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## Maternal passive immunity and dengue hemorrhagic fever in infants

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**Abstract** To understand the role of maternal dengue-specific antibodies in the development of primary Dengue Hemorrhagic Fever (DHF) in infants, we investigated a mathematical model based on a system of nonlinear ordinary differential equations. In this model, we considered the exponential decay of maternal antibodies, the interactions between susceptible and infected target cells, the virus, and maternal antibodies. The neutralization and enhancement activities of maternal antibodies against the virus are represented by a function derived from experimental data and knowledge from medical literature. The analytic study of the model shows the existence of two equilibriums, a disease-free equilibrium and an endemic one. We performed the asymptotic stability analysis for the two equilibriums. The local asymptotic stability of the endemic steady state corresponds to the occurrence of DHF. Numerical results are also presented in order to illustrate the mathematical analysis performed, highlighting the most important parameters that drives the model dynamics. We defined the age at which DHF occurs as the time when the infection take-off, that means at the inflection point of the infected cell population. We showed that this age corresponds to the age at which maximum enhancing activity for dengue infection appears. This critical time for the occurrence of DHF is calculated from the model to be approximately 2 months after the time for maternal dengue neutralizing antibodies to degrade below a protective level, which correspond to what was observed in the experimental data from the literature.

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## 1 Introduction

Dengue virus is a flavivirus primarily transmitted by the hematophagous mosquitoes of genus *Aedes*. In human, the disease symptoms can range from an asymptomatic infection, or a classic Dengue Fever (DF), to severe manifestations such as Dengue Hemorrhagic Fever (DHF), or Dengue Shock Syndrome (DSS) [4, 22]. The transmission of the dengue virus to the human occurs after biting by an infected mosquito. The classic infection in human follows the Susceptible-Infected-Recovered (SIR) dynamics of most epidemiological diseases [2]. Four serotypes of dengue virus are known (DENV 1-4), and they differ by 30-35% in amino acid identity. Life-long immunity after a primary infection is obtained for sequential infections with the homologous serotype, but only a short period of cross-protective immunity is observed against a heterologous serotype. After this primary infection, a secondary one with a different serotype can result in DHF or DSS [16, 17]. Tertiary or quaternary infections are rarely reported, suggesting that the broad range of polyclonal antibodies, generated after two sequential infections with different serotypes, can promote an effective tetravalent protection [29].

The cofactors associated with the severity of secondary dengue infection are still not clear. One hypothesis postulates that cross-reactive antibodies are responsible for the enhancement of the infection, in a phenomenon called Antibody-Dependent Enhancement (ADE) [4]. The explanation is that the pre-existing antibodies against a different serotype of DENV, from a previous infection, bind to the heterologous DENV increasing viral internalization into Fc-receptor-bearing target cells such as monocytes, macrophages and dendritic cells. Data from published studies [18, 19, 23] showed a high number of severe cases occurring in infants (< 1 year of age) born from dengue-immune mothers. In a later publication, [3] reported that the age-specific incidence of infant DHF was 0.5 per 1000 persons over the age of 3-8 months, and it disappeared by age the 9 months. These infants are supposed to develop DHF after a primary infection with DENV. The observed distribution of DHF cases with regarding to the age suggests the existence of a window period of time (between 3-8 months for [3] and between 6-8 months for [18]) in which the infant has levels of maternal antibody concentration (IgG) that are not able to neutralize the virus, but are capable of enhancing DENV infection [7, 24, 26].

The kinetics of both antibody and dengue virus during natural infections has been studied in the recent literature [8, 9]. In these two papers, ordinary differential systems model the dynamics of interaction among susceptible target cells, infected target cells, free virus and antibody levels. The models were fitted to temporal series of virus RNA titer and antibody (IgG and IgM) titers of primary and secondary DENV infections in adults. The authors concluded

that models in which antibody acts either on the virus or on the infected cells can explain the dynamics of viral clearance. They also showed that the variation in model parameters between primary and secondary cases is consistent with the theory of ADE. Besides humoral immune response, other approaches considered the contribution of cellular immune response and cytokines on virus dynamics, exploring the thresholds for the existence and stability of the different model's equilibriums [1]. Although this study addresses only the primary infection, it was able to show that T-cell mediated cytokines play also an important role in virus clearance. Starting with a target cell limited model and adding complexity such as innate, cellular and humoral immune response (by a re-parametrization of the parameter that measures viral infectivity), [25] discussed the contribution of infected and T-cells to disease severity, highlighting the importance of within-host dynamics early in the infection to predict the disease severity. In [5], analytical thresholds for the basic reproductive number of virions and an ADE weakening factor were established. The authors discussed the probability of ADE occurrence in several scenarios with focus on the disease dynamics, not on its equilibrium values, stressing the importance of the size of the initial inoculation of the virus. They conclude that the ADE phenomenon is a trade-off between the strength of proliferation of memory cells and apoptosis of infected macrophages.

The main difficulty associated with the development of mathematical models to study the immunology of dengue's infection is the fact that the available data are obtained during the period of viremia, so the initial dynamic of the infection disease is lost. In addition, the occurrence of ADE in adults is associated with the preexistence of memory cells from a primary infection and its interaction with the secondary response triggered by the secondary heterologous infection [16]. For children, a bimodal distribution with regarding to age at presentation of DHF is observed. The first peak occurs at 6-8 months, and is mostly observed during primary infections; the second one occurs in infants at  $> 3$  years old and is related to secondary infections [18]. Data from [21] show that the increased risk of DHF in infants from dengue-immune mothers correlates positively with the decline in maternal antibodies received at birth. The hypothesis is that maternal dengue antibodies play a dual role by first protecting, and later increasing the risk of development of DHF in infants. An interesting observation is that the critical time for the occurrence of DHF is almost 2 months after the estimated time in which maternal antibodies degrade below a protective level (see also [6, 19]). With this in mind, we propose a mathematical model to assess the role of maternal dengue-specific antibodies in the development of DHF in infants. As far as we know, this is the first mathematical model with this objective.

