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Modelling the relationship between Antibody-Dependent Enhancement and disease severity in secondary dengue infection

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Abstract Sequential infections with different dengue serotypes (DENV-1, 4) significantly increase the risk of a severe disease outcome (fever, shock and hemorrhagic disorders). Two hypotheses have been proposed to explain the severity of dengue disease: (1) antibody-dependent enhancement (ADE); (2) original T cell antigenic sin. In this work, we explored the first hypothesis through mathematical modeling. The proposed model reproduces the dynamic of susceptible and infected target cells, and dengue virus in scenarios of infection-neutralizing and -enhancing antibodies competition induced by two distinct serotypes of dengue virus. The enhancement and neutralization functions are derived from basic concepts of chemical reactions and used to mimic binding to the virus by two distinct populations of antibodies. The analytic study of the model showed the existence of two equilibriums, a disease-free equilibrium and an endemic one. We performed the asymptotic stability analysis for these two equilibriums. The local asymptotic stability of the endemic-equilibrium corresponds to the occurrence of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). We defined the time t_{DHF} at which DHF/DSS occurs as the time when the infected cells (or the virus) population reaches a maximum. This corresponds to the time at which maximum enhancing activity for dengue infection appears. The critical time t_{DHF} was calculated from the model to be few days after the occurrence of the infection, which corresponds to what is observed in the literature. Finally, using as output the basic reproduction number \mathcal{R}_0 we were able to rank the contribution

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of each parameter of the model. In particular, we have highlighted the evidence of the role of enhancing antibodies in cross-reaction and the occurrence of DHF/DSS.

Keywords Dengue Hemorrhagic Fever (DHF) · Dengue Shock Syndrome (DSS) · Mathematical modeling · Local and global stability analyses for ordinary differential system · DENV1-4 · Neutralizing and enhancing antibodies

1 Introduction

Dengue disease is a worldwide health problem that affects mainly tropical and subtropical climate regions. It is a mosquito-borne viral infection whose main vector in Europe and Asia is the *Aedes albopictus* and in Americas is the *Aedes aegypti* (Kamal et al., 2018). The fact that only human can develop the disease and the need of a vector to transmit it, give to dengue its characteristic of an urban and semi-urban disease whose outbreaks are huge in high populate areas which provide all environmental conditions for the establishment of mosquitoes (Chen and Vasilakis, 2011). Beyond that, increasing human mobility and global warming put half of the world's population at risk.

A wide range of symptoms ranging from mild to severe can occur in humans, leading to categorizing cases as dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Despite all the efforts made in recent years, an effective and accessible commercial vaccine is not yet on the market (Prompetchara et al., 2019). Therefore, the disease control methods still be done on vector population, and they include traditional (with applications of adulticides, larvicides and removing of breeding sites) (Yang and Ferreira, 2008) and biological (release of *Wolbachia*-infected mosquito or insect with dominant lethality, sterile insect technique, predators of mosquito and entomopathogenic microorganisms) ones (Benelli et al., 2016; Huang et al., 2017).

Antibodies produced in response to dengue infection with one of the four dengue serotypes (DENV-1, 4) generally provide a protection by neutralizing the virus (Tricou et al., 2011; Reich et al., 2013). Likewise, the fact that the four dengue viruses share a high percentage of amino acid chains provides effective cross-immunity depending on the time-delay between consecutive infections and the immune status of the individual (Clapham et al., 2016). However, previous infection can also induce a non-protective antibody response that can enhance the course of the disease in a second infection (Tricou et al., 2011; Reich et al., 2013; Clapham et al., 2016). In this scenario, the preexisting antibodies bind to the virus but do not interfere with their infectivity because they do not bind to the right region (Schmaljohn, 2013). This virus-antibody complex facilitates the entry of the virus into the host cell (Tirado and Yoon, 2003). Recently, Katzelnick et al. (2017) and Durham et al. (2019) mentioned that the risk of severe dengue disease following a secondary infection is higher

when there is an intermediate amount of preexisting antibodies from the first infection.

There is no specific treatment for dengue, and the simultaneous circulation of different dengue serotypes in a region increases the number of severe dengue cases. Because of that, principally in Asia and Latin America, the number of hospitalization and death among children and adults have been increased in the last few years (Nunes et al., 2019).

Two competing hypotheses have been proposed to explain the severity observed in a secondary dengue infection: (1) Non-neutralizing antibodies which result from a previous infection (with a different serotype) bind with the new virus to form immune complexes which infect monocytes' and macrophages' Fc γ -receptors (Fc γ R). This phenomenon called antibody-dependent enhancement (ADE) indicates that preexisting antibodies are facilitating entry of the virus into target cells (Goncalvez et al., 2007; Guzman et al., 2010; Halstead, 2014); (2) activated T cells during acute DENV infection are cross-reactive with a previously encountered serotype and have low affinity for the currently serotype, leading to suboptimal control of infection and disease pathogenesis (original T cell antigenic sin hypothesis) (Ngono and Shrestha, 2019).

To explore the two hypotheses behind the severe manifestations of dengue, few mathematical models have been developed to analyze the contribution of each adaptive immune response (humoral and cellular) to viral dynamics (Nuraini et al., 2009; Ansari and Hesaaraki, 2012; Clapham et al., 2014; Gujarati and Ambika, 2014; Ben-Shachar and Koelle, 2015; Clapham et al., 2016; Sasmal et al., 2017; Cerón Gómez and Yang, 2018; Adimy et al., 2020). In the three papers Nuraini et al. (2009); Ansari and Hesaaraki (2012) and Clapham et al. (2014), the authors considered the dynamic interaction between free virus, uninfected and infected target cells, and immune cells. In all their models, only T cells play a protective role by clearing infected cells. In Gujarati and Ambika (2014), they considered the dynamic interaction between free virus, uninfected and infected cells, B cells and antibodies (protective or enhancing). In Ben-Shachar and Koelle (2015), they described how the interaction of the immune system (T cells) with dengue virus can lead to increased cytokine production and thereby an increased risk of severe disease. In Clapham et al. (2016), they showed using mathematical modeling that the timing and magnitude of the growth and decline of virus and antibody levels in dengue-infected patients are consistent with antibody playing a key role in controlling infection. In Sasmal et al. (2017), they considered a mathematical model of primary dengue infection consisting of uninfected and infected cells, virus particles, and T-cell mediated adaptive immunity. In Cerón Gómez and Yang (2018), they developed a mathematical model to describe the role of antibody-dependent enhancement in a secondary dengue infection, assuming that antibodies specific to primary dengue virus infection are being produced by immunological memory cells. In the papers Clapham et al. (2014, 2016) and Adimy et al. (2020), thresholds for virus clearance, probability of ADE occurrence, and the importance of model parameters such as virus fitness, and immune status of the individual were assessed. Furthermore, fitting the models to data of RNA

virus titer and antibody titers, several aspects of the humoral response (active and passive) were also studied (Clapham et al., 2014, 2016; Adimy et al., 2020). Although references cited in this section have addressed the phenomenon of ADE using mathematical modeling, none have provided explicit mechanisms by which enhancement and neutralization of the virus by antibodies occur.

The model that we will present here follows the approach described in Adimy et al. (2020). The authors proposed an ordinary differential system to investigate the occurrence of DHF in infants (< 1 year old) born from dengue-immune mothers, during their first dengue infection. The model mimics interactions among susceptible and infected target cells, dengue virus, and maternal dengue-specific antibodies through bilinear and trilinear terms. A virus enhancement and neutralization functions are introduced inspired by experiments *in vitro*. In this paper, we propose to study the occurrence of DHF/DSS in adults after secondary exposure to a different viral serotype. This occurs mainly because of the existence of cross-reactive antibodies from a previous infection. We will explore the ADE hypothesis described above which is the most widely supported theory (Wahala and de Silva, 2011). The novelty of the work is based on the mathematical model which makes possible the exploration of scenarios of competition between neutralizing and enhancing antibodies on the severity of the disease and the occurrence of DHF/DSS. This model can be used as a basis for understanding characterized patterns of disease severity. As for Adimy et al. (2020), our approach is to construct the simplest and in the same time the most complete model that can produce DHF/DSS using ADE hypothesis during a secondary infection and to be able to analyze the dynamics that it can generate (local and global stability of the steady states). We then complete our analysis by numerical simulations. The model we present here is, to our knowledge, the first to describe, using chemical reactions, how competition between preexisting and neutralizing antibodies to bind to dengue virus can lead to increased production of infected cells. In particular, our model was able to show that during a secondary infection the number of infected cells is higher when there is an intermediate amount of preexisting antibodies from the first infection and therefore an increased risk of manifestation of DHF/DSS.

2 The Mathematical model

Based on the previous model from Adimy et al. (2020) and on the knowledge of the immune response against dengue virus under ADE hypothesis, an ordinary differential model is developed to investigate the occurrence of DHF/DSS in adults during their second dengue infection. We denote by V the population of free virus (second DENV-serotype) and by A_1 the free antibody population preexisting in the body from a primary infection with DENV-serotype $V_0 \neq V$. These antibodies are continuously produced by long-lived *plasma B-cells* generated during a primary infection, and in the presence of dengue infected cells, *memory B-cells* are quickly activated to produce a second wave of antibod-

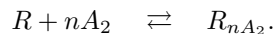
ies A_1 . Furthermore, A_1 are cross-reactive non-neutralizing antibodies for the virus V . When there is an intermediate amount of preexisting antibodies A_1 , they can promote the antibody-dependent enhancement (ADE) (Katzelnick et al., 2017; Durham et al., 2019). By A_2 , we denote the free antibody population generated after the secondary infection with DENV-serotype V due to the activation of *naive B-cells*. A_2 is type-specific neutralizing antibodies against the new serotype V . While neutralizing antibodies A_2 are considered to play a major role in protection from the virus V , infection-enhancing activity of antibodies A_1 is an important mechanism involved in disease severity due to the higher occurrence of DHF/DSS promoted by the ADE phenomenon. The population of susceptible target cells are macrophages and monocytes which are denoted by X , and the corresponding infected ones by Y .

