled by $\Omega - \mu_X X$, where $\Omega > 0$ and $\mu_X > 0$ are the rates of production and mortality of the monocytes, respectively. The term βXV represents the DENV infection. Then, uninfected monocytes in contact with the virus, V, are infected, Y, at a rate $\beta > 0$. The term $\mu_Y Y$ is the natural decay of the infected monocytes with the rate $\mu_Y > 0$.

We are assuming that the virus infects new cells and is produced inside the monocytes, according to the term kY where k is the production rate of the new viruses. The DENV is eliminated with the rate $\delta_V > 0$ and is neutralized with a rate $\gamma > 0$ being the dynamics described by the term γVA [12]. Figure 1 illustrates the complete dynamics as described above.

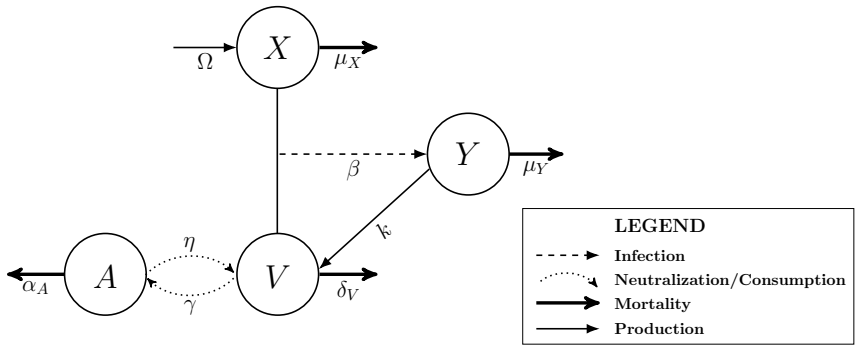

Figure 1: Compartmental model diagram.

According to the above premises, the mathematical model is given by

$$\begin{cases} \dfrac{dA}{dt} &= -\alpha_A A - \eta AV \\ \dfrac{dX}{dt} &= \Omega - \mu_X X - \beta XV \\ \dfrac{dY}{dt} &= \beta XV - \mu_Y Y \\ \dfrac{dV}{dt} &= kY - \delta_V V - \gamma VA \end{cases} . \tag{2.1}$$

The biological parameters of the model (2.1) are shown in Table 2.

Table 2: Summary of model parameters, their description and range of values.

Parameter	Description	Range of values/Unit.	Reference
k	DENV production rate	$10^4 - 10^7$ [RNA copies] [cells]$^{-1}$ [day]$^{-1}$	[8]
$\log(2)\mu_X^{-1}, \log(2)\mu_Y^{-1}$	susceptible and infected cells half-life	0.1 - 30 [day]$^{-1}$	[4], [11]
$\log(2)\alpha_A^{-1}$	antibodies half-life	$(0.014 - 1.5) \times 10^3$ [day]$^{-1}$	[19]
Ω	rate of production of susceptible cells	$4 \times 10^3 - 17.5 \times 10^6$ [cells]$^{-1}$ [day]$^{-1}$	[4]
$\log(2)\delta_V^{-1}$	viral particles half-life	$(2.5 - 17.2) \times 24^{-1}$[day]$^{-1}$	[12]
β	infection rates of X	$10^{-10} - 10^{-8}$ [ml] [RNA copies]$^{-1}$[day]$^{-1}$	[12]
η	antibody neutralizing consumption	$(0.09 - 1) \times 10^{-8}$ [ml] [RNA copies]$^{-1}$[day]$^{-1}$	–
γ	antibody neutralization rate	8×10^{-10} [ml] [molecules]$^{-1}$[day]$^{-1}$	[12]

2.1 Mathematical Analysis

The next section presents the positivity of state variables, the model-associated equilibria 2.1, and the local and global stability analysis of the equilibria.