In particular, the model presented in our work is able to capture all the features described previously, proposing an explanation for the biological mechanisms behind the ADE phenomena in infants, based on the initial concentration of maternal antibodies received by the infant at born, the strength of the competition between virus neutralization and infection enhancement promoted by antibodies, the fitness of the virus, and the mounting of an effective

immunological response that depend on the infant's age. The proposed ordinary differential system models interactions among susceptible and infected target cells, virus, and antibodies through bilinear and trilinear terms. An enhancement and neutralization functions are introduced, both inspired by experiments in vitro [10,13]. The reproductive number of the virus was obtained and a sensitivity analysis showed that the mortality rate of the susceptible target cells is the most important parameter that determine the model dynamics driven the disease to an extinction or an endemic state. Besides, the model can be reparametrized to four parameters, where three of them determine the set up time at which DHF occurs. Surprising, the DHF characterizes a huge change on the behavior of the system and appears as a sharp increase on the number of infected cells, and virus population.

## 2 The Model

A compartmental model is developed to investigate the occurrence of DHF in infants ( $< 1$  year old), born from dengue-immune mothers, during their first dengue infection. Based on observed epidemiological and laboratory data [10,13,21], and on the knowledge of immunological aspects of the disease, the model considers the interaction among maternal dengue antibodies  $B$ , susceptible baby target cells (such as monocytes and macrophages)  $X$ , infected baby cells by dengue virus  $Y$  and free dengue virus  $V$ . We assume that these variables are measured as concentration - number of molecules per unit of volume.

The maternal dengue antibodies are acquired passively by the babies from dengue-immune mothers during pregnancy [7,20,24]. The population of maternal antibodies decays exponentially in the absence of dengue virus ( $V = 0$ ) at rate  $\alpha$  and is consumed in the presence of the DENV at rate  $\nu$  per virion. The susceptible target cells are produced at a constant rate  $A$  in the bone marrow, get invaded by the dengue virus at a rate  $E(B)$ , and get infected at rate  $cE(B)$  per virion, where  $B$  is the maternal antibody concentration in the baby. The natural mortality rate  $\mu_1$  keeps the susceptible population of cells at homeostasis. The population of infected cells decay with rate  $\mu_2 \geq \mu_1$  (natural mortality plus additional mortality due to the infection). Free virus is produced by infected cells at rate  $k$ , has a constant natural mortality rate  $\delta$ , and is consumed by the antibodies at rate  $\gamma$  per antibody. The virus can infect the susceptible target cells even in the absence of antibodies ( $B = 0$ ). We denote by  $E_0$  the rate of invasion of the susceptible target cells by the free

virus. The resulting nonlinear ordinary differential system is given by

$$\begin{cases} \frac{dB}{dt} = -\alpha B - \nu BV, \\ \frac{dX}{dt} = A - \mu_1 X - cE(B) VX, \\ \frac{dY}{dt} = cE(B) VX - \mu_2 Y, \\ \frac{dV}{dt} = kY - (\gamma B + E_0)V - \delta V, \end{cases} \quad (1)$$

where  $E(B)$  has the following (biologically suggested) expression

$$E(B) = (\gamma B + E_0)e^{-\beta\gamma B}.$$

The model can be reparametrized, given that  $C = \gamma B$ . Therefore

$$\begin{cases} \frac{dC}{dt} = -\alpha C - \nu CV, \\ \frac{dX}{dt} = A - \mu_1 X - cE(C) VX, \\ \frac{dY}{dt} = cE(C) VX - \mu_2 Y, \\ \frac{dV}{dt} = kY - (C + E_0)V - \delta V, \end{cases} \quad (2)$$

with, by using the same notation for the parametrized function  $E$ ,

$$E(C) = (C + E_0)e^{-\beta C}.$$

The neutralization rate is defined as

$$N(C) = C + E_0 - E(C) = (C + E_0)(1 - e^{-\beta C}).$$

The explanation of these expressions is as follows. The term  $C + E_0$  corresponds to the rate at which the virus is no longer free. A part,  $E(C)$ , corresponds to the rate of invasion of susceptible target cells by the virus and the other part,  $N(C)$ , to the rate of neutralization of the virus by the antibodies.  $N(0) = 0$  means that the virus cannot be neutralized without the presence of antibodies. However, as we said before, the susceptible target cells can be invaded by the virus even in the absence of antibodies ( $E(0) = E_0 > 0$ ). The maximum and the inflection points of the function  $E(C)$  are obtained at

$$C_1 = \frac{1 - \beta E_0}{\beta} > 0 \quad \text{and} \quad C_2 = C_1 + \frac{1}{\beta} = \frac{2 - \beta E_0}{\beta},$$

by

$$\max_{C \geq 0} E(C) = E(C_1) = \frac{1}{\beta} e^{-(1 - \beta E_0)} \quad \text{and} \quad E(C_2) = \frac{2}{\beta} e^{-(2 - \beta E_0)}.$$

The existence of  $C_1 > 0$  is guaranteed by the assumption  $\beta E_0 < 1$ . The function  $N(C)$  is an increasing function, has an inflection at the same point  $C_2$  as for the function  $E(C)$  and it satisfies

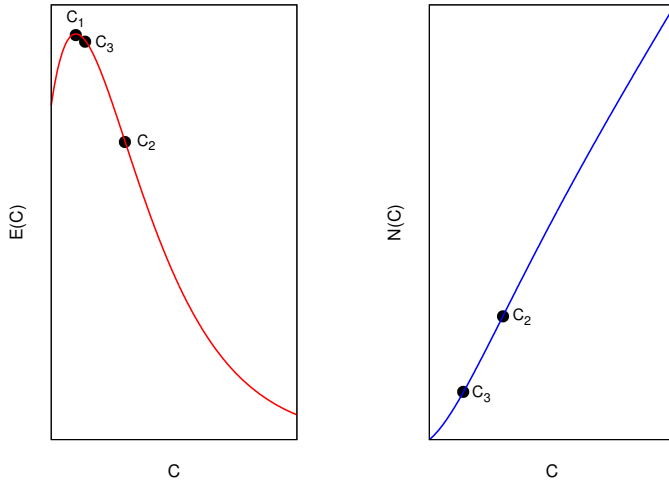
$$N(C_2) = \frac{2}{\beta}(1 - e^{-(2-\beta E_0)}) \quad \text{and} \quad \lim_{C \rightarrow +\infty} \frac{N(C)}{C + E_0} = 1.$$