The activation of the adaptive immune response follows a cascade of events triggered by virus-infected cells that present a peptide fragment derived from the antigen bound to Major Histocompatibility Complex (MHC). In the model, we consider explicitly the role made by the humoral adaptive response on infection-dynamics. The cellular adaptive response is modeled as an increase on the mortality of infected cells. Moreover, we are not dealing with the avalanche of signaling events that trigger B cells activation, proliferation, differentiation and antibody production; but we modeled directly the production of antibody as proportional to the number of infected cells. Therefore, free-antibodies A_1 are produced by plasma cells at a constant rate Λ_1 and diminish at a per capita natural death rate γ_A . This population is also generated by the presence of infected cells Y at a rate α_1 , and consumed when bound to the free virus V at a rate η_1 . Besides, the free-antibodies A_2 are also generated due to the presence of the infected cells at a rate α_2 , have a natural death γ_A , and are bounded to the virus at a rate η_2 .

The population of free virus V is produced at a constant rate Φ per infected cells Y . When the antibodies A_i , $i = 1, 2$, bind the receptor of the virus V , the virus is no longer free at per capita rates $\xi_1 A_1 + \xi_2 A_2$. In addition, the population of the virus V have a per capita rate of natural mortality γ_V .

Susceptible target cells X are produced at a constant rate Ω , have a constant death rate γ_X , and are infected by the virus V depending on the concentrations of antibodies A_1 and A_2 by some mechanisms that will be explained below. Infected cells Y come from susceptible cells X that are infected by the virus V . They can die at a per capita rate γ_Y .

Neutralization, as considered here, is the reduction of viral infectivity by binding of antibodies A_2 to the surface of viral particles, thereby blocking their attachment and entry to the host cells (Luo and Klasse, 2014). To determine the amount of neutralization of the virus by antibodies A_2 in solution, we consider the chemical reaction in which n ligand molecules of A_2 simultaneously bind receptor R of the virus



It follows from Santillán (2008) that at the equilibrium state of the chemical reaction, the fractions of occupied and free molecules R are respectively,

$$H_n(A_2) := \frac{A_2^n}{A_2^n + \theta_2^n} \quad \text{and} \quad H_0(A_2) := \frac{\theta_2^n}{A_2^n + \theta_2^n}, \quad \text{with} \quad H_n(A_2) + H_0(A_2) = 1.$$

We suppose that virions with higher occupancies would be neutralized and loss their infectivity. The parameter θ_2 is the reaction dissociation constant. It is the value of A_2 at which we have $H_n(\theta_2) = 1/2$. It describes how fast the antibody can bind to the virus. Faster binding is represented by a lower dissociation constant θ_2 . The parameter n determines the sigmoidicity of the functions H_n and H_0 (in fact, we have $H'_n(\theta_2) = -H'_0(\theta_2) = n/4\theta_2$). Therefore, the proportion of virus that enters into each cell X is $H_0(A_2)V$ and β_2 is the infection rate of the cells X by the proportion $H_0(A_2)V$ of the virus V .

Not all antibodies that bind the virus are neutralizing it. To deal with this phenomena, we consider an intermediate state of the chemical reaction where the fractions of occupied molecules by the preexisting antibodies A_1 is (Hill-type function)

$$H_p(A_1) := \frac{\theta_1^{n-p} A_1^p}{A_1^n + \theta_1^n}, \quad 0 < p < n.$$

We notice that we also have for all $0 < p < n$, $H_p(\theta_1) = 1/2$ and $H'_p(\theta_1) = (2p - n)/4\theta_1$. Using this idea, we suppose that the proportion of virus V that enters into each cell X (enhancement of the virus by the antibody A_1) is $H_p(A_1)V$ and β_1 is the infection rate of the cells X by the proportion $H_p(A_1)V$ of the virus V .

According to the above discussion the resulting mathematical model is given by

$$\begin{cases} \frac{dA_1}{dt} = A_1 + \alpha_1 Y - \gamma_A A_1 - \eta_1 A_1 V, \\ \frac{dA_2}{dt} = \alpha_2 Y - \gamma_A A_2 - \eta_2 A_2 V, \\ \frac{dX}{dt} = \Omega - \gamma_X X - \frac{\beta_1 \theta_1^{n-p} A_1^p}{A_1^n + \theta_1^n} V X - \frac{\beta_2 \theta_2^n}{A_2^n + \theta_2^n} V X, \\ \frac{dY}{dt} = \frac{\beta_1 \theta_1^{n-p} A_1^p}{A_1^n + \theta_1^n} V X + \frac{\beta_2 \theta_2^n}{A_2^n + \theta_2^n} V X - \gamma_Y Y, \\ \frac{dV}{dt} = \Phi Y - \xi_1 A_1 V - \xi_2 A_2 V - \gamma_V V, \end{cases} \quad (1)$$

where, based on the description done before, we can identify the virus enhancement and neutralization functions as

$$E(A_1) := \frac{\theta_1^{n-p} A_1^p}{A_1^n + \theta_1^n}, \quad N(A_2) := 1 - \frac{\theta_2^n}{A_2^n + \theta_2^n} = \frac{A_2^n}{A_2^n + \theta_2^n}. \quad (2)$$

Table 1 provides the model's parameters with their units and range of values.

Table 1 Summary of model's parameters, their description and range of values (Kliks et al., 1988; Cologna and Rico-Hesse, 2003; Sithisarn et al., 2003; Uzman, 2003; Chau et al., 2009; Gonzalez-Mejia and Doseff, 2009; Beltramello et al., 2010; Clapham et al., 2014; Dowd et al., 2014; Jonsson et al., 2014; Sasmal et al., 2017; Katzelnick et al., 2017).

Param.	Description	Range of values [mol]=[molecules], [d]=[day]
Λ_1	antibodies production by plasma cells	$(0 - 12) \times 10^6$ [mol] [ml] ⁻¹ [d] ⁻¹
α_1, α_2	antibodies production induced by Y	$(0.5 - 8) \times 10^{-5}$ [mol] [cells] ⁻¹ [d] ⁻¹
$\log(2)\gamma_A^{-1}$	antibodies half-life	$(0.014 - 1.5) \times 10^3$ [d]
η_1, η_2	virus-bound antibodies	$(0.09 - 1) \times 10^{-8}$ [ml] [RNA copies] ⁻¹ [d] ⁻¹
Ω	rate of production of susceptible cells	$4.0 \times 10^3 - 17.5 \times 10^6$ [cells] [ml] ⁻¹ [d] ⁻¹
$\log(2)\gamma_X^{-1}, \log(2)\gamma_Y^{-1}$	susceptible and infected cells half-life	1 - 30 [d]
Φ	production of viral particles	$10^4 - 10^7$ [RNA copies] [cells] ⁻¹ [d] ⁻¹
$\log(2)\gamma_V^{-1}$	viral particles half-life	$(2.5 - 17.2) \times 24^{-1}$ [d]
β_1, β_2	infection rates of X	$10^{-8} - 10^{-10}$ [ml] [RNA copies] ⁻¹ [d] ⁻¹
ξ_1, ξ_2	antibodies virus-bound	$0.07 - 0.90$ [ml] [mol] ⁻¹ [d] ⁻¹
θ_1, θ_2	antibodies concentration producing half occupation of the virus receptor	$10^2 - 10^8$ [mol] [ml] ⁻¹ (assumed)
n, p	Hill coefficients	$n = [1, 3], 1 < p < n$ (assumed)

Defining $\bar{A}_i = A_i/\theta_i$ with $i \in \{1, 2\}$, we can simplify the nonlinear ordinary differential system (1) as

$$\begin{cases} \frac{d\bar{A}_1}{dt} = \bar{\Lambda}_1 + \bar{\alpha}_1 Y - \gamma_A \bar{A}_1 - \eta_1 \bar{A}_1 V, \\ \frac{d\bar{A}_2}{dt} = \bar{\alpha}_2 Y - \gamma_A \bar{A}_2 - \eta_2 \bar{A}_2 V, \\ \frac{dX}{dt} = \Omega - \gamma_X X - \beta_1 C_1(\bar{A}_1) X V - \beta_2 C_2(\bar{A}_2) X V, \\ \frac{dY}{dt} = \beta_1 C_1(\bar{A}_1) X V + \beta_2 C_2(\bar{A}_2) X V - \gamma_Y Y, \\ \frac{dV}{dt} = \Phi Y - \bar{\xi}_1 \bar{A}_1 V - \bar{\xi}_2 \bar{A}_2 V - \gamma_V V, \end{cases} \quad (3)$$

where the normalized parameters are

$$\bar{A}_1 = \frac{A_1}{\theta_1}, \quad \bar{\alpha}_i = \frac{\alpha_i}{\theta_i}, \quad \bar{\xi}_i = \theta_i \xi_i, \quad \text{with } i \in \{1, 2\},$$

and

$$C_1(A) = \frac{A^p}{A^n + 1}, \quad \text{and} \quad C_2(A) = \frac{1}{A^n + 1}.$$

3 Model Analysis

We are seeking for solutions of the first-order nonlinear differential system (3) with initial conditions given by

$$\bar{A}_1(0) = \frac{A_1(0)}{\theta_1}, \quad \bar{A}_2(0) = \frac{A_2(0)}{\theta_2}, \quad X(0) = X_0, \quad Y(0) = Y_0 \quad \text{and} \quad V(0) = V_0. \quad (4)$$

The existence and uniqueness of the solution are guaranteed by the regularity of the nonlinear function used in the right-hand side of System (3).