2.1.1 Positivity Analysis

This subsection is devoted to establishing the positivity of all state variables in the model. Since it is related to a biological population problem, the positivity of the model 2.1 is analyzed with the following initial conditions given by the $\mathscr{P}^+$ set.

$$\mathscr{P}^+ = \left\{ \begin{array}{l} (A,\, X,\, Y,\, V) \in \mathbb{R}^4 : A(0) = A_0 \geq 0, \quad X(0) = X_0 \geq 0, \\ Y(0) = Y_0 \geq 0 \quad \text{and} \quad V(0) = V_0 \geq 0 \end{array} \right\}. \tag{2.2}$$

In the hyperplane $AYV = \left\{(A,X,Y,V) \in \mathbb{R}^4 : X = 0\right\}$, the system (2.1) can be rewritten as:

$$\left\{ \begin{array}{rcl} \dfrac{dA}{dt} & = & -\eta AV - \alpha_A A \\ \dfrac{dX}{dt} & = & \Omega \\ \dfrac{dY}{dt} & = & -\mu_Y Y \\ \dfrac{dV}{dt} & = & kY - \delta_V V - \gamma VA \end{array} \right. . \tag{2.3}$$

In the second equation of (2.3), we have $\frac{dX}{dt} = \Omega > 0$ since all parameters are positive. Then, X strictly increases in $\mathscr{P}^+$.

In the hyperplane $AXY = \left\{(A,X,Y,V) \in \mathbb{R}^4 : V = 0\right\}$. For $\frac{dV}{dt} = kY > 0$ it is necessary to verify if $Y > 0$. Then, we need to analyse the differential equation $\frac{dY}{dt} = -\mu_Y Y$. As $Y = Y_0 e^{-\mu_Y t} > 0$, thus conclude $\frac{dV}{dt} > 0$. Thus, V is non-negative in $\mathscr{P}^+$.

In the hyperplane $AXV = \left\{(A,X,Y,V) \in \mathbb{R}^4 : Y = 0\right\}$, we obtain $X > 0$ and $V > 0$. Then, $\frac{dY}{dt} = \beta XV > 0$, and Y remains positive in $\mathscr{P}^+$.

The hyperplane $XYV = \left\{(A,X,Y,V) \in \mathbb{R}^4 : A = 0\right\}$ is an invariant subspace, since we obtain $\frac{dA}{dt} = 0$. Then, $A_0 > 0$ in $\mathscr{P}^+$.

Thus, we conclude that A, X, Y, and V are all positives in the set $\mathscr{P}^+$.

2.1.2 Existence and asymptotic stability of the stationary states

Let $(A^\star, X^\star, Y^\star, V^\star)$ be an equilibrium of the system 2.1. It must satisfy:

$$\left\{ \begin{array}{ll} -\alpha_A A^\star - \eta A^\star V^\star & = 0 \\ \Omega - \mu_X X^\star - \beta X^\star V^\star & = 0 \\ \beta X^\star V^\star - \mu_Y Y^\star & = 0 \\ kY^\star - \delta_V V^\star - \gamma V^\star A^\star & = 0 \end{array} \right. . \tag{2.4}$$

Solving the 2.4 system, we obtain two equilibrium points: a disease-free P_0 and an endemic P_1.

2.1.3 The basic reproductive number $\mathscr{R}_0$ and the local asymptotic stability of the disease-free steady state P_0

In mathematical epidemiology, the basic reproduction number denoted by $\mathscr{R}_0$, is a threshold value to determine whether or not the disease disappears.

This value is the average number of secondary cases generated by a primary infected individual, over the course of its infectious period, introduced in a wholly susceptible population [15]. Indeed, if $\mathscr{R}_0 < 1$ the disease extinguishes, while for $\mathscr{R}_0 > 1$ it persists.