Furthermore, the intersection point between the functions  $E(C)$  and  $N(C)$  is given by

$$C_3 = \frac{\ln(2)}{\beta} \quad \text{and} \quad E(C_3) = N(C_3) = \frac{1}{2\beta}(\ln(2) + \beta E_0).$$

It is easy to see that the intersection between the curves  $E(C)$  and  $N(C)$  happens before the common inflection ( $C_3 < C_2$ ). However,

$$C_1 < C_3 \quad \text{if and only if} \quad 1 - \ln(2) < \beta E_0 < 1.$$



**Fig. 1** The shape of the functions  $E(C)$  and  $N(C)$ , respectively, the rate of invasion of the susceptible target cells by the virus and the rate of neutralization of the virus by the antibodies. The amount of  $C$  increases from left to right, and  $E$  and  $N$  grows from bottom to top.  $C_1$ ,  $C_2$  and  $C_3$  are, respectively, the value of  $C$  at which  $E$  is maximum, the inflection point of the curves, and the point at which the intersection between  $E$  and  $N$  occurs.

Fig. 1 shows the behavior of the functions  $E(C)$  and  $N(C)$  and Table 1 summarizes the model's parameters, their units and their range values. The shape of  $E(C)$  was chosen to reproduce the ADE phenomena [10].

**Table 1** Summary of model parameters, their description and range of values [9, 6, 25, 15, 12, 21]. The parameters highlighted by \* were obtained by fitting several mathematical models to patient data [25].

Param.	Description	Range of values
$\alpha^{-1}$	antibody half-life	21 – 81 days
$A$	rate of production of susceptible target cells	$4.0 \times 10^3 - 17.5 \times 10^6$ cells ml <sup>-1</sup> days <sup>-1</sup>
$\mu_1^{-1}$	susceptible target cells half-life	1 – 30 days
$\mu_2^{-1}$	infected target cells half-life	1 – 30 days
$k$	rate of production of viral particle per infected cell	$10^4 - 10^7$ RNA copies cell <sup>-1</sup> days <sup>-1</sup>
$\delta^{-1}$	viral particle half-live	2.5 – 17.2 hours
$B_0$	anti-DENV IgG	30 – 8200 molecules ml <sup>-1</sup> (PRNT <sub>50</sub> )
$\nu$	virus-bound antibodies rate of decreasing of antibodies	$10^{-8}$ RNA copies <sup>-1</sup> ml days <sup>-1</sup> *
$c$	fraction of susceptible cells converted to infected cells	$(1.51-2.04) \times 10^{-10}$ RNA copies <sup>-1</sup> ml *
$\gamma$	fraction of virus-bound antibodies	0.5 ml molecules <sup>-1</sup> days <sup>-1</sup> (assumed)
$\beta$		0.09 days (assumed)
$E_0$	rate of invasion of the susceptible cells by the free virus	0.05 days <sup>-1</sup> (assumed)

### 3 Model analysis

We concentrate on the solutions of the first order differential system (2) with initial conditions given by

$$C(0) = \gamma B_0, \quad X(0) = X_0, \quad Y(0) = Y_0 \quad \text{and} \quad V(0) = V_0. \quad (3)$$

The local existence and uniqueness of the solutions are guaranteed by the regularity of the nonlinear function used in the second hand side of the system (2).

#### 3.1 Positivity and boundedness

The next result states and proves positivity and boundedness of the solutions of the system (2).

**Proposition 1** *The solutions of the system (2) associated with nonnegative initial conditions (3) are nonnegative and bounded on the interval  $[0, +\infty)$  (The result also means that we have the existence and uniqueness on the interval  $[0, +\infty)$ ).*



*Proof* We first show that the solution of (2) are nonnegative on its interval of existence. By integration of the equation of  $C(t)$  we obtain

$$C(t) = \gamma B_0 e^{-\alpha t - \nu \int_0^t V(s) ds}.$$

As  $\gamma B_0 \geq 0$ , then  $C(t)$  is nonnegative. For the nonnegativity of the solution  $X(t)$ , we assume by contradiction that there exists  $T > 0$  such that  $X(T) = 0$  and  $X(t) > 0$  for  $t < T$ . Then, we obtain  $X'(T) = A > 0$ . This is a contradiction. Then,  $X(t)$  is nonnegative. To prove the nonnegativity of the couple  $(Y, V)$ , we use the fact that  $(Y, V)$  satisfies a non-autonomous linear ordinary differential system. We assume by contradiction that there exists  $T > 0$  such that  $X(T) = 0$  or  $V(T) = 0$  and  $X(t) > 0$ ,  $V(t) > 0$  for  $t < T$ . If  $Y(T) = V(T) = 0$ , then  $Y(t) = V(t) = 0$  for all  $t$ . If  $Y(T) = 0$  and  $V(T) > 0$ , then  $Y'(T) > 0$ . If  $V(T) = 0$  and  $Y(T) > 0$ , then  $V'(T) > 0$ . In all cases, we have a contradiction. Then,  $(Y, V)$  is nonnegative.

Let's prove now that the solution is bounded on its interval of existence. It is clear that for all  $t \geq 0$ ,  $0 \leq C(t) \leq \gamma B_0$ . Which means that  $C(t)$  is bounded. Furthermore, by adding the equations of  $X$  and  $Y$ , we get

$$\frac{d}{dt}(X + Y) \leq A - \mu(X + Y) \quad \text{with } \mu = \min\{\mu_1, \mu_2\} > 0.$$

Then,

$$0 \leq X(t) + Y(t) \leq \max \left\{ X_0 + Y_0, \frac{A}{\mu} \right\}.$$

Consequently,  $X(t)$  and  $Y(t)$  are bounded. The last equation of (2) and the nonnegativity of  $C(t)$  implies that

$$V'(t) \leq kY(t) - (E_0 + \delta)V(t) \leq k \sup_{s \geq 0} (Y(s)) - (E_0 + \delta)V(t).$$

Then,

$$0 \leq V(t) \leq \max \left\{ V_0, \frac{k \sup_{s \geq 0} (Y(s))}{E_0 + \delta} \right\}.$$

We proved that the solutions are bounded on their interval of existence. This implies that they are defined on the interval  $[0, +\infty)$  and from the results established above, we can see that they are bounded on  $[0, +\infty)$ .