3.1 Global Existence, Positivity and Boundedness of the Solutions

The next classical result states the existence, uniqueness, positivity and boundedness of the solution of System (3) on the whole interval $[0, +\infty)$.

Proposition 1 *The solution of System (3) associated with nonnegative initial condition (4) is nonnegative and defined on all the interval $[0, +\infty)$. The result states also the existence and uniqueness of the solution on the whole interval $[0, +\infty)$.*

Proof First of all, it is clear that the solution of System (3) associated with nonnegative initial condition (4) is nonnegative on its interval of existence $[0, T)$.

Now let us show that the solution is bounded on $[0, T)$. By adding the equations of X and Y , we get

$$\frac{d}{dt}(X + Y) = \Omega - \gamma_X X - \gamma_Y Y \leq \Omega - \gamma(X + Y), \quad \text{with } \gamma = \min\{\gamma_X, \gamma_Y\} > 0.$$

Then,

$$0 \leq X(t) + Y(t) \leq e^{-\gamma t}(X_0 + Y_0) + \frac{\Omega}{\gamma}(1 - e^{-\gamma t}).$$

This implies that

$$\limsup_{t \rightarrow T} (X(t) + Y(t)) \leq \frac{\Omega}{\gamma}.$$

Therefore, $X(t)$ and $Y(t)$ are bounded. Besides, the last equation of (3) and the nonnegativity of \bar{A}_1 and \bar{A}_2 imply that

$$\frac{d}{dt}V(t) \leq \Phi Y(t) - \gamma_V V(t) \leq \Phi \bar{Y} - \gamma_V V(t),$$

where $\bar{Y} = \sup_{0 \leq s < T} Y(s)$. Then, we obtain

$$\limsup_{t \rightarrow T} V(t) \leq \frac{\Phi \bar{Y}}{\gamma_V}.$$

Consequently, $V(t)$ is bounded. In the same way, using the previous results and according to the second equation of (3), we have

$$\frac{d}{dt} \bar{A}_2(t) \leq \bar{\alpha}_2 \bar{Y} - \left(\gamma_A + \eta_2 \frac{\Phi \bar{Y}}{\gamma_V} \right) \bar{A}_2(t).$$

Using the same technique, we get

$$\limsup_{t \rightarrow T} \bar{A}_2 \leq \frac{\gamma_V \bar{\alpha}_2 \bar{Y}}{\gamma_V \gamma_A + \eta_2 \Phi \bar{Y}}.$$

Therefore, $\bar{A}_2(t)$ is bounded. Finally, the first equation of (3) gives

$$\frac{d}{dt} \bar{A}_1(t) \leq \bar{\Lambda}_1 + \bar{\alpha}_1 \bar{Y} - \left(\gamma_A + \eta_1 \frac{\Phi \bar{Y}}{\gamma_V} \right) \bar{A}_1(t).$$

Thus,

$$\limsup_{t \rightarrow T} \bar{A}_1(t) \leq \frac{\gamma_V (\bar{\Lambda}_1 + \bar{\alpha}_1 \bar{Y})}{\gamma_V \gamma_A + \eta_1 \Phi \bar{Y}}.$$

Consequently, $\bar{A}_1(t)$ is bounded. We proved that all the solutions are bounded on their intervals of existence $[0, T)$. This implies that they are all defined on the whole interval $[0, +\infty)$, ($T = +\infty$) and, from the results established above, they are bounded on $[0, +\infty)$.

3.2 Existence and asymptotic stability of the steady states

Let $(\bar{A}_1^*, \bar{A}_2^*, X^*, Y^*, V^*)$ be an equilibrium (or steady state) of the system (3). Therefore, it has to satisfy

$$\begin{cases} \bar{A}_1 + \bar{\alpha}_1 Y^* - \gamma_A \bar{A}_1^* - \eta_1 \bar{A}_1^* V^* & = 0, \\ \bar{\alpha}_2 Y^* - \gamma_A \bar{A}_2^* - \eta_2 \bar{A}_2^* V^* & = 0, \\ \Omega - \gamma_X X^* - \beta_1 C_1(\bar{A}_1^*) X^* V^* - \beta_2 C_2(\bar{A}_2^*) X^* V^* & = 0, \\ \beta_1 C_1(\bar{A}_1^*) X^* V^* + \beta_2 C_2(\bar{A}_2^*) X^* V^* - \gamma_Y Y^* & = 0, \\ \Phi Y^* - \xi_1 \bar{A}_1^* V^* - \xi_2 \bar{A}_2^* V^* - \gamma_V V^* & = 0. \end{cases} \quad (5)$$

After solving System (5), we obtain two steady states: a *disease-free steady state* P_0 and under some conditions an *endemic steady state* P_1 .

3.2.1 The basic reproduction number \mathcal{R}_0 and local asymptotic stability of the disease-free steady state P_0

In mathematical epidemiology, the *basic reproduction number* denoted by \mathcal{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 whole susceptible population. Indeed, if $\mathcal{R}_0 < 1$ the disease dies out while for $\mathcal{R}_0 > 1$ it persists. This corresponds to the local asymptotic stability and instability of the *disease-free equilibrium* of the system (3) which is given by

$$P_0 = \left(\frac{\bar{A}_1}{\gamma_A}, 0, \frac{\Omega}{\gamma_X}, 0, 0 \right).$$

P_0 represents the state without infection and it always exists. The *next-generation matrix* method (Diekmann and Heesterbeek, 2000; Van den Driessche and Watmough, 2002) is the most common procedure to determine \mathcal{R}_0 . With this method, \mathcal{R}_0 is defined as the dominant eigenvalue of a matrix KT^{-1} , where K is the matrix of infection terms and T the matrix of the transition terms:

$$\mathcal{R}_0 := \rho(KT^{-1}).$$

System (3) has two infected states Y and V . The linearization of the transmission of the infection around the disease-free steady state P_0 gives the following linear system

$$\begin{cases} \frac{dY}{dt} = \left(\beta_1 \frac{(\bar{A}_1/\gamma_A)^p}{(\bar{A}_1/\gamma_A)^n + 1} + \beta_2 \right) \frac{\Omega}{\gamma_X} V - \gamma_Y Y, \\ \frac{dV}{dt} = \Phi Y - \left(\gamma_V + \bar{\xi}_1 \frac{\bar{A}_1}{\gamma_A} \right) V. \end{cases} \quad (6)$$

It describes the production of new infected cells at a rate

$$\left(\beta_1 \frac{(\bar{A}_1/\gamma_A)^p}{(\bar{A}_1/\gamma_A)^n + 1} + \beta_2 \right) \frac{\Omega}{\gamma_X},$$

new viruses at a rate Φ , and highlights the changes in the states of the infected individuals, including the deaths. Then, the matrices K and T (Van den Driessche and Watmough, 2002) are given by

$$K = \begin{pmatrix} 0 & \left(\beta_1 \frac{(\bar{A}_1/\gamma_A)^p}{(\bar{A}_1/\gamma_A)^n + 1} + \beta_2 \right) \frac{\Omega}{\gamma_X} \\ 0 & 0 \end{pmatrix} \text{ and } T = \begin{pmatrix} -\gamma_Y & 0 \\ \Phi & -\left(\gamma_V + \bar{\xi}_1 \frac{\bar{A}_1}{\gamma_A} \right) \end{pmatrix},$$

from which we obtain the basic reproduction number

$$\mathcal{R}_0 = \frac{1}{\gamma_Y} \times \frac{\Omega}{\gamma_X} \times \left(\frac{\Phi}{\gamma_V + \bar{\xi}_1 \frac{\bar{A}_1}{\gamma_A}} \right) \times \left(\beta_1 \frac{(\bar{A}_1/\gamma_A)^p}{(\bar{A}_1/\gamma_A)^n + 1} + \beta_2 \right). \quad (7)$$

Then, we can conclude on the local asymptotic stability and instability of P_0 (Van den Driessche and Watmough, 2002).

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

3.2.2 Existence of endemic steady state P_1

According to System (5), an endemic equilibrium satisfies

$$\begin{cases} \gamma_A \bar{A}_1^* + \eta_1 \bar{A}_1^* V^* & = \bar{A}_1 + \bar{\alpha}_1 Y^*, \\ \gamma_A \bar{A}_2^* + \eta_2 \bar{A}_2^* V^* & = \bar{\alpha}_2 Y^*, \\ \gamma_X X^* + \beta_1 C_1(\bar{A}_1^*) X^* V^* + \beta_2 C_2(\bar{A}_2^*) X^* V^* & = \Omega, \\ \beta_1 C_1(\bar{A}_1^*) X^* V^* + \beta_2 C_2(\bar{A}_2^*) X^* V^* & = \gamma_Y Y^*, \\ \bar{\xi}_1 \bar{A}_1^* V^* + \bar{\xi}_2 \bar{A}_2^* V^* + \gamma_V V^* & = \Phi Y^*, \end{cases} \quad (8)$$

where

$$C_1(A) = \frac{A^p}{A^n + 1} \quad \text{and} \quad C_2(A) = \frac{1}{A^n + 1}.$$

From the third and fourth equations of (8), we get

$$X^* = \frac{1}{\gamma_X} (\Omega - \gamma_Y Y^*), \quad \text{with } 0 < Y^* < \frac{\Omega}{\gamma_Y}. \quad (9)$$

Let's start by assuming that the quantities η_1 and η_2 are negligible

$$\eta_1 = \eta_2 = 0. \quad (10)$$

Using the first and second equation of (8), we obtain

$$\bar{A}_1^* = \frac{\bar{A}_1 + \bar{\alpha}_1 Y^*}{\gamma_A} \quad \text{and} \quad \bar{A}_2^* = \frac{\bar{\alpha}_2 Y^*}{\gamma_A}. \quad (11)$$