The next-generation matrix method [3, 15] is the most common procedure to determine $\mathscr{R}_0$. In our case, system 2.1 has two infected states, Y and V, and the *disease-free equilibrium* is given by:

$$P_0 = \left(0, \frac{\Omega}{\mu_X}, 0, 0\right), \tag{2.5}$$

which represents the state without infection that always exists. The linearization of the differential equation related to (Y,V) around the disease-free steady state P_0 gives the following system:

$$\begin{cases} \dfrac{dY}{dt} &= \beta\left(\frac{\Omega}{\mu_X}\right)V - \mu_Y Y \\ \dfrac{dV}{dt} &= kY - \delta_V V \end{cases}.$$

The matrices K and T are given by:

$$K = \begin{pmatrix} 0 & \beta\frac{\Omega}{\mu_X} \\ 0 & 0 \end{pmatrix} \quad T = \begin{pmatrix} -\mu_Y & 0 \\ k & -\delta_V \end{pmatrix}, \quad \text{and} \quad T^{-1} = \begin{pmatrix} -\frac{1}{\mu_Y} & 0 \\ -\frac{k}{\mu_Y\delta_V} & -\frac{1}{\delta_V} \end{pmatrix}.$$

With this method, $\mathscr{R}_0$ is defined as the dominant eigenvalue, ρ, of a matrix $-KT^{-1}$, where K is the matrix of the infection terms and T the matrix of the transition terms:

$$\mathscr{R}_0 := \rho\left(-KT^{-1}\right),$$

from which we obtain the basic reproduction number

$$\mathscr{R}_0 = \frac{1}{\mu_Y}\frac{\Omega}{\mu_X}\frac{k}{\delta_V}\beta, \tag{2.6}$$

where each infected cell produces k free virus an average during its lifetime μ_Y^{-1}, which during the time period δ_V^{-1} infects a fraction $\frac{\Omega}{\mu_X}$ of healthy cells at a rate β.

In summary, $\mathscr{R}_0$ is the average number of newly-infected cells produced by an infected primary cell during its lifetime.

Theorem 2.1. *The disease-free equilibrium, P_0, is locally asymptotically stable if $\mathscr{R}_0 < 1$ and unstable if $\mathscr{R}_0 > 1$.*

Proof. Let the matrix $J(P_0)$, the Jacobian matrix associated with the model 2.1 analyzed at the equilibrium point P_0, given by:

$$J(P_0) = \begin{vmatrix} -\alpha_A & 0 & 0 & 0 \\ 0 & -\mu_X & & \beta\frac{\Omega}{\mu_X} \\ 0 & 0 & -\mu_Y & -\beta\frac{\Omega}{\mu_X} \\ 0 & 0 & k & -\delta_V \end{vmatrix}.$$

The characteristic equation is given by:

$$\det(\lambda I - J(P_0)) = \begin{vmatrix} \lambda+\alpha_A & 0 & 0 & 0 \\ 0 & \lambda+\mu_X & & -\beta\frac{\Omega}{\mu_X} \\ 0 & 0 & \lambda+\mu_Y & \beta\frac{\Omega}{\mu_X} \\ 0 & 0 & k & \lambda+\delta_V \end{vmatrix} = 0,$$

in which, the eigenvalues are $-\alpha_A - \mu_X$. The other eigenvalues are given by the characteristic polynomial:

$$\lambda^2 + \lambda(\mu_Y + \delta_V) - k\beta\frac{\Omega}{\mu_X} = 0. \tag{2.7}$$

By the Routh-Hurwitz criteria, quadratic polynomials have negative eigenvalues if, and only if, the coefficients a_1 and a_2 are positives. Then, we can rewrite the characteristic polynomial (2.7) as follows:

$$\lambda^2 + a_1\lambda + a_2,$$

in which

$$\begin{aligned} a_1 &= \mu_Y + \delta_V > 0, \\ a_2 &= \delta_V\mu_Y - k\beta\frac{\Omega}{\mu_X} > 0. \end{aligned}$$

Since a_1 and a_2 are positives, by the Routh-Hurwitz criterion the roots are negative if, and only if, $\mathscr{R}_0 < 1$.