### 3.2 Existence of the steady states of the system

Let  $(C^*, X^*, Y^*, V^*)$  be a steady state of the system (2). After solving the associated algebraic system, we obtain two steady states

$$P_0 = \left( 0, \frac{A}{\mu_1}, 0, 0 \right)$$

that always exists and it is called the disease-free steady state, and

$$P_1 = \left( 0, \frac{\mu_2(E_0 + \delta)}{kcE_0}, Y^*, \frac{k}{E_0 + \delta} Y^* \right),$$

with

$$Y^* = \frac{A}{\mu_2} - \frac{\mu_1(E_0 + \delta)}{kcE_0},$$

that exists if and only if

$$c > c_0 := \frac{\mu_1\mu_2(E_0 + \delta)}{kAE_0}.$$

$P_1$  is called the endemic steady state and it corresponds to the persistence of the infection.

### 3.3 Local and global asymptotic stability of the disease-free steady state

As for infectious disease epidemiology, we use the basic reproduction number  $\mathcal{R}_0$  as a threshold value to determine whether or not the disease dies out. The Next Generation Matrix method, [11, 28], is the natural basis for the definition and calculation of  $\mathcal{R}_0$ . The system (2) has two infected states  $Y$  and  $V$  and two uninfected states,  $C$  and  $X$ . The component  $C$  has only 0 as steady state. Then, at the disease-free steady state  $Y = V = 0$ , we have necessarily  $C = 0$  and  $X = A/\mu_1$ . The linearization of the transmission of the disease (infection subsystem) around the disease-free steady state gives the following system

$$\begin{cases} Y' = -\mu_2 Y + cE_0 \frac{A}{\mu_1} V, \\ V' = kY - (E_0 + \delta)V. \end{cases} \quad (4)$$

It describes the production of new infected individuals with a rate  $cE_0 \frac{A}{\mu_1}$  and changes in the states of the infected individuals, including the death. We introduce the matrix  $K$  corresponding to transmissions and the matrix  $T$  corresponding to transitions as follows

$$K = \begin{pmatrix} 0 & cAE_0 \\ 0 & \mu_1 \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad T = \begin{pmatrix} -\mu_2 & k \\ 0 & -(E_0 + \delta) \end{pmatrix}.$$

The dominant eigenvalue of the matrix  $-KT^{-1}$  gives the basic reproduction number

$$\mathcal{R}_0 := \rho(-KT^{-1}) = \frac{A}{\mu_1} \times \frac{cE_0}{\mu_2} \times \frac{k}{E_0 + \delta}.$$

Observe that in the expression of  $\mathcal{R}_0$ , the term  $A/\mu_1$  is the average number of susceptible target cells,  $cE_0/\mu_2$  is the fraction of these susceptible cells that get infected, and  $k/(E_0 + \delta)$  is the average number of free virus produced by an infected cell. Therefore, when  $\mathcal{R}_0 > 1$  the infection is able to persist. Hence, we have the following result.

**Theorem 1** *The disease-free steady state  $P_0$  is locally asymptotically stable if  $\mathcal{R}_0 < 1$  and unstable if  $\mathcal{R}_0 > 1$ .*

We observe that

$$\mathcal{R}_0 < 1 \quad \text{if and only if} \quad c < c_0 := \frac{\mu_1 \mu_2 (E_0 + \delta)}{k A E_0}.$$

In fact, under the condition  $\mathcal{R}_0 < 1$  the disease-free steady state is globally asymptotically stable. Let's assume that  $\mu_1 = \mu_2 = \mu$ .

**Theorem 2** *If  $c < c_0$ , that is if  $\mathcal{R}_0 < 1$ , the disease-free steady state  $P_0$  is globally asymptotically stable.*

*Proof* We first prove the existence of a global attractor for all the solutions. Observe that

$$\frac{d}{dt}(X + Y) = A - \mu(X + Y).$$

Then,

$$\lim_{t \rightarrow +\infty} (X + Y)(t) = \frac{A}{\mu}.$$

Furthermore, we have

$$\frac{dC}{dt} = -\alpha C - \nu C V \leq -\alpha C.$$

This means that  $\lim_{t \rightarrow \infty} C(t) = 0$ . By continuity,  $\lim_{t \rightarrow \infty} E(C(t)) = E_0$ . Let  $\epsilon > 0$  small enough. There exists  $T_\epsilon > 0$  such that for all  $t \geq T_\epsilon$ , we have  $0 \leq C(t) < C_1$  and  $0 < E(C(t)) < E_0 + \epsilon$ . As the function  $\bar{E}$  is increasing on the interval  $[0, C_1)$ , then  $0 \leq C(t) < E^{-1}(E_0 + \epsilon)$ . Together these results imply that for all  $t \geq T_\epsilon$  the solutions lie in the set

$$\Omega_\epsilon = \left\{ (C, X, Y, V) \in \mathbb{R}_+^4 : 0 \leq C < E^{-1}(E_0 + \epsilon) \text{ and } 0 \leq X + Y < \frac{A}{\mu} + \epsilon \right\}.$$

By the latter result, for any choose of the initial conditions on the set  $\Omega_\epsilon$ , the solutions remain in  $\Omega_\epsilon$  and satisfy the system

$$\begin{cases} \frac{dC}{dt} & \leq -\alpha C, \\ \frac{d}{dt}(X + Y) & = A - \mu(X + Y), \\ \frac{dY}{dt} & \leq -\mu_2 Y + c(E_0 + \epsilon) \left( \frac{A}{\mu_1} + \epsilon \right) V, \\ \frac{dV}{dt} & \leq kY - (\delta + E_0)V. \end{cases}$$

The couple  $(Y, V)$  can be compared to the solutions  $(y, v)$  of the linear system

$$\begin{cases} \frac{dy}{dt} = -\mu y + c(E_0 + \epsilon) \left( \frac{A}{\mu} + \epsilon \right) v, \\ \frac{dv}{dt} = ky - (\delta + E_0)v, \end{cases} \quad (5)$$

since  $0 \leq Y(t) \leq y(t)$  and  $0 \leq V(t) \leq v(t)$ .

