

Research Article

Modeling Dengue Immune Responses Mediated by Antibodies: Insights on the Biological Parameters to Describe Dengue Infections

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Dengue fever is a viral mosquito-borne disease, a significant global health concern, with more than one third of the world population at risk of acquiring the disease. Caused by 4 antigenically distinct but related virus serotypes, named DENV-1, DENV-2, DENV-3, and DENV-4, infection by one serotype confers lifelong immunity to that serotype and a short period of temporary cross immunity to other related serotypes. Severe dengue is epidemiologically associated with a secondary infection caused by a heterologous serotype via the so-called antibody-dependent enhancement (ADE), an immunological process enhancing a new infection. Within-host dengue modeling is restricted to a small number of studies so far. With many open questions, the understanding of immunopathogenesis of severe disease during recurrent infections is important to evaluate the impact of newly licensed vaccines. In this paper, we revisit the modeling framework proposed by Sebayang et al. and perform a detailed sensitivity analysis of the well-known biological parameters and its possible combinations to understand the existing data sets. Using numerical simulations, we investigate features of viral replication, antibody production, and infection clearance over time for three possible scenarios: primary infection, secondary infection caused by homologous serotype, and secondary infection caused by heterologous serotype. Besides, describing well the infection dynamics as reported in the immunology literature, our results provide information on parameter combinations to best describe the differences on the immunological dynamics of secondary infections with homologous and heterologous viruses. The results presented here will be used as baseline to investigate a more complex within-host dengue model.

1. Introduction

Dengue fever (DF), a mosquito-borne viral infection, is a major public health concern, with more than 390 million dengue cases estimated to occur every year [1], particularly in tropical and subtropical areas [2] of the globe.

Transmitted by the bite of a female *Aedes* mosquito [3, 4], DF is caused by 4 antigenically distinct but related viruses, named DENV1 to DENV-4 serotypes. Dengue infection has a wide spectrum of clinical manifestation,

ranging from asymptomatic and mild symptoms up to more severe signs with hemorrhagic manifestations.

Infection by one serotype confers lifelong immunity to that serotype and also a short period of temporary cross immunity to other related serotypes. A primary natural dengue infection is often asymptomatic or mild, a self-restricting illness with fever, migraines, muscle or joint pain, and skin rash [5]. Recovered individuals develop antibodies that although cross-react with the heterologous serotypes confer lifelong protection against reinfection with a

homologous serotype. Nevertheless, upon recovery, the human host is considered susceptible to acquire a secondary infection caused by a heterologous serotype. [6, 7].

Individuals undergoing a secondary dengue infection with a heterologous serotype have a higher risk of developing the severe form of the disease, in former times called dengue hemorrhagic fever (DHF), and without proper treatment, evolving to dengue shock syndrome (DSS) and eventually death. This finding is epidemiologically associated with the immunological process called antibody-dependent enhancement (ADE), where the preexisting antibodies to previous dengue infection do not neutralize the heterologous serotype but rather enhance the new infection [8–12].

Treatment of uncomplicated dengue cases is only supportive, and severe dengue cases require hospitalization. A safe, effective, and affordable dengue vaccine against the four strains would represent a significant advance for the control of the disease and could be an important tool for reducing disease transmission and mortality.

Due to the dengue-specific complexities described above, vaccine development focuses on the generation of a tetravalent vaccine aimed at providing long-term protection against all dengue virus serotypes [13]. Several candidates of tetravalent vaccines are at various stages of development. Two tetravalent dengue vaccines have now completed phase 3 clinical trial: Dengvaxia [14], a product developed by Sanofi Pasteur that is now licensed in more than 20 countries; and the DENVax vaccine, developed by Takeda Pharmaceutical Company [15, 16]. Dengvaxia resulted in a higher rate of hospitalized severe dengue cases when given to seronegative children, compared with age-matched seronegative controls [14], with the risks of Dengvaxia administration being discussed [17] exhaustively. An age structured mathematical model was developed, based on Sanofi's recommendation, and its analysis has shown a significant increase in the number of hospitalizations in a population when this vaccine was administered without population screening [18]. Moreover, the individual serostatus prior to vaccination was found to be determinant of Dengvaxia efficacy and adverse events [19, 20]. DENVax vaccine efficacy against virologically confirmed dengue disease and hospitalization were shown to be higher than the efficacies reported for the Dengvaxia vaccine, with a more balanced efficacy in seronegatives and seropositives [15, 16]. However, similarly as observed for Dengvaxia, the individual serostatus prior to vaccination was also observed to be determinant of DENVax vaccine efficacy, with vaccine efficacy continuing to decrease over time [21]. Hence, long-term surveillance consisting of prudent and careful observation of the DENVax vaccine phase 3 recipients is required.

Mathematical models describing dengue fever epidemiological dynamics are found back from 1970 [22]. A careful review of dengue modeling framework was recently published [23], where the three main structural modeling approaches were considered: the vector-host, the host-to-host, and the within-host which is restricted to a small number of studies so far, with many open questions. In this paper, a modeling framework that is able to describe the dengue immunological response mediated by antibodies [24] is presented. Models

for primary dengue infection (A), secondary dengue infection with the same (homologous) virus (B), and secondary dengue infection with a different (heterologous) dengue virus (C) are revisited, and a detailed sensitivity analysis of the most important parameters is performed. In the absence of significant amount of laboratory data, the aim of this study is to describe qualitatively the dengue immunological responses mediated by antibodies and to explore the feature of antibody production and ADE when preexisting antibodies are present in the human host.