2.1.4 Existence of endemic steady state P_1

By the 2.4 system, we have that the endemic equilibrium point P_1, in terms of $\mathscr{R}_0$, is given by:

$$P_1 = \left(0, \quad \frac{\Omega}{\mu_X}\frac{1}{\mathscr{R}_0}, \quad \frac{\mu_X\delta_V}{k\beta}(\mathscr{R}_0 - 1), \quad \frac{\mu_X}{\beta}(\mathscr{R}_0 - 1)\right).$$

The Jacobian matrix J of the model 2.1 evaluated at P_1 is:

$$J(P_1) = \begin{vmatrix} -(\eta V^\star + \alpha_A) & 0 & 0 & -\eta A^\star \\ 0 & -(\mu_X + \beta V^\star) & 0 & -\beta X^\star \\ 0 & \beta V^\star & -\mu_Y & \beta X^\star \\ -\gamma V^\star & 0 & k & -(\delta_V + \gamma A^\star) \end{vmatrix}.$$

Similarly, we have the endemic equilibrium point associated at characteristic equation:

$$\det(\lambda I - J(P_1)) = (\eta V^\star + \alpha_A + \lambda)\mathscr{B} = 0,$$

where $\mathscr{B} = (\mu_X + \beta V^\star + \lambda)(\lambda^2 + \lambda(\mu_Y + \delta_V) + \mu_Y\delta_V - k\beta X^\star) + k\beta^2 X^\star V^\star$ and I are the identity matrix. One of its solutions is given by:

$$\lambda = -\eta V^\star - \alpha_A$$

and the other satisfies

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

where

$$a_1 = \mu_Y + \delta_V + \mu_X\mathscr{R}_0, \quad a_2 = \mu_X\mathscr{R}_0(\mu_Y + \delta_V) \quad \textit{and} \quad a_3 = \mu_X\mu_Y\delta_V\mathscr{R}_0.$$

Considering again that all parameters are positive, if $\mathscr{R}_0 > 1$, the Routh–Hurwitz conditions for the stability of the linearized system are satisfied in $\mathscr{P}^+$, since

$$\begin{aligned} a_1 &= \mu_Y + \delta_V + \mu_X\mathscr{R}_0 > 0; \\ a_3 &= \mu_X\mu_Y\delta_V\mathscr{R}_0 > 0; \\ a_1a_2 - a_3 &= (\mu_Y + \delta_V + \mu_X\mathscr{R}_0)(\mu_X\mathscr{R}_0(\mu_Y + \delta_V)) - \mu_X\mu_Y\delta_V\mathscr{R}_0 \\ &= 2\mu_X\mu_Y\delta_V\mathscr{R}_0 + \mu_X\mathscr{R}_0(\mu_Y^2 + \delta_V^2) + (\mu_X\mathscr{R}_0)^2(\mu_Y + \delta_V) - \mu_X\mu_Y\delta_V\mathscr{R}_0 > 0. \end{aligned}$$

Thus, $a_1a_2 > a_3$, which results in P_1, is asymptotically stable, and P_0 is unstable.

2.1.5 Global Stability

Here we present the global stability for the endemic equilibrium P_1, based on the references [10, 14, 16]. Let

$$\begin{aligned} L(\mathscr{W}) &= h_1\left(X - X^\star - X^\star\ln\left(\frac{X}{X^\star}\right)\right) + h_2\left(Y - Y^\star - Y^\star\ln\left(\frac{Y}{Y^\star}\right)\right) \\ &+ h_3\left(V - V^\star - V^\star\ln\left(\frac{V}{V^\star}\right)\right) + h_4A, \end{aligned}$$

with $\mathscr{W} = (A, X, Y, V) \in \mathbb{R}^{*4}_+$, $h_i,\ i = 1, \ldots 4$ and $L : \mathbb{R}^4 \to \mathbb{R}$. Note that, $L(0, X^\star, Y^\star, V^\star) = 0$.