The characteristic equation of the system (5) is

$$\lambda^2 + (\mu + E_0 + \delta)\lambda + \mu(E_0 + \delta) + kc(E_0 + \epsilon) \left( \frac{A}{\mu} + \epsilon \right) = 0.$$

Thanks to Routh-Hurwitz stability criterion, the system (5) is asymptotically stable if and only if

$$\mu(E_0 + \delta) + kc(E_0 + \epsilon) \left( \frac{A}{\mu} + \epsilon \right) > 0.$$

This inequality is equivalent to

$$R_\epsilon := \frac{kc(E_0 + \epsilon) \left( \frac{A}{\mu} + \epsilon \right)}{\mu(E_0 + \delta)} < 1.$$

Since  $R_0 < 1$  and  $\epsilon > 0$  can be arbitrary chosen, there exists  $\epsilon > 0$  such that  $R_\epsilon < 1$ . As the set  $\Omega_\epsilon$  is globally attractive, we conclude that the disease-free steady state is globally asymptotically stable.

### 3.4 Local asymptotic stability of the endemic steady state

The linearization of the system (2) around the endemic steady state

$$P_1 = \left( 0, \frac{\mu_2(E_0 + \delta)}{kcE_0}, Y^*, \frac{k}{E_0 + \delta} Y^* \right),$$

with

$$Y^* = \frac{A}{\mu_2} - \frac{\mu_1(E_0 + \delta)}{kcE_0},$$

is given by the system

$$\begin{cases} \frac{db}{dt} = -(\alpha + \nu V^*)b, \\ \frac{dx}{dt} = -cE'(0)V^*X^*b - (\mu_1 + cE_0V^*)x - cE_0X^*v, \\ \frac{dy}{dt} = cE'(0)V^*X^*b + cE_0V^*x - \mu_2y + cE_0X^*v, \\ \frac{dv}{dt} = -V^*b + ky - (E_0 + \delta)v. \end{cases}$$

The characteristic equation is given by

$$(\lambda - \lambda_0) (\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0) = 0,$$

with

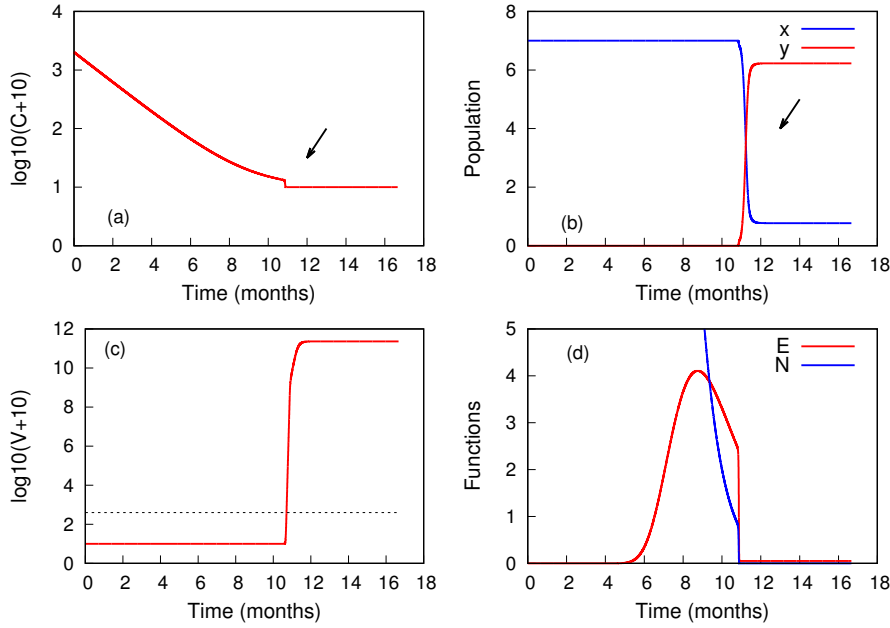
$$\begin{cases} \lambda_0 = -\alpha - \nu V^* < 0, \\ a_0 = \mu_1\mu_2(E_0 + \delta)(\mathcal{R}_0 - 1), \\ a_1 > 0, \quad a_2 > 0 \quad \text{and} \quad a_1a_2 - a_0 > 0. \end{cases}$$

We conclude, using the Routh-Hurwitz criterion, that  $P_1$  is locally asymptotically stable if and only if  $a_0 > 0$  that is if and only if  $\mathcal{R}_0 > 1$ .