2. Modeling Dengue Immune Response Mediated by Antibodies

Dengue fever infection is resolved within twelve to fourteen days. Symptoms usually last for 2–7 days and a patient developing severe disease, more common during a secondary infection, enters in the so-called critical phase within 3–7 days after illness onset. During a primary dengue infection, the IgM type antibody is the first antibody to be produced in response to a serotype antigen, followed by the production of the IgG antibody type, which is specific for the serotype causing the infection. While in primary dengue infection, the IgM antibody type is produced faster and to higher levels than the IgG antibody type, and the reverse is true in secondary dengue infection. Besides conferring life-long protective immunity against a specific serotype, the IgG antibody is able to cross-react with heterologous DENV serotypes. In a secondary infection with a homologous serotype, the preexisting IgG is the responsible for clearing the infection, while the adaptive humoral response is slowly contributing with a lower increment of antibody levels which are produced while the infection is cleared and the serotype antigen is presented. In a secondary infection with a heterologous serotype, the immunological response is complex. Instead of neutralizing the new dengue serotype, the preexisting antibodies promote the enhancement of the infection by facilitating the entry of the complex antibody-heterologous virus into target cells. This disease augmentation phenomenon is called antibody-dependent enhancement (ADE) and its occurrence in dengue has been used to explain the etiology of severe disease [8–12], which has been shown to be correlated with higher viral loads [22, 23, 25, 26]. Early dengue diagnosis is important for the clinical management of the patient. The most commonly used technique for dengue routine diagnosis is the enzyme-linked immunosorbent assay (ELISA), with primary or secondary infections being characterized based on the concentration of immunoglobulins M and G from the blood sample, the so-called IgM and IgG antibodies, respectively.

In this section, we revisit the proposed modeling framework to describe dengue immunological responses mediated by antibodies [24]. The models depend on body cells and free viral particles which on interaction with each other results in infected cells and trigger the antibodies production and infection clearance. A sensitivity analysis for the most important models parameters are performed and the dynamics of models A, B, and C are compared in respect to the viral load and antibodies production dynamics during a primary and secondary dengue infections.

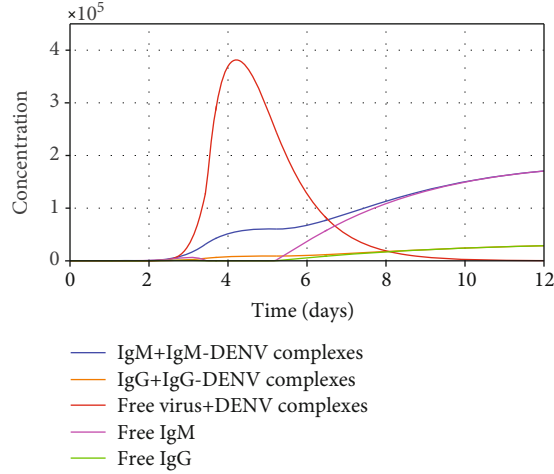


FIGURE 1: Model simulation for a primary dengue infection: immunological responses mediated by antibodies. Overall viral particles are plotted in red: free virus and Antibody-DENV complexes ($IgM - DENV \cdot 4 + IgG - DENV + V$). Free IgM is shown in magenta and free IgG in green. Antibody-DENV complexes $IgM - DENV$ and $IgG - DENV$ are shown in blue and orange, respectively. Parameter values used for the model simulation are available at [22], if not otherwise stated here.

2.1. Primary Dengue Infection: Model (A). A primary dengue infection, shown in Figure 1, occurs in individuals with no history of previous dengue infections. Infected mosquito bites a naive human host, releasing free virus in the blood circulation (not shown).

Within-host, susceptible target cells (monocytes/dendritic cells) S , become infected cells I , after meeting free viral particles V , with infection rate aSV . Free virus replicates within the infected cells and released in the blood circulation with rate $\kappa\mu_i$, once the infected cells die. Free viral particles are removed during the infection process of a target cells (bSV). We assume that more than one viral particle is needed to infect a single cell, and therefore, $b > a$.

Macrophages are also considered in the system as susceptible target cell S_m . Macrophages phagocytose the free virus with rate $a_m S_m V$, and differentiate into presenting cells P , initiating the adaptive humoral response. Free viral particles are also removed during the phagocytosis process at rate $b_m S_m V$. In its simplicity, presenting cells triggers the production of antibodies, first IgM-antibody type M , with rate $\alpha_M P$, which is able to bind and neutralize the virus, followed by the production of the IgG-antibody type G , with rate $\alpha_G P$, which is specific to neutralize the virus causing the infection. IgG specific antibodies are cross-reactive to related dengue serotypes. Antibodies IgM and IgG bind into the free virus with rates $\gamma_M M$ and $\gamma_G G$, respectively, reducing the free virus concentration with rates $d_M MV$ and $d_G MV$, respectively, and producing the complexes antibody-virus, IgM-DENV C_M and IgG-DENV C_G , with rates $\gamma_M M \gamma_G G$, respectively. The complex antibody-virus is assumed to clear the infection, after being recognized by killer cells. Note that $d_M > d_G$ since the IgM antibody is a pentamer molecule, able to bind into up to 5 viral particles at once, while the IgG antibody is a monomer molecule, able to bind into 1 viral particle only.

We assume natural mortality rate of susceptible target cells to be μ_S and the disease mortality rate of infected cells

to be μ_i and μ_p , respectively, for monocytes/dendritic cells and macrophages, which are recruited at constant rate π_S and π_M , respectively. Free antibodies and complexes are removed at rates μ_M , μ_G , μ_{C_M} and μ_{C_G} as shown in Equation (1).