We need to prove that $L(\mathscr{W}) > 0$. Let the $P(X) := X - X^\star - X^\star\ln\left(\frac{X}{X^\star}\right)$, $P(Y) := Y - Y^\star - Y^\star\ln\left(\frac{Y}{Y^\star}\right)$ and $P(V) := V - V^\star - V^\star\ln\left(\frac{V}{V^\star}\right)$, we will show that $P(X) > 0$ and the result follows analogously to $P(Y)$ and $P(V)$. Note that,

$$P(X) := X^\star\left(\frac{X}{X^\star} - 1 - \ln\left(\frac{X}{X^\star}\right)\right).$$

Let $x = \frac{X}{X^\star} > 0$, then $P(X) \geq 0$, since the function $g(x) = x - 1 - \ln(x)$ satisfies the following properties:

i) $g'(x) = 0 \Rightarrow \frac{x-1}{x} = 0 \Rightarrow x = 1$ is the only critical point;

ii) $g''(x) = \frac{1}{x^2} > 0$;

iii) $x = 1$ is the global minimal point;

iv) $g(1) = 0$.

Thus, $g(x) > 0$, $\forall x > 0, x \neq 1$. We also note that $A > 0$ and therefore $L(W) > 0$. It is important to note that $L(\mathscr{W}) \to +\infty$, if $||\mathscr{W}|| \to +\infty$, i.e., $L(\mathscr{W})$ is unbounded.

Let us now prove that $L'(\mathscr{W}) \leqslant 0$. The derivative of $L(\mathscr{W})$ is:

$$L'(\mathscr{W}) = h_1\left(1 - \frac{X^\star}{X}\right)X' + h_2\left(1 - \frac{Y^\star}{Y}\right)Y' + h_3\left(1 - \frac{V^\star}{V}\right)V' + h_4A'.$$

By means of (2.1)

$$\begin{aligned} L'(\mathscr{W}) &= h_1\left(1 - \frac{X^\star}{X}\right)(\Omega - \mu_X X - \beta XV) + h_2\left(1 - \frac{Y^\star}{Y}\right)(\beta XV - \mu_Y Y) \\ &+ h_3\left(1 - \frac{V^\star}{V}\right)(kY - \delta_V V - \gamma VA) + h_4(-\eta AV - \alpha_A A). \end{aligned}$$

Thus, considering $X' = 0$, $Y' = 0$ and $V' = 0$ at the equilibrium point, P_1, we get the following expressions

$$\Omega = \mu_X X^\star + \beta X^\star V^\star, \quad \mu_Y = \beta\frac{X^\star V^\star}{Y^\star} \quad \text{and} \quad \delta_V = k\frac{Y^\star}{V^\star},$$

since $A^\star = 0$ at the equilibrium point. Then,

$$\begin{aligned} L'(\mathscr{W}) &= -h_1\mu_X\frac{(X - X^\star)^2}{X} + h_1\beta X^\star V^\star - h_1\beta\frac{(X^\star)^2V^\star}{X} - h_1\beta XV + h_1\beta X^\star V \\ &+ h_2\beta XV - h_2\frac{Y^\star}{Y}\beta XV - h_2\beta\frac{X^\star V^\star}{Y^\star}Y + h_2\beta\frac{Y^\star}{Y}\frac{X^\star V^\star}{Y^\star}Y \\ &+ h_3kY - h_3k\frac{V^\star}{V}Y - h_3k\frac{Y^\star}{V^\star}V + h_3k\frac{V^\star}{V}\frac{Y^\star}{V^\star}V - \gamma h_3AV \\ &+ \gamma h_3\frac{V^\star}{V}AV + h_4(-\eta AV - \alpha_A A). \end{aligned}$$

Choosing

$$h_1 = h_2 = 1, \quad h_3 = \frac{\beta X^\star V^\star}{kY^\star} \quad \text{and} \quad h_4 = \frac{\gamma\beta X^\star V^\star V^\star}{\alpha_A kY^\star}.$$