#### 4 Numerical results

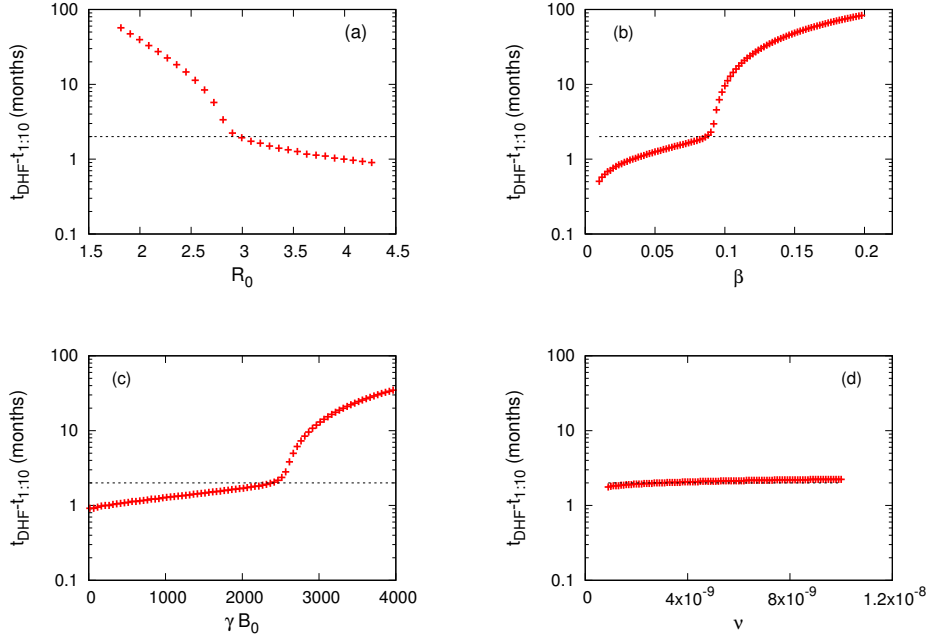
Fig. 2 shows the temporal evolution of the antibodies population,  $C(t) = \gamma B(t)$ , susceptible and infected target cells,  $X(t)$  and  $Y(t)$ , respectively, and free dengue virus,  $V(t)$ . System (2) was solved using a Runge-Kutta 4th order method. We chose the parameter set as  $\alpha = 0.0198$ ,  $\mu_1 = \mu_2 = 0.1429$ ,  $\delta = 0.22$ ,  $E_0 = 0.05$  which are in  $\text{days}^{-1}$ ,  $A = 10^6$  cells  $\text{ml}^{-1}$   $\text{days}^{-1}$ ,  $k = 10^4$  (RNA copies)  $\text{cell}^{-1}$   $\text{days}^{-1}$ ,  $c = 10^{-10}$  ml (RNA copies) $^{-1}$ ,  $\gamma = 0.5$  ml molecules $^{-1}$   $\text{days}^{-1}$ ,  $\beta = 0.09$  days,  $\nu = 10^{-8}$  ml (RNA copies) $^{-1}$   $\text{days}^{-1}$ . The initial conditions were for  $C(0) = 2000$  molecules  $\text{ml}^{-1}$   $\text{days}^{-1}$ ,  $X(0) = A/\mu_1$  cells  $\text{ml}^{-1}$ ,  $Y(0) = 0$  cells  $\text{ml}^{-1}$ ,  $V(0) = 100$  RNA copies  $\text{cell}^{-1}$ . We considered  $t = 0$  as the time at which the baby was born, and that  $C(0)$  is the amount of maternal antibodies received at birth. The arrows in Fig. 2(a) and Fig. 2(b) indicate the exact time when the mother antibodies fails to control the dengue virus and the DHF can occurs. The dashed line in Fig. 2(c) represents the assay limit of detection of virus population measured in serial plasma samples from patients [27]. In vitro experiments, virus titer depends on the concentration and type of antibody, incubation time, temperature, and inoculation size (for this, the limit of detection is below the one highlighted in Fig. 2(c) [14]).

Four parameters determine the dynamics of the ordinary differential system given by (2),  $\mathcal{R}_0$ ,  $\beta$ ,  $\nu$  and  $C(0)$  (observe that  $C(0) = \gamma B_0$  gives the initial amount of mother antibodies, and  $\mathcal{R}_0$  is a combination of other parameters). Fig. 3 shows the influence of each one of the four parameters on the difference defined by  $\Delta t = t_{DHF} - t_{1:10}$ , where  $t_{1:10}$  is the time at which the mother antibodies fails to control the virus and  $t_{DHF}$  is the time at which DHF occurs. Both are highlighted at Fig. 2 and they comprise the time during the evolution of the population,  $t_{1:10}$  for antibodies and  $t_{DHF}$  for infected cells, at which an abrupt change of the population dynamics is observed. For the antibodies population, it corresponds to the threshold limit for detection,  $B < 10$  molecules  $\text{ml}^{-1}$ , and for the infected cells it is defined numerically as the time at which the maximum of the derivative of this curve is observed (the inflection point of the  $Y$  curve). Observe that  $t_{DHF}$  can be seen (Fig. 2(d))



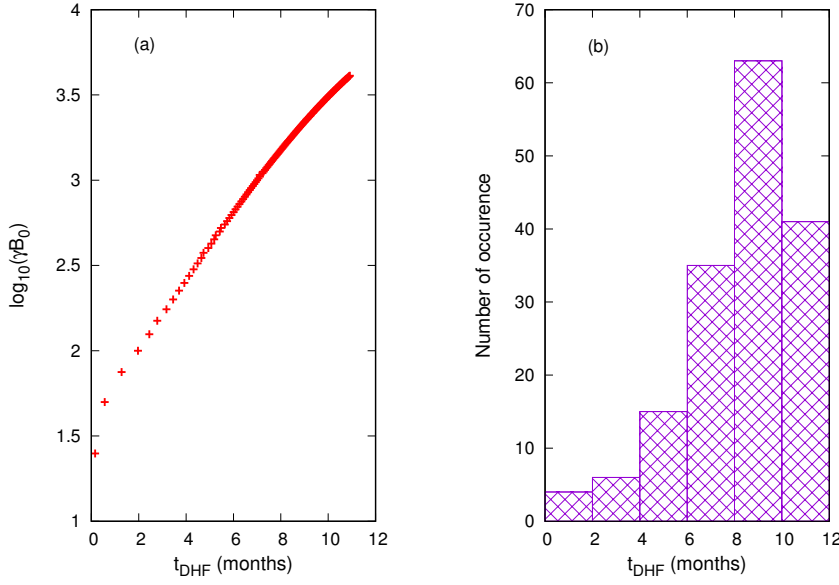
**Fig. 2** Temporal evolution of the populations of (a) antibodies, (b) susceptible and infected target cells, and (c) virus. In (d) temporal evolution of the functions  $t \mapsto E(C(t))$  and  $t \mapsto N(C(t))$ , where  $C \mapsto E(C)$  and  $C \mapsto N(C)$  are given by the two curves in Fig. 1. The parameters are  $\alpha = 0.0198$ ,  $\mu_1 = \mu_2 = 0.1429$ ,  $\delta = 0.22$ ,  $E_0 = 0.05$  all in  $\text{days}^{-1}$ ,  $A = 10^6$  cells  $\text{ml}^{-1}$   $\text{days}^{-1}$ ,  $k = 10^4$  (RNA copies)  $\text{cell}^{-1}$   $\text{days}^{-1}$ ,  $c = 10^{-10}$  ml (RNA copies) $^{-1}$ ,  $\gamma = 0.5$  ml molecules $^{-1}$   $\text{days}^{-1}$ ,  $\beta = 0.09$  days,  $\nu = 10^{-8}$  ml (RNA copies) $^{-1}$   $\text{days}^{-1}$ . The model was rescaled by  $x = X/A$  and  $y = Y/A$ . The initial conditions are  $C(0) = 2000$  molecules  $\text{ml}^{-1}$ ,  $X(0) = A/\mu_1$  cells  $\text{ml}^{-1}$ ,  $Y(0) = 0$  cells  $\text{ml}^{-1}$ ,  $V(0) = 100$  RNA copies  $\text{cell}^{-1}$ . The arrows in (a) and (b) indicate the exact time when the mother antibodies fails to control the dengue virus and the DHF can occurs. The dashed line in (c) represents the assay limit of detection of virus population measured in serial plasma samples from patients.