The complete modeling framework including each step presented in Figure 2 is written as a system of ordinary differential equations (ODEs) as follows.

$$\begin{aligned}
 \frac{dS}{dt} &= \pi_S - \mu_S S - aSV, \\
 \frac{dI}{dt} &= aSV - (\mu_i + \mu_S)I, \\
 \frac{dV}{dt} &= \kappa\mu_i I - bSV - b_m S_m V - d_M MV - d_G GV, \\
 \frac{dS_m}{dt} &= \pi_m - \mu_S S_m - a_m S_m V, \\
 \frac{dP}{dt} &= a_m S_m V - (\mu_S + \mu_P)P, \\
 \frac{dM}{dt} &= \alpha_M P - \mu_M M - \gamma_M MV, \\
 \frac{dG}{dt} &= \alpha_G P - \gamma_G GV - \mu_G G, \\
 \frac{dC_M}{dt} &= \gamma_M MV - \mu_{C_M} C_M, \\
 \frac{dC_G}{dt} &= \gamma_G GV - \mu_{C_G} C_G.
 \end{aligned} \tag{1}$$

Figures 3(a) and 3(b) show the dynamical behaviour of free virus during a primary dengue infection. With an initial condition of $V_0 = 3$ and fixing the viral replication rate to $\kappa = 60$, free viral particles increase exponentially and decrease over time. The viral load peak is reached around

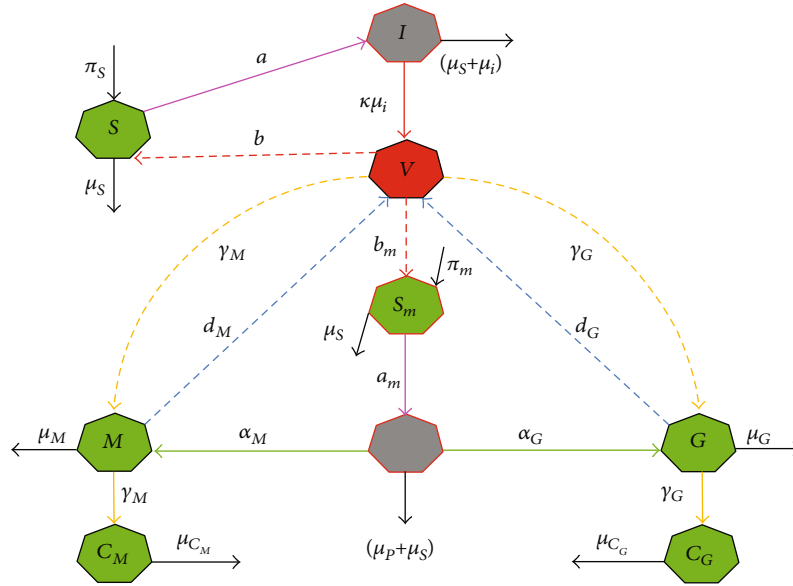


FIGURE 2: Flow chart: Immunological responses mediated by antibodies for a primary dengue infection. Magenta lines represent the transitions of infection related stages, with susceptible target cells, monocytes/dendritic cells, and macrophages, becoming infected cells and presenting cells, respectively. The full red line represents the viral replication, proportional to the death rate of an infected cell. Dashed red lines represent the viral particles removal during the infection process of a susceptible cell. The green lines represent the production rates of the antibodies by the presenting cells, first *IgM* (left hand side) and then *IgG* (right hand side) antibody types. Dashed blue and orange lines represent the binding and removal rates for antibodies-virus and virus-antibodies, respectively. The full orange lines represent the transitions of free antibodies particles to antibody-DENV complexes, after the free antibody binds into the free viral particle. Black lines represent the recruitment and decay rates of the model variables.

day 4 of infection, with the infection cleared (reduced viral particles concentration) after day 5 of infection.

A sensitivity analysis for the viral replication parameter κ is shown in Figures 3(c) and 3(d). Viral load behaviour varies significantly in function of the parameter κ , with higher viral load levels directly correlated with the viral replication factor κ . The viral load reach its peak soon or later for lower or higher κ values, revealing a possible viral replication threshold value to be between $\kappa = 50$ (in purple) and $\kappa = 60$ (in green), with a significant change in the viral curve behaviour (Figure 3(d)).

We continue our analysis for the viral replication behaviour with the sensitivity analysis for the parameters a , the infection rate of susceptible cells, and b , the viral particle removal rate when a monocyte/dendritic cells become infected. Here, the viral replication factor κ is fixed above and below 50.

The viral load behaviour in function of the infection rate parameter a , for a fixed viral replication factor $\kappa = 45$ and $\kappa = 60$, is shown in Figures 4(a) and 4(c).

While for lower κ values the viral load dynamics shows a wider variation in function of the a parameter, for higher κ values, the viral load dynamics are shown to be not very sensitive to the variations of a . Note that for the simulations in Figures 4(a) and 4(c), we have fixed the value of the parameter $a = 0.02$. Figures 4(b) and 4(d) shows the viral load behaviour in function the viral removal rate parameter b . For the simulations presented in Figures 4(b) and 4(d), we have fixed the parameter $b = a \cdot 15$.