Then, substituting (11) in the last equation of (8), we get

$$V^* \left(\bar{\xi}_1 \frac{\bar{A}_1 + \bar{\alpha}_1 Y^*}{\gamma_A} + \bar{\xi}_2 \frac{\bar{\alpha}_2 Y^*}{\gamma_A} + \gamma_V \right) = \Phi Y^*.$$

At the end, we have

$$V^* = \frac{\gamma_A \Phi Y^*}{(\bar{\xi}_1 \bar{\alpha}_1 + \bar{\xi}_2 \bar{\alpha}_2) Y^* + \bar{\xi}_1 \bar{A}_1 + \gamma_A \gamma_V}. \quad (12)$$

To sum up, we expressed \bar{A}_1^* , \bar{A}_2^* , X^* and V^* as functions of $Y^* \in \left[0, \frac{\Omega}{\gamma_Y}\right]$ through the expressions (9), (11) and (12). For $Y^* = 0$ we obtain the disease-free equilibrium P_0 . We now have to find an equation satisfied by $Y^* > 0$. From the fourth equation of (8), we obtain

$$[\beta_1 C_1(\bar{A}_1^*(Y^*)) + \beta_2 C_2(\bar{A}_2^*(Y^*))] X^*(Y^*) V^*(Y^*) = \gamma_Y Y^*.$$

As we are looking for $Y^* > 0$, the previous equation becomes

$$\frac{\gamma_A \Phi}{\gamma_X \gamma_Y} \times \frac{[\beta_1 C_1 (\bar{A}_1^*(Y^*)) + \beta_2 C_2 (\bar{A}_2^*(Y^*))] (\Omega - \gamma_Y Y^*)}{(\bar{\xi}_1 \bar{\alpha}_1 + \bar{\xi}_2 \bar{\alpha}_2) Y^* + \bar{\xi}_1 \bar{A}_1 + \gamma_A \gamma_V} = 1,$$

where

$$C_1 (\bar{A}_1^*(Y^*)) = \frac{\gamma_A^{n-p} (\bar{A}_1 + \bar{\alpha}_1 Y^*)^p}{\gamma_A^n + (\bar{A}_1 + \bar{\alpha}_1 Y^*)^n} \quad \text{and} \quad C_2 (\bar{A}_2^*(Y^*)) = \frac{\gamma_A^n}{\gamma_A^n + (\bar{\alpha}_2 Y^*)^n}.$$

We consider the function $I : \left[0, \frac{\Omega}{\gamma_Y}\right] \mapsto [0, \bar{I}]$ defined by

$$I(Y^*) := \frac{\gamma_A \Phi}{\gamma_X \gamma_Y} \times \frac{[\beta_1 C_1 (\bar{A}_1^*(Y^*)) + \beta_2 C_2 (\bar{A}_2^*(Y^*))] (\Omega - \gamma_Y Y^*)}{(\bar{\xi}_1 \bar{\alpha}_1 + \bar{\xi}_2 \bar{\alpha}_2) Y^* + \bar{\xi}_1 \bar{A}_1 + \gamma_A \gamma_V},$$

where

$$\bar{I} := \max \left\{ I(Y^*) : 0 \leq Y^* \leq \frac{\Omega}{\gamma_Y} \right\}.$$

The problem is transformed to solve

$$I(Y^*) = 1, \quad 0 \leq Y^* \leq \frac{\Omega}{\gamma_Y}.$$

Remark that

$$I(0) = \mathcal{R}_0 \quad \text{and} \quad I\left(\frac{\Omega}{\gamma_Y}\right) = 0.$$

If $\mathcal{R}_0 > 1$, there exists $0 < Y^* < \frac{\Omega}{\gamma_Y}$ such that $I(Y^*) = 1$. For the uniqueness of Y^* , we remark that the Hill function

$$Y^* \mapsto C_2 (\bar{A}_2^*(Y^*)) = \frac{\gamma_A^n}{\gamma_A^n + (\bar{\alpha}_2 Y^*)^n}$$

is decreasing on the interval $\left[0, \frac{\Omega}{\gamma_Y}\right]$ with $C_2 (\bar{A}_2^*(0)) = 1$. However, the derivative of the function

$$Y^* \mapsto C_1 (\bar{A}_1^*(Y^*)) = \frac{\gamma_A^{n-p} (\bar{A}_1 + \bar{\alpha}_1 Y^*)^p}{\gamma_A^n + (\bar{A}_1 + \bar{\alpha}_1 Y^*)^n}$$

vanishes at the point $\tilde{Y} = \frac{\gamma_A}{\bar{\alpha}_1} \left(\frac{1}{(n/p - 1)^{1/n}} - \frac{\bar{A}_1}{\gamma_A} \right)$ if and only if $0 \leq \tilde{Y} \leq \Omega/\gamma_Y$. In fact, we have three cases:

- (i) $\tilde{Y} \leq 0$. Then, $Y^* \mapsto C_1 (\bar{A}_1^*(Y^*))$ is decreasing on the interval $[0, \Omega/\gamma_Y]$.
- (ii) $\tilde{Y} \geq \Omega/\gamma_Y$. Then, $Y^* \mapsto C_1 (\bar{A}_1^*(Y^*))$ is increasing on the interval $[0, \Omega/\gamma_Y]$.
- (iii) $0 < \tilde{Y} < \Omega/\gamma_Y$. Then, $Y^* \mapsto C_1 (\bar{A}_1^*(Y^*))$ is increasing on the interval $[0, \tilde{Y}]$ and decreasing on the interval $[\tilde{Y}, \Omega/\gamma_Y]$.

We will consider the case (i) by assuming

$$\frac{1}{(n/p - 1)^{\frac{1}{n}}} \leq \frac{\bar{A}_1}{\gamma_A}. \quad (13)$$

Then, the function I is decreasing on $\left[0, \frac{\Omega}{\gamma_Y}\right]$ and there exists a unique $0 < Y^* < \frac{\Omega}{\gamma_Y}$ solution of $I(Y^*) = 1$ if and only if $\mathcal{R}_0 > 1$.

The quantity $\frac{1}{(n/p - 1)^{\frac{1}{n}}}$ in the inequality (13) is in fact the value of \bar{A}_1^* where the function C_1 achieves its maximum. In particular, if we choose $\frac{\bar{A}_1}{\gamma_A} \geq 1$, then the condition (13) is satisfied for $1 \leq p \leq \frac{n}{2}$. The hypothesis (13) is sufficient but not necessary to have uniqueness of Y^* . Furthermore, this hypothesis is not satisfied by all the values of the parameters in Table 1. Nevertheless, when $\mathcal{R}_0 > 1$, all the values of the parameters in Table 1 give the uniqueness of Y^* (obtained by numerical simulations).

3.2.3 Stability analysis of the Endemic Steady State P_1

In this section, we assume that the conditions (10), (13) and $\mathcal{R}_0 > 1$ are satisfied. Then, we have the existence of a unique endemic steady state $P_1 = (\bar{A}_1^*, \bar{A}_2^*, X^*, Y^*, V^*)$, where $0 < Y^* < \Omega/\gamma_Y$ is the unique solution of $I(Y^*) = 1$ and $X^*, \bar{A}_1^*, \bar{A}_2^*, V^*$ are given by (9), (11) and (12). In order to prove the local asymptotic stability of P_1 , we consider the linearization of the system (3) around P_1

$$\begin{cases} \frac{d\bar{a}_1}{dt} &= \bar{\alpha}_1 y - \gamma_A \bar{a}_1, \\ \frac{d\bar{a}_2}{dt} &= \bar{\alpha}_2 y - \gamma_A \bar{a}_2, \\ \frac{dx}{dt} &= -\gamma_X x - (\beta_1 C_1(\bar{A}_1^*) + \beta_2 C_2(\bar{A}_2^*)) X^* v - (\beta_1 C_1(\bar{A}_1^*) + \beta_2 C_2(\bar{A}_2^*)) V^* x \\ &\quad - \beta_1 C_1'(\bar{A}_1^*) X^* V^* \bar{a}_1 - \beta_2 C_2'(\bar{A}_2^*) X^* V^* \bar{a}_2, \\ \frac{dy}{dt} &= -\gamma_Y y + (\beta_1 C_1(\bar{A}_1^*) + \beta_2 C_2(\bar{A}_2^*)) X^* v + (\beta_1 C_1(\bar{A}_1^*) + \beta_2 C_2(\bar{A}_2^*)) V^* x \\ &\quad + \beta_1 C_1'(\bar{A}_1^*) X^* V^* \bar{a}_1 + \beta_2 C_2'(\bar{A}_2^*) X^* V^* \bar{a}_2, \\ \frac{dv}{dt} &= \Phi y - (\bar{\xi}_1 \bar{A}_1^* + \bar{\xi}_2 \bar{A}_2^* + \gamma_V) v - \bar{\xi}_1 V^* \bar{a}_1 - \bar{\xi}_2 V^* \bar{a}_2. \end{cases} \quad (14)$$

The characteristic equation associated to System (14) is given by

$$\begin{vmatrix} \lambda + \gamma_A & 0 & 0 & -\bar{\alpha}_1 & 0 \\ 0 & \lambda + \gamma_A & 0 & -\bar{\alpha}_2 & 0 \\ \bar{C}'_1 X^* V^* & \bar{C}'_2 X^* V^* & \lambda + \gamma_X + \bar{C}V^* & 0 & \bar{C}X^* \\ -\bar{C}'_1 X^* V^* & -\bar{C}'_2 X^* V^* & -\bar{C}V^* & \lambda + \gamma_Y & -\bar{C}X^* \\ \bar{\xi}_1 V^* & \bar{\xi}_2 V^* & 0 & -\bar{\Phi} & \lambda + \gamma_V + \bar{\xi}^* \end{vmatrix} = 0,$$

with

$$\bar{C} = \beta_1 C_1(\bar{A}_1^*) + \beta_2 C_2(\bar{A}_2^*), \quad \bar{C}'_1 = \beta_1 C'_1(\bar{A}_1^*), \quad \bar{C}'_2 = \beta_2 C'_2(\bar{A}_2^*) \quad \text{and} \quad \bar{\xi}^* = \bar{\xi}_1 \bar{A}_1^* + \bar{\xi}_2 \bar{A}_2^*.$$