as the time in which the phenomenon of Antibody-Dependent Enhancement is set up. The main parameter set used in the simulation was  $\alpha = 0.0198$ ,  $\mu_1 = \mu_2 = 0.1429$ ,  $\delta = 0.22$ ,  $E_0 = 0.05$  which are in  $\text{days}^{-1}$ ,  $A = 10^6$  cells  $\text{ml}^{-1}$   $\text{days}^{-1}$ ,  $k = 10^4$  (RNA copies)  $\text{cell}^{-1}$   $\text{days}^{-1}$ ,  $c = 3.2 \times 10^{-11}$  ml (RNA copies) $^{-1}$ ,  $\gamma = 0.5$  ml molecules $^{-1}$   $\text{days}^{-1}$ ,  $\beta = 0.09$  days,  $\nu = 10^{-8}$  ml (RNA copies) $^{-1}$   $\text{days}^{-1}$ . The initial conditions were for  $C(0) = 2500$  molecules  $\text{ml}^{-1}$   $\text{days}^{-1}$ ,  $X(0) = A/\mu_1$  cells  $\text{ml}^{-1}$ ,  $Y(0) = 0$  cells  $\text{ml}^{-1}$ ,  $V(0) = 100$  RNA copies  $\text{cell}^{-1}$ . The variation of  $\mathcal{R}_0$  was done through changes on the parameter  $c$  from  $2 \times 10^{-11}$  to  $4.8 \times 10^{-11}$  (Fig. 3(a)). The parameter  $\beta$  varies from 0.01 to 0.2 (Fig 3(b)), the parameter  $C$  from 15 to 4100 (Fig 3(c)), and the parameter  $\nu$  varies from  $9 \times 10^{-10}$  to  $1 \times 10^{-8}$  (Fig 3(d)). As  $\mathcal{R}_0$  increases the difference  $\Delta t$  decreases. The increasing of the other parameters promotes the decreasing of  $\Delta t$ . The dashed line in each panel indicates the observed 2 months of difference between the occurrence of hemorrhagic fever and the limit of the protective level of mother antibodies.



**Fig. 3**  $\Delta t = t_{DHF} - t_{1;10}$  versus model parameters. The main parameter set is  $\alpha = 0.0198$ ,  $\mu_1 = \mu_2 = 0.1429$ ,  $\delta = 0.22$ ,  $E_0 = 0.05$  which are in  $\text{days}^{-1}$ ,  $A = 10^6$   $\text{cells ml}^{-1} \text{ days}^{-1}$ ,  $k = 10^4$  (RNA copies)  $\text{cell}^{-1} \text{ days}^{-1}$ ,  $c = 3.2 \times 10^{-11}$   $\text{ml (RNA copies)}^{-1}$ ,  $\gamma = 0.5$   $\text{ml molecules}^{-1} \text{ days}^{-1}$ ,  $\beta = 0.09$   $\text{days}$ ,  $\nu = 10^{-8}$   $\text{ml (RNA copies)}^{-1} \text{ days}^{-1}$ . The initial conditions were for  $C(0) = 2500$   $\text{molecules ml}^{-1} \text{ days}^{-1}$ ,  $X(0) = A/\mu_1$   $\text{cells ml}^{-1}$ ,  $Y(0) = 0$   $\text{cells ml}^{-1}$ ,  $V(0) = 100$   $\text{RNA copies cell}^{-1}$ .

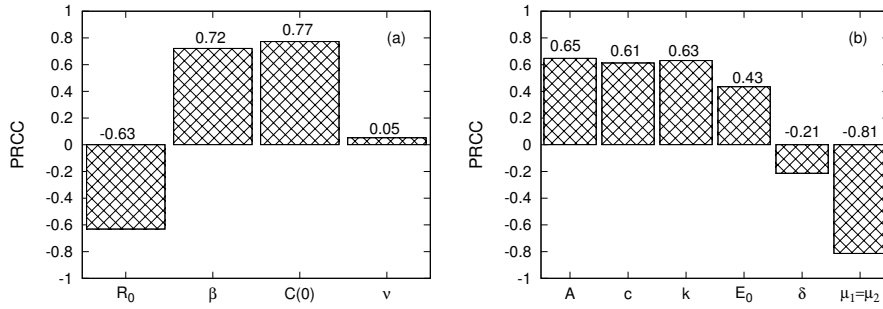
Fig. 4 shows the relation between  $C(0) = \gamma B_0$  and  $t_{DHF}$  and the histogram of the number of occurrence of DHF cases by  $t_{DHF}$ . The first one shows a fast initial increased until a saturation behavior starts to be observed. The histogram was construct using the observed  $t_{DHF}$  obtained at Fig. 4(a). The largest number of DHF occurs at 8-10 months. This depends strongly on the parameter set used in the simulations. For the parameter set chose,  $\mathcal{R}_0 = 36.3$ . The initial condition for  $B_0$  was varied from 30 to 8200  $\text{molecules ml}^{-1}$ . Changes on the shape of the enhancement and neutralization function (by varying the parameters  $\beta$  and  $\gamma$ ) increase or decrease the age at which the peak of DHF cases is seen without changing the  $\mathcal{R}_0$  of the virus, which means that the steady state of the system is the same, but the transient dynamics is different. Overall, the decrease on  $\beta$  and  $\gamma$  promotes the decrease of the age at which the peak of DHF occurs, while the increase of  $\mathcal{R}_0$  has an opposite effect over it.