Here, for lower κ values, the viral load behaviour is observed to vary significantly in function of the parameters a and b , showing a significant variation of viral load peak levels and time. While larger a values lead to a faster viral load peak, the larger b values show an opposite behaviour. This behaviour can be explained as follows. The larger the infection rate a is, the higher the free virus concentration will be, with the viral load peak showing a direct relation with time, as more body cells become infected, and hence, releasing more viral particles to the blood circulation of the human host, (Figure 4(a)). On the other hand, a high viral removal rate b leads to lower viral load concentration in the blood circulation of the human host, hence, needing longer time to reach its peak. Here, the viral load peak shows an inverse relation with time (Figure 4(b)). This behaviour can be explained as follows. The higher is the number of virus being removed, while infecting a susceptible target cell, the less free virus will be circulating in the blood of the host, hence, decreasing the probability of a susceptible target cells to become infected, and hence, with less free virus being released after an infected cell dies. While fixing the replication factor to $\kappa = 60$, the viral dynamics seems to not be much sensitive to the changes of the parameters a and b . Figure 4(c) shows that the variation of a has no significant role on the viral load behaviour. Moreover, the number of virus required to infect a single target cells plays a minor role on the viral load dynamics as well (Figure 4(d)), showing a more steep curves, as compared to the dynamics shown in Figure 4(b), but only small variation for the time reaching

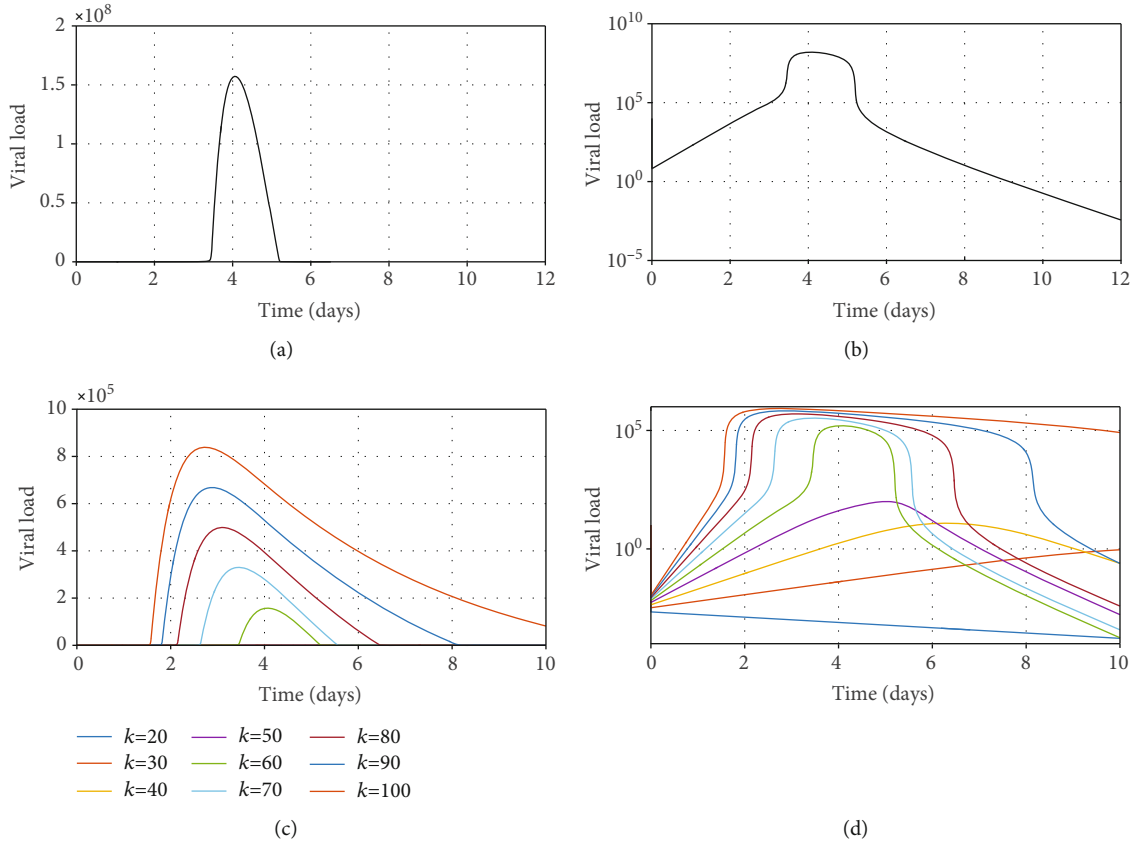


FIGURE 3: Behaviour of free virus during a primary dengue infection: (a–b) shows the viral load concentration over time, in natural and in semi-logarithmic scale. The viral replication parameter is fixed to $\kappa = 60$. (c–d) shows the viral load curve, in natural and in semi-logarithmic scale, in function of the variation of the viral replication parameter $\kappa \in [20,100]$.

the viral load peaks. Those are very important observations to be taking into consideration during the parameter estimation using the available empirical data.

The dynamics for the antibodies production during a primary infection is shown in Figure 5. The IgM antibody type (magenta) is observed to appear at day 2 of the infection, followed by the production of the IgG antibody type (green). Free IgM appears first as a small hump between day 2–3 of infection, and then become undetectable, only observed again after day 5, hence, after the infection is cleared. That is because, while participating during the infection clearance, all existing free IgM are used to generate the well-known complexes IgM-DENV. The free IgM molecules are exhausted after binding into the free viral particles, shaping the viral load curve (black). This result is reported for the first time here, consistent with the current dengue serologic test recommendation, i.e., 7 days after symptom onset. This result is of great importance and validates the best use of diagnostic tests to be used during a disease outbreak.

Figure 5(a) shows the dynamical behaviour described above for a 12 days period. Levels of free IgM are found to be very low up to day 5 of infection. This observation can explain why the dengue IgM-ELISA test should be only performed after day 6 or 7 after symptoms to avoid the so-called false negative results that will be expected, when the blood sample is collect at early stages of the infection, hence, dur-

ing the period in time when free IgM is not present. For that, a PCR test or viral isolation technique are advised to detect the infection by detection of genetic material from virus causing the infection. The IgG test would show the presence of a past infection and, for the same reasons described above, its diagnostic capacity is also restricted to blood samples collected at later stages of infection.