Then,

$$\begin{aligned} L'(\mathscr{W}) &= -\mu_X \frac{(X-X^\star)^2}{X} + \beta X^\star V^\star - \beta \frac{(X^\star)^2 V^\star}{X} - \beta XV + \beta X^\star V \\ &+ \beta XV - \frac{Y^\star}{Y}\beta XV - \beta \frac{X^\star V^\star}{Y^\star}Y + \beta \frac{Y^\star}{Y}\frac{X^\star V^\star}{Y^\star}Y \\ &+ \left(\frac{\beta X^\star V^\star}{kY^\star}\right)kY - \left(\frac{\beta X^\star V^\star}{kY^\star}\right)k\frac{V^\star}{V}Y - \left(\frac{\beta X^\star V^\star}{kY^\star}\right)k\frac{Y^\star}{V^\star}V \\ &+ \left(\frac{\beta X^\star V^\star}{kY^\star}\right)k\frac{V^\star}{V}\frac{Y^\star}{V^\star}V - \gamma\left(\frac{\beta X^\star V^\star}{kY^\star}\right)AV \\ &+ \gamma\left(\frac{\beta X^\star V^\star}{kY^\star}\right)\frac{V^\star}{V}AV + \left(\frac{\gamma\beta X^\star V^\star V^\star}{\alpha_A kY^\star}\right)(-\eta AV - \alpha_A A). \end{aligned} \tag{2.8}$$

Since we need to prove that $L'(\mathscr{W}) \leqslant 0$, the positive terms from (2.8) need to be handled. Thus,

$$\begin{aligned} L'(\mathscr{W}) &= -\mu_X \frac{(X-X^\star)^2}{X} \\ &+ \beta X^\star V^\star \left(3 - \left(\frac{X^\star}{X} + \frac{VXY^\star}{V^\star X^\star Y} + \frac{YV^\star}{Y^\star V}\right)\right) \\ &- \frac{\beta}{k}\frac{X^\star V^\star}{Y^\star}\gamma AV - \frac{\gamma\beta X^\star V^\star V^\star}{\alpha_A kY^\star}\eta AV. \end{aligned}$$

Since

$$\frac{X^\star}{X}\frac{VXY^\star}{V^\star X^\star Y}\frac{YV^\star}{Y^\star V} = 1 \quad \text{and} \quad \frac{x_1+x_2+\cdots+x_n}{n} \geqslant (x_1x_2\cdots x_n)^{1/n},$$

then,

$$\frac{1}{3}\left(\frac{X^\star}{X} + \frac{VXY^\star}{V^\star X^\star Y} + \frac{YV^\star}{Y^\star V}\right) \geqslant (1)^{1/3} = 1,$$

i.e.,

$$\left(\frac{X^\star}{X} + \frac{VXY^\star}{V^\star X^\star Y} + \frac{YV^\star}{Y^\star V}\right) \geqslant 3.$$

Therefore, $L'(\mathscr{W}) < 0$.

We also need to analyse the set of points where $L'(\mathscr{W}) = 0$. This occurs if, and only if,

$$X = X^\star, \qquad \frac{X^\star}{X} + \frac{VXY^\star}{V^\star X^\star Y} + \frac{YV^\star}{Y^\star V} = 3 \quad \text{and} \quad A = 0. \tag{2.9}$$

Since $X = X^\star$, then $\frac{dX}{dt} = 0$. From the second equation of (2.1), $V = V^\star$. Then, by the second equation of the (2.9)

$$\frac{Y}{Y^\star} + \frac{Y^\star}{Y} = 2,$$

if, and only if, $Y = Y^\star$.

Therefore, $L'(\mathscr{W}) = 0$ has only the equilibrium point $\mathscr{W} = (0, X^\star, Y^\star, V^\star)$ and thus $\mathscr{W}$ is globally stable.

3 NUMERICAL SIMULATIONS

Numerical simulations of the model 2.1 are presented here in order to illustrate the mathematical analysis performed in the previous sections and also to understand DENV passive immunity. To better understand our numerical results, let's first consider the general assumptions as follows:

- The age of the infant is considered to be 4 to 6 months [2];
- The initial amount of antibodies is given by A_0 in t_0;
- The initial time of the dengue infection in the infants is $t_0 = 0.0$.