We suppose that the virus does not affect cell mortality

$$\gamma_X = \gamma_Y := \gamma. \quad (15)$$

First, we add lines 3 and 4 that we substitute to line 4, and second we subtract columns 3 and 4 that we substitute to column 4. Then, we get

$$\begin{vmatrix} \lambda + \gamma_A & 0 & 0 & \bar{\alpha}_1 & 0 \\ 0 & \lambda + \gamma_A & 0 & \bar{\alpha}_2 & 0 \\ \bar{C}'_1 X^* V^* & \bar{C}'_2 X^* V^* & \lambda + \gamma + \bar{C}V^* & \lambda + \gamma + \bar{C}V^* & \bar{C}X^* \\ 0 & 0 & \lambda + \gamma & 0 & 0 \\ \bar{\xi}_1 V^* & \bar{\xi}_2 V^* & 0 & \bar{\Phi} & \lambda + \gamma_V + \bar{\xi}^* \end{vmatrix} = 0.$$

Thereby, we can see from line 4 that $\lambda = -\gamma < 0$ is an eigenvalue. The other eigenvalues are given by

$$(\lambda + \gamma_A)D_1 + \bar{\alpha}_1 D_2 = 0$$

with

$$D_1 = \begin{vmatrix} \lambda + \gamma_A & \bar{\alpha}_2 & 0 \\ \bar{C}'_2 X^* V^* & \lambda + \gamma + \bar{C}V^* & \bar{C}X^* \\ \bar{\xi}_2 V^* & \bar{\Phi} & \lambda + \gamma_V + \bar{\xi}^* \end{vmatrix}$$

and

$$D_2 = \begin{vmatrix} 0 & \lambda + \gamma_A & 0 \\ \bar{C}'_1 X^* V^* & \bar{C}'_2 X^* V^* & \bar{C}X^* \\ \bar{\xi}_1 V^* & \bar{\xi}_2 V^* & \lambda + \gamma_V + \bar{\xi}^* \end{vmatrix}.$$

Thus, we obtain

$$D_1 = (\lambda + \gamma_A) [(\lambda + \gamma + \bar{C}V^*) (\lambda + \gamma_V + \bar{\xi}^*) - \bar{\Phi} \bar{C}X^*] \\ - \bar{\alpha}_2 [\bar{C}'_2 X^* V^* (\lambda + \gamma_V + \bar{\xi}^*) - \bar{\xi}_2 V^* \bar{C}X^*]$$

and

$$D_2 = -(\lambda + \gamma_A) V^* X^* [\bar{C}'_1 (\lambda + \gamma_V + \bar{\xi}^*) - \bar{\xi}_1 \bar{C}].$$

Therefore, it can be seen that $\lambda = -\gamma_A < 0$ is an eigenvalue and the other eigenvalues are solutions of

$$\begin{aligned} & (\lambda + \gamma_A) [(\lambda + \gamma + \bar{C}V^*) (\lambda + \gamma_V + \bar{\xi}^*) - \Phi \bar{C}X^*] \\ & - X^*V^* (\bar{\alpha}_2 [\bar{C}'_2 (\lambda + \gamma_V + \bar{\xi}^*) - \bar{\xi}_2 \bar{C}] + \bar{\alpha}_1 [\bar{C}'_1 (\lambda + \gamma_V + \bar{\xi}^*) - \bar{\xi}_1 \bar{C}]) = 0. \end{aligned}$$

We assume that

$$\bar{\alpha}_1 = \bar{\alpha}_2 = \bar{\alpha}. \quad (16)$$

Then, the last equation becomes

$$\begin{aligned} & (\lambda + \gamma_A) [(\lambda + \gamma + \bar{C}V^*) (\lambda + \gamma_V + \bar{\xi}^*) - \Phi \bar{C}X^*] \\ & - \bar{\alpha} X^*V^* [(\lambda + \gamma_V + \bar{\xi}^*) \bar{C}' - (\bar{\xi}_1 + \bar{\xi}_2) \bar{C}] = 0, \end{aligned}$$

with

$$\bar{C}' = \bar{C}'_2 + \bar{C}'_1.$$

Expanding the last equation, we can rewrite it as follows

$$\begin{aligned} & \lambda^3 + \lambda^2 (\gamma_V + \bar{\xi}^* + \gamma + \bar{C}V^* + \gamma_A) + \lambda [(\gamma_V + \bar{\xi}^*) (\gamma + \bar{C}V^*) \\ & + \gamma_A (\gamma_V + \bar{\xi}^* + \gamma + \bar{C}V^*) - \Phi \bar{C}X^* - \bar{\alpha} X^*V^* \bar{C}'] \\ & + \gamma_A (\gamma_V + \bar{\xi}^*) (\gamma + \bar{C}V^*) - \bar{\alpha} X^*V^* (\gamma_V + \bar{\xi}^*) \bar{C}' \\ & + \bar{\alpha} \bar{C}X^*V^* (\bar{\xi}_1 + \bar{\xi}_2) - \Phi \bar{C}X^* \gamma_A = 0. \end{aligned}$$

Finally, the equation to find the last eigenvalues is given by

$$\lambda^3 + k_1 \lambda^2 + k_2 \lambda + k_3 = 0 \quad (17)$$

with

$$\begin{aligned} k_1 &= \gamma_V + \bar{\xi}^* + \gamma + \bar{C}V^* + \gamma_A, \\ k_2 &= (\gamma_V + \bar{\xi}^*) (\gamma + \bar{C}V^*) + \gamma_A (\gamma_V + \bar{\xi}^* + \gamma + \bar{C}V^*) - \Phi \bar{C}X^* \\ & \quad - \bar{\alpha} X^*V^* \bar{C}', \\ k_3 &= \gamma_A (\gamma_V + \bar{\xi}^*) (\gamma + \bar{C}V^*) - \bar{\alpha} X^*V^* (\gamma_V + \bar{\xi}^*) \bar{C}' \\ & \quad + \bar{\alpha} \bar{C}X^*V^* (\bar{\xi}_1 + \bar{\xi}_2) - \Phi \bar{C}X^* \gamma_A, \end{aligned}$$

where

$$\bar{C}(Y^*) = \beta_1 C_1(\bar{A}_1^*(Y^*)) + \beta_2 C_2(\bar{A}_2^*(Y^*)), \quad \bar{C}'(Y^*) = \beta_1 C'_1(\bar{A}_1^*(Y^*)) + \beta_2 C'_2(\bar{A}_2^*(Y^*)),$$

and

$$\bar{\xi}^*(Y^*) = \bar{\xi}_1 \bar{A}_1^*(Y^*) + \bar{\xi}_2 \bar{A}_2^*(Y^*).$$

Theorem 2 Assume that (10), (13), (15), (16) and $\mathcal{R}_0 > 1$ are satisfied. Then, the endemic steady state P_1 is locally asymptotically stable.

Proof By the Routh-Hurwitz criteria, P_1 is locally asymptotically stable if and only if the coefficients of the polynomial function (17) satisfy

$$k_i > 0, \quad i = \{1, 2, 3\} \quad \text{and} \quad k_1 k_2 > k_3.$$

In order to prove the above inequalities, we rewrite k_1 , k_2 and k_3 using the following equalities coming from the steady state conditions

$$\begin{cases} \gamma_A \bar{A}_1^* & = \bar{A}_1 + \bar{\alpha} Y^*, \\ \gamma_A \bar{A}_2^* & = \bar{\alpha} Y^*, \\ \gamma X^* + \bar{C} X^* V^* & = \Omega, \\ \bar{C} X^* V^* & = \gamma Y^*, \\ \bar{\xi}^* V^* + \gamma_V V^* & = \Phi Y^*. \end{cases}$$

It is clear that $k_1 = \gamma_V + \bar{\xi}^* + \gamma + \bar{C} V^* + \gamma_A > 0$. After some calculations, we obtain for $Y^* \in (0, \Omega/\gamma)$,

$$k_2 = \Phi \frac{Y^*}{V^*} \left(\frac{\Omega}{X^*} - \gamma \right) + \gamma_A \left(\Phi \frac{Y^*}{V^*} + \frac{\Omega}{X^*} \right) - \bar{\alpha} X^* V^* \bar{C}' > 0,$$

and

$$k_3 = \gamma_A \Phi \frac{Y^*}{V^*} \left(\frac{\Omega}{X^*} - \gamma \right) + \bar{\alpha} (\bar{\xi}_1 + \bar{\xi}_2) \bar{C} X^* V^* - \bar{\alpha} \Phi \frac{Y^*}{V^*} \bar{C}' X^* V^* > 0,$$

because $\bar{C}' < 0$ and as $\mathcal{R}_0 > 1$, we have the existence of $0 < X^* < \frac{\Omega}{\gamma}$, $V^* > 0$ and $Y^*/V^* > 0$ given by the expressions (9) and (12). We still have to show that

$$k := k_1 k_2 - k_3 > 0, \quad \text{for all } Y^* \in \left(0, \frac{\Omega}{\gamma} \right).$$