Figure 5(b) shows the dynamics after a 150 days period. Here we can clearly see the dynamics of the antibody levels for production and decay. We observed a high concentration of IgM antibodies for the first 30 days, whereas the IgG antibodies appear to increase in a much slower scale than the IgM, reaching a low concentration level for the same time period. While the IgM starts decaying after day 30, reaching very low levels after 90 days, the IgG levels are observed to be stable over longer time, hence, conferring the so-called memory antibody and providing the lifelong immunity against that specific virus. Again, these observations can explain the limitation of using an IgM-ELISA test for dengue infections at early stages of infection, when the free IgM are not present at detectable levels in human blood sample. The IgG-ELISA test would however indicate a past infection, able to detect the preexisting antibodies.

The complete model dynamics describing the primary dengue infection is shown in Figure 1. The combined viral load curve (in red) shows the overall viral particles

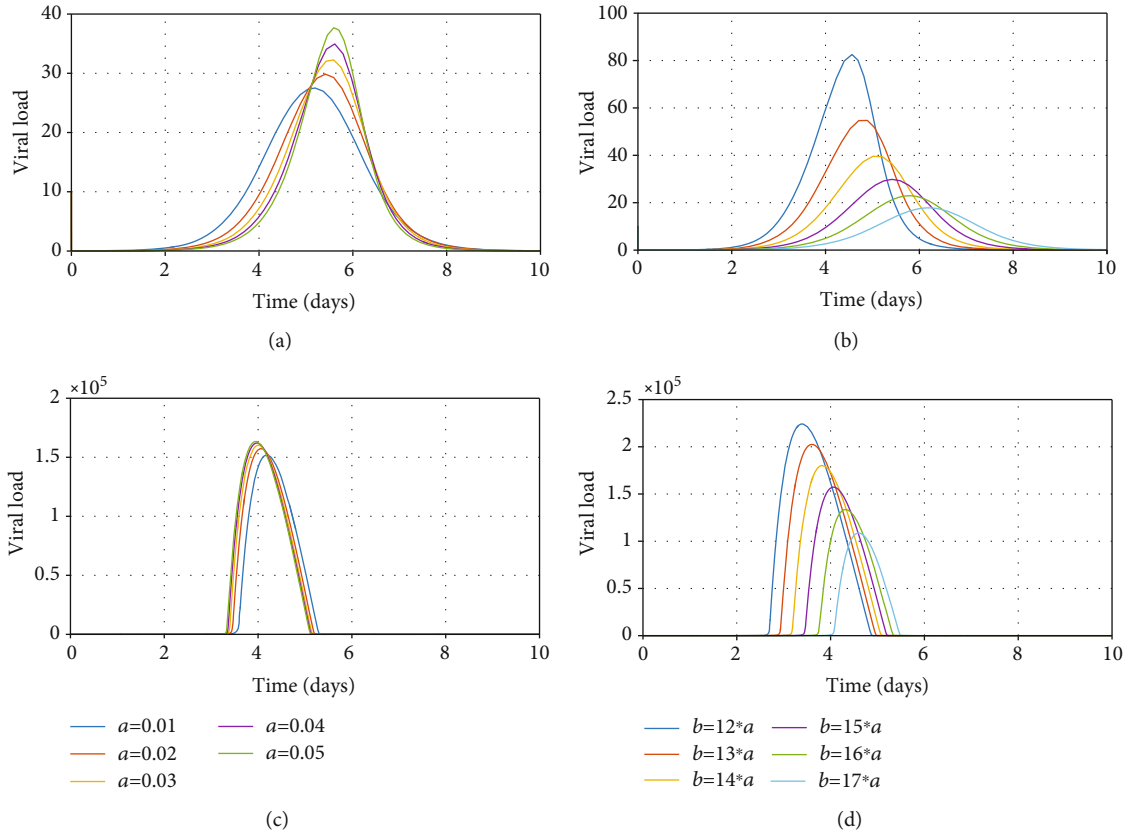


FIGURE 4: Behaviour of viral load in primary infection for varying parameters in (a) we produce variation of a for $K = 45$, and (b) we have the variation b while $K = 45$, while in (c) we have the variation of a at a higher $K = 60$, and in (d) we have variation of b with fixed $K = 60$ for 12 days.

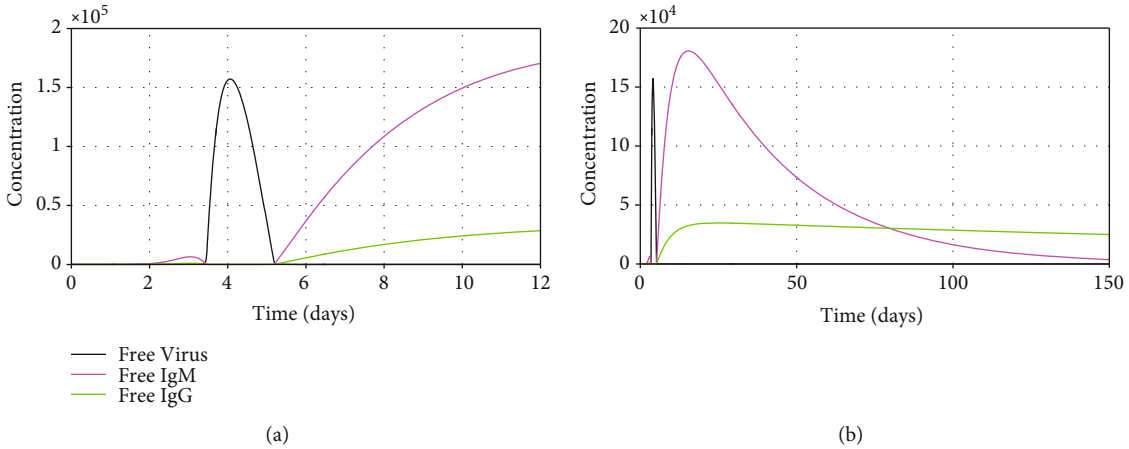


FIGURE 5: Behaviour of viral load and antibodies production and decay for a primary dengue infection. In (a) the dynamics for 12 days period and in (b) the dynamics for a 150 days period.