We define parameter set as $\alpha_A = 0.0301$, $\mu_X = 0.0231$, $\mu_Y = 3.4657$ and $\delta_V = 10$ all in days^{-1}, $\Omega = 6 \times 10^3$ cells day^{-1}, $k = 1 \times 10^4$ RNA copies cells^{-1} day^{-1}, $\gamma = 8 \times 10^{-10}$ ml molecules^{-1} day^{-1}, $\eta = 1 \times 10^{-8}$ ml RNA copies^{-1} day^{-1} and $\beta = 4 \times 10^{-8}$ ml RNA copies^{-1} day^{-1}. This gives us $\mathscr{R}_0 = 2.997 > 1$ and the stability of the endemic equilibrium. The system 2.1 was solved using the Runge-Kutta fourth-order method with initial condition as $A_1(0) = 1 \times 10^4$ in molecules ml^{-1}, $X(0) = \Omega/\mu_X$ and $Y(0) = 3 \times 10^{-4}$ in cells ml^{-1}, and $V(0) = 357$ RNA copies ml^{-1}.

The scenario under study simulates primary infection by one of the dengue serotypes. $t = 0.0$ defines the time the infant is born and $A(0)$ is the number of maternal antibodies received until birthed by her immune mother.

Figure 2 shows the temporal evolution of the $A(t)$ antibody population, susceptible and infected cells, respectively $X(t)$ and $Y(t)$, and the dengue free virus $V(t)$. This figure also shows the behavior of the infection function, $I(t) = \beta X(t)V(t)$. The arrows indicate the moment when there is an increase in the number of infected cells, an increase in the infection function, and the appearance of peaks in $V(t)$, $Y(t)$ and $I(t)$, which occur at almost the same time. The mother's antibodies that are unable to neutralize the dengue virus can thus result in DHF. The dashed line in Figure 2 (c) of the virus population represents the limit of detection of the virus measured in plasma samples in a series of patients [17]. It is known that a large number of antibodies from immune mothers are able, to neutralize the virus and decrease V and Y (case of disease-free balance).

Figure 3 shows the sensitivity analysis for the $\mathscr{R}_0$ via *partial classification correlation coefficient* (PRCC). The input parameters were chosen from a uniform distribution using *latin hypercube sampling* (LHS). The value ranges for each parameter were taken from Table 2. A total of $N = 10000$ sets of parameters were drawn. The increase of Ω, β and k promotes the increase of $\mathscr{R}_0$. The opposite effect is observed for the parameters μ_X, μ_Y and δ_V. The order of importance related to the contribution of each parameter to $\mathscr{R}_0$ is $\{\Omega, \beta, k, \mu_X, \mu_Y\}$ with the largest contribution and δ_V with the lowest contribution.

The most important parameters are related to the production of susceptible cells, virus production, half-life of infected and susceptible cells, and infection rate, respectively.