After some calculations, we get

$$\begin{aligned} k &= \frac{\Omega}{X^*} \left[\Phi \frac{Y^*}{V^*} \left(\frac{\Omega}{X^*} - \gamma \right) + \gamma_A \frac{\Omega}{X^*} - \bar{\alpha} \bar{C}' X^* V^* \right] \\ &+ \Phi \frac{Y^*}{X^*} \left[\Phi \frac{Y^*}{V^*} \left(\frac{\Omega}{X^*} - \gamma \right) + \gamma_A \Phi \frac{Y^*}{V^*} \right] \\ &+ \gamma_A \left[\Phi \frac{Y^*}{V^*} \left(\frac{\Omega}{X^*} - \gamma \right) + \gamma_A \left(\Phi \frac{Y^*}{V^*} + \frac{\Omega}{X^*} \right) - \bar{\alpha} \bar{C}' X^* V^* \right] \\ &+ \gamma \frac{Y^*}{V^*} (\gamma_A \Phi - \bar{\alpha} (\bar{\xi}_1 + \bar{\xi}_2) V^*). \end{aligned}$$

Recall that

$$V^* = \frac{\gamma_A \Phi Y^*}{\bar{\alpha} (\bar{\xi}_1 + \bar{\xi}_2) Y^* + \bar{\xi}_1 \bar{A}_1 + \gamma_A \gamma_V}.$$

Then, as $\mathcal{R}_0 > 1$ we get

$$\gamma_A \Phi - \bar{\alpha} (\bar{\xi}_1 + \bar{\xi}_2) V^* > 0.$$

Because $\bar{C}' < 0$ and $\mathcal{R}_0 > 1$, we conclude that

$$k := k_1 k_2 - k_3 > 0.$$

Then, the endemic equilibrium P_1 is locally asymptotically stable.

3.3 Global asymptotic stability of the disease-free steady state P_0

We assume that (10), (15) and $\mathcal{R}_0 < 1$ are satisfied. We first prove that if a trajectory of the system (3) enters the subset

$$\mathbb{D} := \{(\bar{A}_1, \bar{A}_2, X, Y, V) \in \mathbb{R}_+^5 : \bar{A}_1 \geq \bar{A}_1/\gamma_A\}$$

it will never leave it. We put

$$B_1 = \bar{A}_1 - \frac{\bar{A}_1}{\gamma_A}, \quad B_2 = \bar{A}_2 \quad \text{and}$$

$$Z = \begin{cases} \frac{\Omega}{\gamma} - (X + Y), & \text{if } X + Y \leq \Omega/\gamma, \\ (X + Y) - \frac{\Omega}{\gamma}, & \text{if } X + Y > \Omega/\gamma. \end{cases}$$

The function Z is continuously differentiable because, if $X + Y = \Omega/\gamma$ then, $X' + Y' = 0$. With the new functions B_1 , B_2 and Z , the system (3) becomes

$$\begin{cases} \frac{dB_1}{dt} = \bar{\alpha}_1 Y - \gamma_A B_1, \\ \frac{dB_2}{dt} = \bar{\alpha}_2 Y - \gamma_A B_2, \\ \frac{dZ}{dt} = -\gamma Z, \\ \frac{dY}{dt} = \left(\beta_1 C_1 \left(B_1 + \frac{\bar{A}_1}{\gamma_A} \right) + \beta_2 C_2(B_2) \right) \left(\frac{\Omega}{\gamma} + \nu Z \right) V - \gamma Y, \\ \quad - \left(\beta_1 C_1 \left(B_1 + \frac{\bar{A}_1}{\gamma_A} \right) + \beta_2 C_2(B_2) \right) V Y, \\ \frac{dV}{dt} = \Phi Y - \bar{\xi}_1 B_1 V - \bar{\xi}_2 B_2 V - \left(\bar{\xi}_1 \frac{\bar{A}_1}{\gamma_A} + \gamma_V \right) V, \end{cases} \quad (18)$$

where

$$\nu = \begin{cases} -1, & X + Y \leq \Omega/\gamma, \\ +1, & X + Y > \Omega/\gamma. \end{cases}$$

In both cases, $\frac{\Omega}{\gamma} + \nu Z \geq 0$. Furthermore, the disease-free steady state P_0 becomes $0_{\mathbb{R}^5}$ and the set \mathbb{D} is transformed to the nonnegative orthant \mathbb{R}_+^5 . We also have the properties

$$\left. \frac{dB_i(t)}{dt} \right|_{B_i(t)=0} \geq 0, \quad \left. \frac{dZ(t)}{dt} \right|_{Z(t)=0} = 0, \quad \left. \frac{dY(t)}{dt} \right|_{Y(t)=0} \geq 0 \quad \text{and} \quad \left. \frac{dV(t)}{dt} \right|_{V(t)=0} \geq 0.$$

Thus, the solutions of System (18) initiating from \mathbb{R}_+^5 stay in \mathbb{R}_+^5 . In fact, we have proved the following result for System (3).

Proposition 2 *Assume that (10), (15) and $\mathcal{R}_0 < 1$ are satisfied. Then, the subset \mathbb{D} is invariant under the system (3).*

Now we will use the following comparison result for ordinary differential systems (Kirkilionis and Walcher, 2004).

Lemma 1 *Consider two differential systems $x' = f(x)$ and $x' = g(x)$ given on an invariant subset U of \mathbb{R}^k , $f, g : U \rightarrow \mathbb{R}^k$ are locally Lipschitz functions. Then, the following two conditions are equivalent:*

- (i) *For each $x_0, y_0 \in U$ the inequality $x_0 \leq y_0$ implies $x(t) \leq y(t)$ for all $t \geq 0$, where $x'(t) = f(x(t))$ and $y'(t) = g(y(t))$, $t \geq 0$, with $x(0) = x_0$, $y(0) = y_0$.*
- (ii) *For all $i = 1, \dots, k$, the inequality*

$$f_i(x_1, \dots, x_{i-1}, x_i, x_{i+1}, \dots, x_n) \leq g_i(\bar{x}_1, \dots, \bar{x}_{i-1}, \bar{x}_i, \bar{x}_{i+1}, \dots, \bar{x}_n)$$

holds whenever $x_j \leq \bar{x}_j$ for all $j \neq i$ and $x_i = \bar{x}_i$.

We first consider the case $\nu = -1$ and we suppose that the condition (13) is satisfied. Then, on the set \mathbb{D} the solutions of the system (18) satisfy the inequalities

$$\begin{cases} \frac{dB_1}{dt} = \bar{\alpha}_1 Y - \gamma_A B_1, \\ \frac{dB_2}{dt} = \bar{\alpha}_2 Y - \gamma_A B_2, \\ \frac{dZ}{dt} = -\gamma Z, \\ \frac{dY}{dt} \leq \left(\beta_1 C_1 \left(\frac{\bar{A}_1}{\gamma_A} \right) + \beta_2 C_2(0) \right) \frac{\Omega}{\gamma} V - \gamma Y, \\ \frac{dV}{dt} \leq \Phi Y - \left(\bar{\xi}_1 \frac{\bar{A}_1}{\gamma_A} + \gamma_V \right) V, \end{cases} \quad (19)$$

because the functions

$$B_1 \mapsto C_1 \left(B_1 + \frac{\bar{A}_1}{\gamma_A} \right) \quad \text{and} \quad B_2 \mapsto C_2(B_2)$$

are decreasing on $[0, +\infty)$. In fact, we are comparing the system (18) to the following linear system

$$\begin{cases} \frac{dB_1}{dt} = \bar{\alpha}_1 Y - \gamma_A B_1, \\ \frac{dB_2}{dt} = \bar{\alpha}_2 Y - \gamma_A B_2, \\ \frac{dZ}{dt} = -\gamma Z, \\ \frac{dY}{dt} = \left(\beta_1 C_1 \left(\frac{\bar{A}_1}{\gamma_A} \right) + \beta_2 C_2(0) \right) \frac{\Omega}{\gamma} V - \gamma Y, \\ \frac{dV}{dt} = \Phi Y - \left(\bar{\xi}_1 \frac{\bar{A}_1}{\gamma_A} + \gamma_V \right) V. \end{cases} \quad (20)$$

The characteristic equation of this last system is given by

$$(\lambda + \gamma_A)^2 (\lambda + \gamma) \left[\lambda^2 + \lambda \left(\gamma + \frac{\bar{\xi}_1 \bar{A}_1}{\gamma_A} + \gamma_V \right) + \gamma \left(\frac{\bar{\xi}_1 \bar{A}_1}{\gamma_A} + \gamma_V \right) (1 - \mathcal{R}_0) \right] = 0. \quad (21)$$

It can be seen that the eigenvalues are $-\gamma_A$, $-\gamma$ and the roots of the polynomial

$$\lambda^2 + \lambda \left(\gamma + \frac{\bar{\xi}_1 \bar{A}_1}{\gamma_A} + \gamma_V \right) + \gamma \left(\frac{\bar{\xi}_1 \bar{A}_1}{\gamma_A} + \gamma_V \right) (1 - \mathcal{R}_0),$$

which by Routh-Hurwitz criteria are negative if and only if $\mathcal{R}_0 < 1$. Then, the trivial steady state of the linear system (20) is globally asymptotically stable. We conclude by Lemma 1 that for the same initial condition on the set \mathbb{D} , the solution of (18) is between $0_{\mathbb{R}^5}$ and the solution of the system (20). This means that if $\mathcal{R}_0 < 1$, the trivial steady state P_0 is globally asymptotically stable on the set \mathbb{D} .