dynamics, that counts the free virus and the viral particles bound to the antibody-virus complexes. Free IgM antibodies (in magenta) are observed at very low levels until day 5 of infection. That is because they are all used to generate the IgM-DENV complexes (in blue). We assume that each antibody IgM, which is a pentamer molecule, binds (and hence remove) 4 viral particles on average. Free IgM appears to be at detectable levels from day 6

onward, once the infection is cleared and the viral particles are removed by the complexes C_M and C_G , remaining at a detectable levels for approximately 3 months. The level of free IgG (in green) and free and IgG-DENV complexes (in orange) are appearing around day 3 of infection, at very low levels as compared to the levels of IgM and IgM-DENV complexes, not playing a significant role on the viral clearance. Free IgG reaches a much lower

concentration level, in comparison with the free IgM levels, but with a constant concentration, it lasts much longer, assumed to confer the life-long immunity against that particular serotype.

2.2. Secondary Dengue Infection with a Homologous Serotype: Model (B). After a period of temporary cross-immunity, the human host is considered susceptible again, able to acquire a new dengue infection. In this section, we present the dynamics of a secondary dengue infection with a homologous serotype, shown in Figure 6. The presence of a new infection activates the preexisting IgG antibodies ($\alpha_{G_{\text{sec}}}V$) which are able to bind into the new virus. Being a homologous virus, these preexisting IgG is also able to neutralize the virus and therefore, becoming the main responsible for the clearance of the new infection. The concentration of the antibodies type M and type G is reversed to the dynamics presented in the first infection, with the immunological response showing first the increase of preexisting IgG, occurring much faster than the production of IgM and IgG antibodies by adaptive humoral response ($\alpha_M P$ and $\alpha_G P$, respectively).

Model B can be written as a system of ordinary differential equations (Equation (2)). We extend the system developed for the primary dengue infection (Equation (1)), by only including an additional term $\alpha_{G_{\text{sec}}}V$ (in green), to describe the activation of the preexisting IgG antibodies that were produced during the primary dengue infection.

$$\begin{aligned}
\frac{dS}{dt} &= \pi_S - \mu_S S - aSV, \\
\frac{dI}{dt} &= aSV - (\mu_i + \mu_S)I, \\
\frac{dV}{dt} &= \kappa\mu_i I - bSV - b_m S_m V - d_M MV - d_G GV, \\
\frac{dS_m}{dt} &= \pi_m - \mu_S S_m - a_m S_m V, \\
\frac{dP}{dt} &= a_m S_m V - (\mu_S + \mu_P)P, \\
\frac{dM}{dt} &= \alpha_M P - \mu_M M - \gamma_M MV, \\
\frac{dG}{dt} &= \alpha_G P - \gamma_G GV - \mu_G G + \alpha_{G_{\text{sec}}} V, \\
\frac{dC_M}{dt} &= \gamma_M MV - \mu_{C_M} C_M, \\
\frac{dC_G}{dt} &= \gamma_G GV - \mu_{C_G} C_G.
\end{aligned} \tag{2}$$

Model B describes the secondary dengue infection with a homologous dengue serotype. The full model dynamics for the immunological response is shown in Figure 7. The overall viral particle concentration is shown in red, reaching much lower levels than the viral load observed in a primary dengue infection. This is because the activated preexisting IgG is able to clear the infection (much faster than the pro-

duction of antibodies by the adaptive humoral response), not depending on the antibody production process. As such, the antibodies type detection levels are switched, with IgG appearing first than the IgM. In this scenario, the IgG-DENV complexes (in orange) are the main responsible for the new infection clearance.

2.3. Secondary Dengue Infection with a Heterologous Serotype: Model (C). Similarly to the process described above, we investigate the dynamics of a secondary infection with a heterologous dengue serotype. The distinction here lies in the capacity of the preexisting IgG antibodies to bind into the new virus but instead of neutralizing it, enhances the infection by facilitating the entry of the preexisting IgG-DENV complexes into susceptible target cells (Figure 8). As such, the viral replication is increased, reaching very high levels within a very short time, a process called antibody dependent-enhancement (ADE).

Equation (3), now includes additional terms $a_{ADE}SC_G$ and $b_{ADE}SC_G$ (displayed in blue) to describe the enhancement of infection via the inactivated preexisting IgG-DENV complexes infected susceptible target cells. As a result, a higher viral replication is observed, leading to a faster and higher viral load curve. The complete model for the secondary dengue infection with a heterologous dengue serotype is shown in Figure 9.

$$\begin{aligned}
\frac{dS}{dt} &= \pi_S - \mu_S S - aSV_{\text{blue}} - a_{ADE}SC_G, \\
\frac{dI}{dt} &= aSV - (\mu_i + \mu_S)I_{\text{blue}} + a_{ADE}SC_G, \\
\frac{dV}{dt} &= \kappa\mu_i I - bSV - b_m S_m V - d_M MV - d_G GV, \\
\frac{dS_m}{dt} &= \pi_m - \mu_S S_m - a_m S_m V, \\
\frac{dP}{dt} &= a_m S_m V - (\mu_S + \mu_P)P, \\
\frac{dM}{dt} &= \alpha_M P - \mu_M M - \gamma_M MV, \\
\frac{dG}{dt} &= \alpha_G P - \gamma_G GV - \mu_G G + \alpha_{G_{\text{sec}}} V, \\
\frac{dC_M}{dt} &= \gamma_M MV - \mu_{C_M} C_M, \\
\frac{dC_G}{dt} &= \gamma_G GV - \mu_{C_G} C_G_{\text{blue}} - b_{ADE}SC_G.
\end{aligned} \tag{3}$$