**Fig. 4**  $C(0) = \gamma B_0$  versus  $t_{DHF}$  and histogram of the number of DHF occurrence by the time at which DHF occurs,  $t_{DHF}$ . The parameters are  $\alpha = 0.0198$ ,  $\mu_1 = \mu_2 = 0.1429$ ,  $\delta = 0.22$ ,  $E_0 = 0.05$  all in  $\text{days}^{-1}$ ,  $A = 10^6$   $\text{cells ml}^{-1} \text{ days}^{-1}$ ,  $k = 10^4$  (RNA copies)  $\text{cell}^{-1} \text{ days}^{-1}$ ,  $c = 4 \times 10^{-10}$   $\text{ml (RNA copies)}^{-1}$ ,  $\gamma = 0.5$   $\text{ml molecules}^{-1} \text{ days}^{-1}$ ,  $\beta = 0.09$   $\text{days}$ ,  $\nu = 10^{-8}$   $\text{ml (RNA copies)}^{-1} \text{ days}^{-1}$ . The initial conditions for  $C(0)$  varies from 15 to 4100  $\text{molecules ml}^{-1}$ . The others are fixed as  $X(0) = A/\mu_1$   $\text{cells ml}^{-1}$ ,  $Y(0) = 0$   $\text{cells ml}^{-1}$ ,  $V(0) = 100$   $\text{RNA copies cell}^{-1}$ .

Fig. 5 show the Partial Rank Correlation Coefficient (PRCC) obtained for the sensitivity analysis using  $\Delta t$  and  $\mathcal{R}_0$  as the output. The input parameters were chosen from a uniform distribution using the Latin Hypercube Sampling (LHS); the ranges of the parameters were taken from Fig. 3 for panel (a) and from Table 1 for panel (b). In Fig. 5(a), we can see that the increase of  $\mathcal{R}_0$  promotes the decrease of  $\Delta t$ , while the increase of  $\beta$ ,  $C(0)$  and  $\nu$  promotes the decrease of  $\Delta t$ . The order (decreasing order) of importance related to the contribution of each parameter to  $\Delta t$  is  $C(0)$ ,  $\beta$ ,  $\mathcal{R}_0$  and  $\nu$ . In Fig. 5(b), the increase of  $A$ ,  $c$ ,  $k$ ,  $E_0$  promotes the increase of  $\mathcal{R}_0$ , while the increase of  $\delta$ ,  $\mu_1$  and  $\mu_2$  promotes the decrease of  $\mathcal{R}_0$ . The order (decreasing order) of importance related to the contribution of each parameter to  $\mathcal{R}_0$  is  $\{\mu_1, \mu_2\}$  (equal contribution, given that  $\mu_1 = \mu_2$  in the simulations),  $\{A, c, k\}$  (equal contribution) and  $\delta$ .





**Fig. 5** Sensitivity analysis using  $\Delta t$  (in (a)) and  $\mathcal{R}_0$  (in (b)) as the output. The input parameters were chosen from an uniform distribution using the Latin Hypercube Sampling. The ranges of the parameters were taken from Fig. 3 for panel (a) and from Table 1 for panel (b).

## 5 Discussion

The introduction and the co-circulation of several dengue virus in many countries had caused the increase on the number of hospitalizations and severe dengue cases among infants, children and adults. The occurrence of DHF on primary infections on infants and on secondary infections in children and adults is associated with the enhancement of the infection promoted by the presence of dengue antibody from a previous infection or acquired passive from dengue-immune mothers. This feature turns the development of vaccines for dengue immunization a challenge.

The absence of an experimental model, and the difficult of obtained data of virus and immune system dynamics since the beginning of the infection makes the advance of the acknowledging of the mechanisms of virus invasion, replication and control by the immunological system longstanding. The complexity of the study of virus-immune system interactions in adults can be overcome by addressing the problem in infants, where the role of antibodies in DENV-induced disease can be separated from the others components of the immune response.

Neonates have an immature immune system that fails to generate a strongly response against infections. Their immune protection is booster by maternal antibodies transferred before birth transplacentally from mother to the offspring. This antibodies decay naturally during child develops, followed by the maturation of their immune system. The kinetics of maternal antibody decline is correlated to the amount of maternal antibody present in the neonate after birth, in such a way that higher antibody titers persists for a longer time, being 6-12 months the mean time.

Neutralization of the virus by antibodies involves a stoichiometry that exceeds a threshold and is governed by antibody affinity and epitope accessibility. Paradoxically enhance virus replication is mediated by antibody-dependent en-

hancement, where subneutralizing antibody titers leads to a booster on virus uptake and replication in target cells.

Following the biological hypothesis described above, we proposed an ODE model that mimics the occurrence of DHF in infants triggered, basically, by three model's parameters  $\mathcal{R}_0$ ,  $C(0) = \gamma B_0$  and  $\beta$  (Fig. 3). The first one measure virus fitness, the second one the protection promotes by mother's antibodies, and the third one the shape of neutralization and enhancement functions.  $\mathcal{R}_0$  is a threshold for disease persistence, if  $\mathcal{R}_0 < 1$  the asymptotic stability of disease-free equilibrium given by the dynamical model is disease extinction, and if  $\mathcal{R}_0 > 1$  we have an unique endemic equilibrium where the disease persists. Moreover, the survive of the target cells is the most important parameter that impacts positively  $\mathcal{R}_0$ , in a way that increasing survive of target cells promotes the increase of  $\mathcal{R}_0$ . Competition between neutralization and enhancement is provided by the consumption of antibodies given by virus and antibodies concentration (Fig. 2). These two functions are shaped by  $\gamma$ ,  $\beta$  and  $E_0$  values which were setted up to reproduce the data of dengue hemorrhagic in babies given at Fig. 4. Antibodies concentration arrives at titer 1:10 ( $t_{1:10}$ ) before DHF is settled up ( $t_{DHF}$ ). The difference  $\Delta t = t_{DHF} - t_{1:10}$  depends on the three main parameters described before, in such away that increase on  $\mathcal{R}_0$  promotes the decrease of  $\Delta t$ , and the increase on the others two parameters promotes the increase of  $\Delta t$ . Therefore, for a predefined, knowing and fixed enhancement and neutralization function, the delay on the DHF is related to the amount of antibodies received by the infant and virus kinetics (Fig. 5).

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