We now consider the case $\nu = 1$. Then, from the equation of Z we have for all $\epsilon > 0$ and all $Z_0 > 0$, the existence of $T_\epsilon \geq 0$, for instance $T_\epsilon = \max\{0, (1/\gamma) \ln(Z_0/\epsilon)\}$, such that $0 < Z(t) < \epsilon$, for all $t > T_\epsilon$. Then, we are comparing, for $t > T_\epsilon$ the system (18) to

$$\begin{cases} \frac{dB_1}{dt} = \bar{\alpha}_1 Y - \gamma_A B_1, \\ \frac{dB_2}{dt} = \bar{\alpha}_2 Y - \gamma_A B_2, \\ \frac{dZ}{dt} = -\gamma Z, \\ \frac{dY}{dt} = \left(\beta_1 C_1 \left(\frac{\bar{A}_1}{\gamma_A} \right) + \beta_2 C_2(0) \right) \left(\frac{\Omega}{\gamma} + \epsilon \right) V - \gamma Y, \\ \frac{dV}{dt} = \Phi Y - \left(\bar{\xi}_1 \frac{\bar{A}_1}{\gamma_A} + \gamma_V \right) V. \end{cases} \quad (22)$$

This last system has the same characteristic equation as system (20), except that \mathcal{R}_0 is replaced by

$$\mathcal{R}_\epsilon = \frac{1}{\gamma} \times \left(\frac{\Omega}{\gamma} + \epsilon \right) \times \left(\frac{\Phi}{\gamma_V + \xi_1 \frac{\bar{A}_1}{\gamma_A}} \right) \times \left(\beta_1 \frac{(\bar{A}_1/\gamma_A)^p}{(\bar{A}_1/\gamma_A)^n + 1} + \beta_2 \right).$$

Under the condition $\mathcal{R}_0 < 1$, we can choose $\epsilon > 0$ small enough such that $\mathcal{R}_\epsilon < 1$. So, the trivial solution of the linear system (22) is globally asymptotically stable. We conclude from Lemma 1 that the disease-free steady state P_0 is globally asymptotically stable on the set \mathbb{D} .

To complete our study on the global asymptotic stability of the disease-free steady state P_0 , we consider a nonnegative solution that does not start on the set \mathbb{D} , that is such that $\bar{A}_1(0) < \bar{A}_1/\gamma_A$. Suppose that there exists $\bar{t} > 0$ such that $\bar{A}_1(t) < \bar{A}_1/\gamma_A$ for $0 \leq t < \bar{t}$ and $\bar{A}_1(\bar{t}) = \bar{A}_1/\gamma_A$. From the differential system (3), we can see that \bar{A}_1 is an increasing function on $[0, \bar{t}]$, with $\bar{A}'_1(\bar{t}) = \bar{\alpha}Y(\bar{t}) \geq 0$. Then, the solution enters the set \mathbb{D} at time \bar{t} and then tends to the disease-free steady state P_0 . If $\bar{A}_1(t) < \bar{A}_1/\gamma_A$ for all $t \geq 0$, then \bar{A}_1 is an increasing function on $[0, +\infty)$. This implies that there exists a limit $l := \lim_{t \rightarrow +\infty} \bar{A}_1(t) \leq \bar{A}_1/\gamma_A$ and $\lim_{t \rightarrow +\infty} \bar{A}'_1(t) = 0$. We deduce from the equation of \bar{A}_1 that

$$\lim_{t \rightarrow +\infty} Y(t) = \frac{\gamma_A l - \bar{A}_1}{\bar{\alpha}_1} \leq 0.$$

Then, the only possibility is

$$\lim_{t \rightarrow +\infty} Y(t) = 0 \quad \text{and} \quad \lim_{t \rightarrow +\infty} \bar{A}_1(t) = \frac{\bar{A}_1}{\gamma_A}.$$

We proved that the set \mathbb{D} is globally attractive for System (3). Then, we conclude on the global asymptotic stability of the the disease-free equilibrium P_0 .

Theorem 3 *Assume that (10), (13), (15) and $\mathcal{R}_0 < 1$ are satisfied. Then, the disease-free equilibrium P_0 is globally asymptotically stable.*

Although some assumptions like (10), (13), (15) and (16) were done during the analysis of the model, they are not always necessary. Therefore, in the numerical simulations, we will sometimes relax them.

3.4 Numerical results

Forward, the baseline parameter set is $\gamma = \gamma_X = \gamma_Y = 0.0231$, $\gamma_A = 0.0495$, $\gamma_V = 5.5452$, all in days^{-1} , $\eta_1 = \eta_2 = 0$ ml [RNA copies] $^{-1}$ days^{-1} , $\alpha_1 = 8 \times 10^{-5}$ and $\alpha_2 = 2.4 \times 10^{-4}$ molecules cells $^{-1}$ days^{-1} , $\Omega = 5 \times 10^4$ cells ml $^{-1}$ days^{-1} , $\Phi = 10^4$ [RNA copies] cells $^{-1}$ days^{-1} , $A_1 = 5$ molecules ml $^{-1}$ days^{-1} , $\xi_1 = \xi_2 = 0.15$ ml molecules $^{-1}$ days^{-1} , $\theta_1 = 10^2$, $\theta_2 = 3 \times 10^2$, both in molecules ml $^{-1}$, $\beta_1 = \beta_2 = 4 \times 10^{-9}$ ml [RNA copies] $^{-1}$ days^{-1} , $n = 3$

and $p = 1$. This gives us $\mathcal{R}_0 \approx 271$ (Equation (7)). With these values of the parameters, the conditions (10), (13) and (15) are satisfied. Then, we have the persistence of the infection. The system (1) was solved by Runge-Kutta fourth-order method with initial condition as $A_1(0) = 10$ and $A_2(0) = 0$ in molecules ml^{-1} , $X(0) = \Omega/\gamma$ and $Y(0) = 0$ in cells ml^{-1} , and $V(0) = 100$ [RNA copies] ml^{-1} .

Figure 1 shows the time evolution of the antibody populations $A_1(t)$ and $A_2(t)$, the normalized susceptible and infected target cells, respectively $x(t) := X(t)/(\Omega/\gamma)$ and $y(t) := Y(t)/(\Omega/\gamma)$, and the free dengue virus $V(t)$. The figure also displays the behavior of enhancement and neutralization functions $t \mapsto E(A_1(t))$ and $t \mapsto N(A_2(t))$ (Equation (2)). This scenario mimics a second infection with a dengue serotype V different from serotype V_0 of the first infection. We can see that the increase of the number of infected cells occurs when the enhancement function $t \mapsto E(A_1(t))$ reaches its maximum. This occurs before the activation of the neutralization $N(A_2(t))$. This also increases the amount of the virus, which quickly reaches a maximum. Then, the large quantity of infected cells activates the production of antibodies A_2 which are able, during the infection to neutralize the virus and to make V decreasing, which in turn make the infected cells decrease. We denote by t_{DHF} the time when the peak of the infected cells y_{DHF} (it corresponds also to the peak of the virus V_{DHF}) is reached and then DHF can occur. t_{DHF} is the time when the phenomenon of antibody-dependent enhancement occurs (the enhancement function $t \mapsto E(A_1(t))$ reaches its maximum at time t_{DHF}).

Figure 2 shows the maximum value observed for the normalized infected cells y_{DHF} and the time t_{DHF} at which this occurs as a function of α_1 and α_2 , which represent the rate of antibodies production, respectively, A_1 and A_2 . In panel (a) we have $\alpha_2 = 8 \times 10^{-4}$ molecules cells $^{-1}$ days $^{-1}$, in (b) we have $\alpha_1 = 8 \times 10^{-5}$ molecules cells $^{-1}$ days $^{-1}$. In all cases, we have $\mathcal{R}_0 \approx 271$ (it does not depend on these two parameters). While the increase of α_2 promotes protection from infection, and as a consequence the observed y_{DHF} curve is a monotonic decreasing function of α_2 , a peak is observed on the curve of y_{DHF} as a function of α_1 . This behavior is linked to the enhancement effect promoted by the antibodies generated by the first infection. The dashed horizontal lines highlight the thresholds, for both set of parameters, at which the number of infected cells cross the number of susceptible cells, in (a) it occurs at $\alpha_1 = 0.00028$ and in (b) at $\alpha_2 = 0.001$. The threshold for α_1 is smaller than the one for α_2 because the preexisting antibodies A_1 are produced at a constant rate λ_1 (independently of the number of infected cells), while the antibodies A_2 are produced only by infected cells. It is interesting to note that in panel (a) t_{DHF} , depending on α_1 , first increases until it reaches a peak and then decreases, while in panel (b) it always increases when α_2 is increasing.

Figure 3a shows y_{DHF} and t_{DHF} as functions of $A_1(0)$ (initial preexisting antibodies). A large amount of $A_1(0)$ means a recently recovering from a first infection. In this case, it is expected that the antibodies A_1 produced from the first infection are able to promote enough level of cross-immunity to protect the individual from a second infection. As time pass, $A_1(0)$ decreases because of

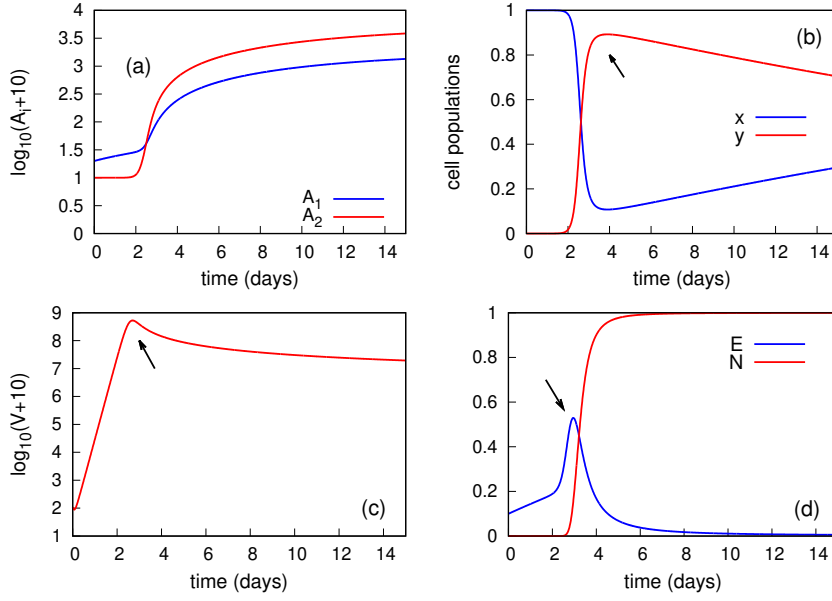


Fig. 1 Temporal evolution of the populations of (a) antibodies, (b) normalized susceptible ($x := X/(\Omega/\gamma)$) and infected ($y := Y/(\Omega/\gamma)$) target cells, and (c) virus. In (d), we can see the evolution of the enhancement $t \mapsto E(A_1(t))$ and neutralization $t \mapsto N(A_2(t))$. The arrows indicate the time at which DHF/DSS occurs.