In comparison with the results shown for models A and B, this scenario C shows a much higher viral load levels that are generated in a short period of time. Being correlated with severe symptoms, this enhanced viral load behaviour can explain the higher risk of patients developing severe disease during a secondary dengue infection with a heterologous serotype. Here, the preexisting IgG-DENV complexes are responsible for the occurrence of the ADE process. To clear the infection, the adaptive humoral response starts

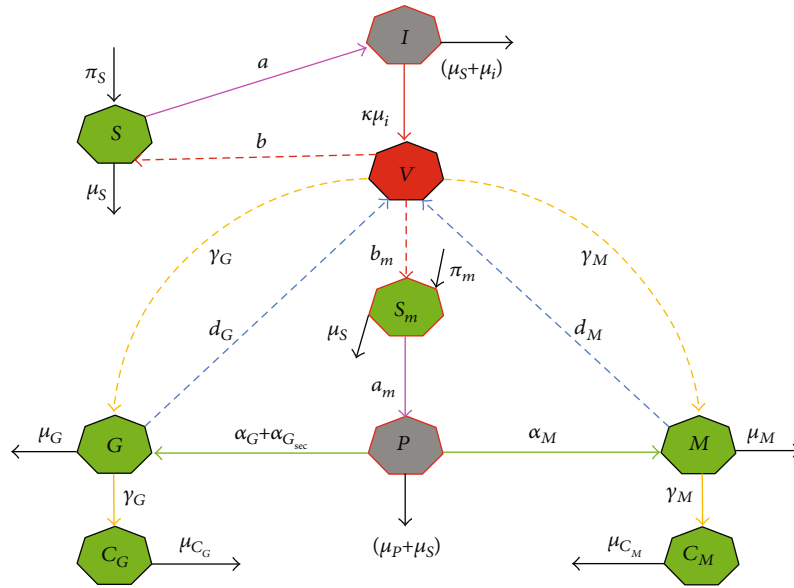


FIGURE 6: Flow chart: dengue infection immunological responses mediated by antibodies for the secondary dengue infection with homologous serotype. Similarly to the Figure 2 description, magenta lines represent the transitions and movement of susceptible target cells (monocytes/dendritic cells and macrophages) from one to another class (infected and presenting cells) with the respective transmission rates indicated. The full red line represents the viral replication, proportional to the death rate of an infected cell. Dashed red lines represent the viral particles removal during the infection process of a susceptible cell. The main difference lies on the description of the green lines that represent the activation of the preexisting IgG at rate $\alpha_{G_{sec}} V$ together with the production rates of the antibodies by the presenting cells $\alpha_G P$ (on the left hand side) and $\alpha_M P$ (on the right hand side). In this scenario, the IgG levels increases first and much faster than the *IgM* levels. Dashed blue and orange lines represent the binding and removal rates for antibodies-virus and virus-antibodies, respectively. The full orange lines represent the transitions of free antibodies particles to antibody-DENV complexes after biding into the free viral particle, with the respective transmission rates indicated. Black lines represent the recruitment and decay rates of the model variables.

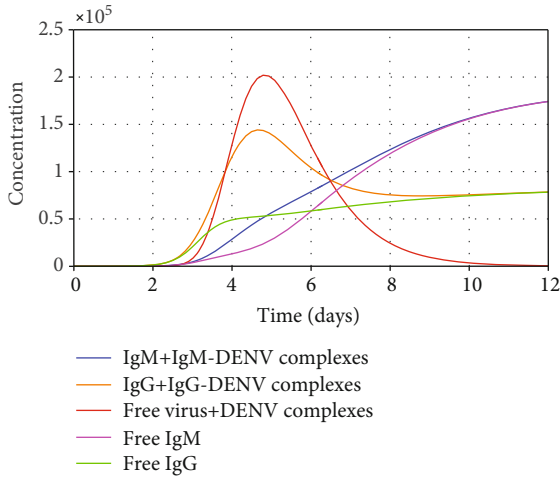


FIGURE 7: Model simulation for secondary dengue infection with a homologous serotype: immunological responses mediated by antibodies. Overall viral particles are plotted in red: free virus and Antibody-DENV complexes ($IgM - DENV \cdot 4 + IgG - DENV + V$). Free IgM is shown in magenta and free IgG in green. Antibody-DENV complexes $IgM - DENV$ and $IgG - DENV$ are shown in blue and orange, respectively. Parameter values used for the model simulation are available at [22], if not otherwise stated here.

producing first the IgM antibody type (in magenta), which is needed at high given the enhanced viral replication. The enhanced immunological response via the IgM antibodies are assumed to play a significant role during the infection clearance, ultimately leading to hemorrhagic manifestations that without appropriate treatment might lead to death.

3. Insights on the Immunopathogenesis of the Severe Disease

As shown in this study, the IgM antibody type is responsible to clear the primary dengue infection. The IgM molecules are produced after the antigen presentation, binding into the free virus, generating the IgM-DENV complexes already at the early stage of the infection. The IgM reaches high levels while clearing the infection, decaying after a month up to an undetectable level in approximately 3 months. The specific antibody IgG or memory antibody is produced while the infection is cleared. IgG are kept to a lower but constant level, providing the so-called long-life immunity against that specific serotype. This specific antibody is able to bind and to neutralize a homologous dengue serotype. After the so-called cross-immunity period, the human host is considered susceptible again, able to acquire a new infection.