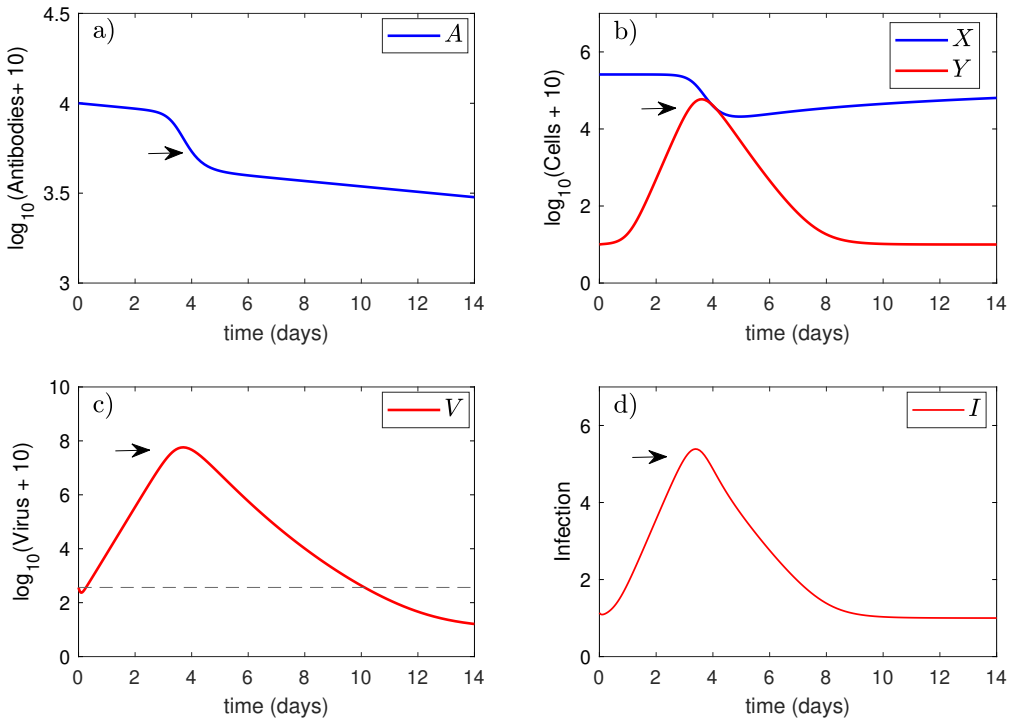

Figure 2: Temporal evolution of populations of (a) antibodies, (b) susceptible (X) and infected (Y) target cells, (c) virus and (d) infection I(t).

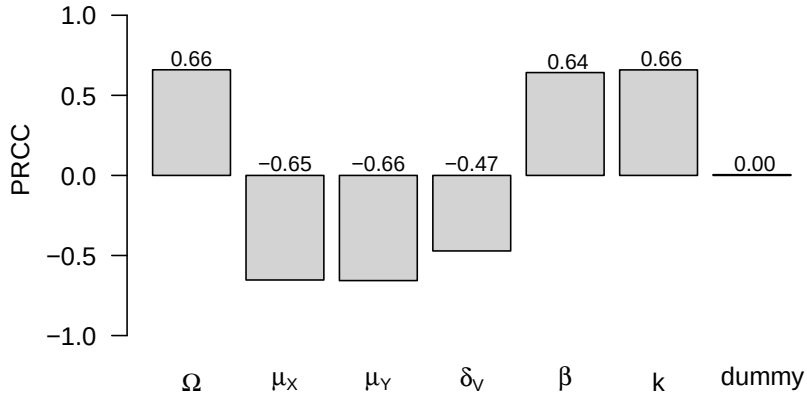

Figure 3: Sensitivity analysis of $\mathscr{R}_0$.

4 CONCLUDING REMARKS

In this paper, a nonlinear dimensional model described by ordinary differential equations was developed to understand the basic immunological aspects related to dengue hemorrhagic fever in infants.

This model has been analyzed mathematically. Two equilibria were found: the disease-free equilibrium (elimination of DENV) and the endemic equilibrium (persistence of DENV over time). A threshold called the basic reproductive number, $\mathscr{R}_0$ was found to be the key to the stability of these equilibria.

By the derived local stability analysis, $\mathscr{R}_0 < 1$ implies that the disease-free equilibrium point is locally asymptotically stable, which corresponds to DENV elimination. By the derived global stability analysis, $\mathscr{R}_0 > 1$ implies that the endemic equilibrium point is globally stable.

We performed the sensitivity analysis that allowed us to determine the parameters that most influenced the output, $\mathscr{R}_0$. In addition to the agreement with the analytical results, the reported numerical results were used to illustrate the dynamics generated by the model, supporting discussions of a biological nature.

In the scenario where there is the persistence of DENV (endemic balance), peak formations are observed. Due to these peaks and also the persistence of the virus in the host organism, under the hypothesis of passive immunity to DENV, it can be said that this behavior is an illustration of the occurrence of the severe case of the disease (that is, DHF in infants).

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