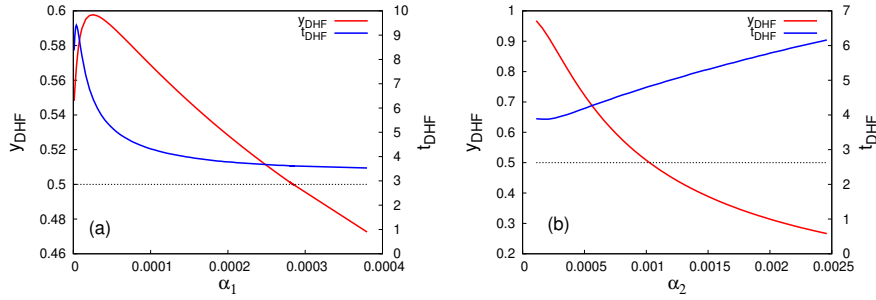


Fig. 2 Maximum value of the normalized infected cell versus α_1 and α_2 . The horizontal dashed line highlight the thresholds at which the number of infected cells cross the number of susceptible cells, in (a) it occurs at $\alpha_1 = 0.00028$ and in (b) at $\alpha_2 = 0.001$ molecules $\text{cells}^{-1} \text{days}^{-1}$.

the absence of the first virus V_0 ; therefore, protection through cross-immunity becomes less effective. It is also shown the threshold for $A_1(0)$ at which the number of infected cells cross the number of susceptible cells, and the equilibrium value of the normalized number of infected cells $y := Y/(\Omega/\gamma)$, respectively, the dashed black and red lines. Observe that t_{DHF} increases as $A_1(0)$ increases. In panel (b) of Figure 3, we have $\beta_1 = 4 \times 10^{-10}$ and $\beta_2 = 1 \times 10^{-10}$ ml [RNA copies] $^{-1} \text{days}^{-1}$. The other parameters are the same as for Figure

1. We can see the contradictory role of antibodies A_1 which can protect when their number is high, or promote infection when their quantity is within a specific window.

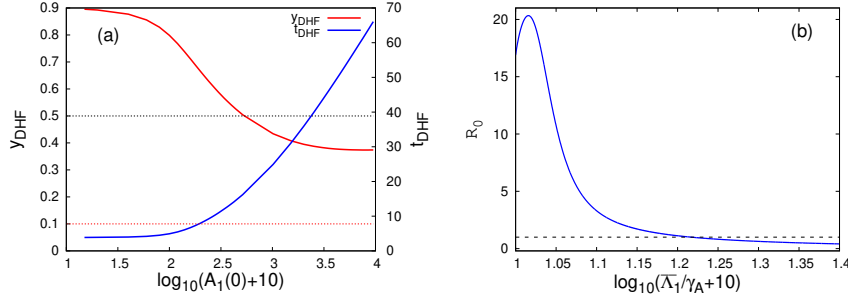


Fig. 3 In (a) we have the maximum value of the normalized infected cells versus $A_1(0)$, and in (b) \mathcal{R}_0 versus \bar{A}_1/γ_A .

Figure 4 shows the partial rank correlation coefficient (PRCC) obtained from the sensitivity analysis. In this case, the output is \mathcal{R}_0 . The input parameters were chosen from a uniform distribution using the latin hypercube sampling (LHS). The minimum and maximum value of each parameter were taken from Table 1. A total of 15000 parameter sets were drawn; those for which $p < n$ were used in the analysis ($N = 7471$). The increase of $Q_2 := \Omega/\gamma_X$, Φ , β_1 , β_2 and p promotes the increase of \mathcal{R}_0 . The opposite effect is observed for the other parameters $Q_1 := \bar{A}_1/\gamma_A$, γ_Y , ξ_1 , n and Q_3 (dummy parameter). The order of importance related to the contribution of each parameter to \mathcal{R}_0 is $\{Q_1, Q_2\}$ (equal contribution), $\{\Phi, \gamma_Y, \xi_1, \beta_2\}$, $\{\beta_1, n, p\}$ (equal contribution). Finally, the contribution of γ_V is not significant. We want to emphasize that first ranked parameters $Q_1 := \bar{A}_1/\gamma_A$, $Q_2 := \Omega/\gamma_X$ and Φ are related, respectively, to the production of cross-reactive antibody, to the production of target healthy cells, and to the production of free virus by the infected cells.

4 Discussion

The development of a vaccine that is able to promote effective protection against the four different serotypes of dengue remains a challenge. The incomplete understanding of the immune response mechanisms that drive protection or enhancement of the infection is one of major obstacles. The only vaccine currently licensed, Sanofi Pasteur's Dengvaxia, involves 3 doses given at 6-month intervals and can be used in people aged 9 years or over, leaving out of protection an important and vulnerable group. World Health Organization (WHO) recommends that this vaccine only be given to individuals with confirmed prior dengue virus infection. Low vaccine uptake, incomplete vaccinations, short follow-up, lack of a faithful animal model, and lack of reliable

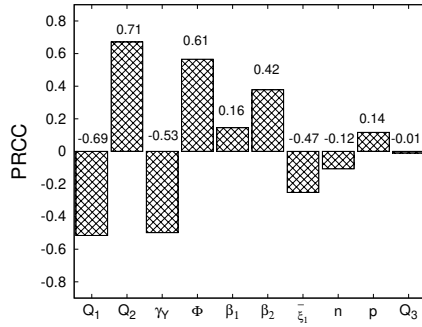


Fig. 4 Sensitivity analysis of \mathcal{R}_0 . The parameters Q_1, Q_2, Q_3 are respectively $\bar{\Lambda}_1/\gamma_A, \Omega/\gamma_X$ and a dummy parameter.

immunological and viral markers are some of the factors that have limited progress in measurement of vaccine efficacy and long-term protection.

Sequential infections with different types of DENV significantly increase the risk of severe disease resulting in death. Two hypotheses have been proposed to explain the severity observed in secondary infections: (1) antibody-dependent enhancement (ADE); (2) original T cell antigenic sin. In this work, we explore using mathematical modeling, the first hypothesis (ADE). A new ordinary differential model is proposed to reproduce cells (infected and uninfected) and virus dynamics under a scenarios of antibody competition for virus receptors. Enhancement and neutralization functions inspired from experiments done *in vitro* were drawn from basic concepts of chemical reactions and used to mimics virus uptake by two distinct populations of antibodies, classified as cross-reactive or type-specific ones. The analytic study of the model showed the existence of two equilibriums, a disease-free equilibrium and an endemic one. We performed the asymptotic stability analysis for these two equilibriums. The basic reproduction number \mathcal{R}_0 provides a simple metric to decide when the disease will persist or not in the population. The local and global stability analysis of disease free-equilibrium were addressed by the next generation matrix method and by comparison principle for ordinary differential systems. The local asymptotic stability of the endemic-equilibrium corresponds to the occurrence of DHF/DSS. It was analytically proved with some restrictive conditions (in particular, Condition (13)) on the parameters. Knowing that disease progression is ultimately caused by DENV-host interaction, we explored the range of parameters through sensitivity analysis and temporal evolution of populations to understand the role of both antibodies, from the first and the second infection, on disease severity. For this, we defined the time t_{DHF} at which DHF/DSS occurs as the time when the population of infected cells reaches a maximum. We showed that t_{DHF} corresponds to the time at which maximal enhancing activity for dengue infection occurs. Using the base reproduction number \mathcal{R}_0 as an output, we were able to rank the contribution of each parameter, highlighting the role of the cross-reactive

antibody, the production of target cells, and the production of free virus by the infected cells to dengue disease progression (see Figure 4).

The dual role of cross-reactive antibodies against DENV affects the temporal dynamics of the disease in several aspects; in high quantity, they can promote protection by reducing the number of infected cells (Figure 2a), as well as the value of \mathcal{R}_0 (Figure 3b). When their number is not large enough to neutralize the virus, the same antibodies can do the opposite, that is, to enhance the infection. In addition, cross-reactive antibodies contribute to reducing the time of outbreak of the disease (Figure 2a). On the other hand, fast growth of neutralizing antibodies can efficiently halt disease progression (Figure 2b). According to the literature, the course of DHF/DSS is approximately 7 to 10 days. Finally, data from blood samples (humoral immune response and cell dynamics) from individuals with sequential dengue infections could be used to fit the model, thereby improving the prediction of disease outcome.

5 Conclusion

The course of the disease in a second dengue infection correlates with the virus-host interaction, the production of target cells and the amount of cross-reacting antibodies, as well as the main factors that modulate the time course of the disease. Competition of antibodies for the virus receptor promotes viral clearance or enhancement of infection depending on the amount of cross-reacting antibody from the first infection and the rapid activation of a new population of neutralizing antibodies.

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