In a scenario of a new infection cause by a homologous serotype, the preexisting IgG antibody is activated and plays a major role during the clearance of this new infection. Due

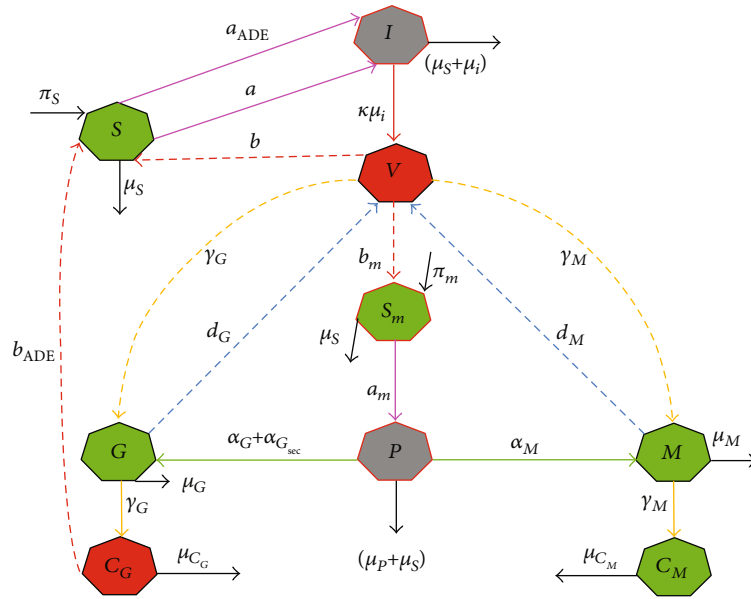


FIGURE 8: Flow chart: dengue infection immunological responses mediated by antibodies for the secondary dengue infection with heterologous serotype. Similarly to the Figure 6 description, magenta lines represent the transitions and movement of susceptible target cells (monocytes/dendritic cells and macrophages) from one to another class (infected and presenting cells) with the respective transmission rates indicated. The full red line represents the viral replication, proportional to the death rate of an infected cell. The difference here lies on the dashed red lines represent: the viral particles removal during the infection process of a susceptible cell, the so-called ADE process, which enhances the infection, increasing the viral replication. The green lines represent the activation of the preexisting IgG at rate $\alpha_{G_{sec}}$ V together with the production rates of the antibodies by the presenting cells $\alpha_G P$ (on the left hand side) and $\alpha_M P$ (on the right hand side). In this scenario, the IgG levels increases first and much faster then the IgM levels. The viral load is much higher than the observed levels for models A and B. Dashed blue and orange lines represent the binding and removal rates for antibodies-virus and virus-antibodies, respectively. The full orange lines represent the transitions of free antibodies particles to antibody-DENV complexes after biding into the free viral particle, with the respective transmission rates indicated. Black lines represent the recruitment and decay rates of the model variables.

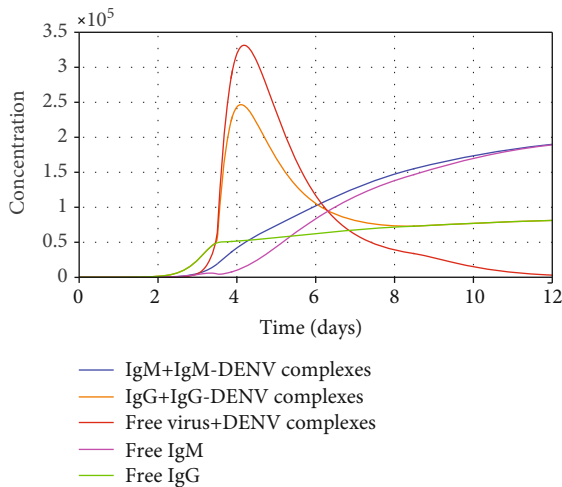


FIGURE 9: Model simulation for a secondary dengue infection with a heterologous serotype: immunological responses mediated by antibodies. Overall viral particles are plotted in red: free virus and Antibody-DENV complexes ($IgM - DENV \cdot 4 + IgG - DENV + V$). Free IgM is shown in magenta and free IgG in green. Antibody-DENV complexes $IgM - DENV$ and $IgG - DENV$ are shown in blue and orange, respectively. Parameter values used for the model simulation are available at [22], if not otherwise stated here.

its specificity, the preexisting IgG-DENV complex can clear the new infection keeping the production of new antibodies to a very low level.

In a scenario of a new infection cause by a heterologous serotype, the preexisting IgG antibody is activated, able to bind into the new virus but not able to neutralize it. Here, the preexisting-IgG-DENV is responsible for the ADE process, enhancing the viral replication, which is correlated to severe symptoms.

Figure 10 shows the dynamics of antibodies-DENV complexes generated for all three scenarios. Figure 10(a) refers to the IgM-DENV complexes production, while Figure 10(b), refers to the IgG-DENV complexes production. With disease symptoms assumed to be correlated with the viral load levels and therefore, respectively, to the levels of antibodies produced to clear the infection, results presented here can be used to explain why a primary infection is often asymptomatic or mild. For a secondary infection with a homologous serotype, mostly undetectable, it is observed that the preexisting IgG antibody type is immediately responding to the new infection, able to neutralize the virus and to clear the new infection much faster than in a primary infection. With a very low viral load level, in this scenario we assume that individuals would develop no symptoms and eventually will not be able to transmit the disease.

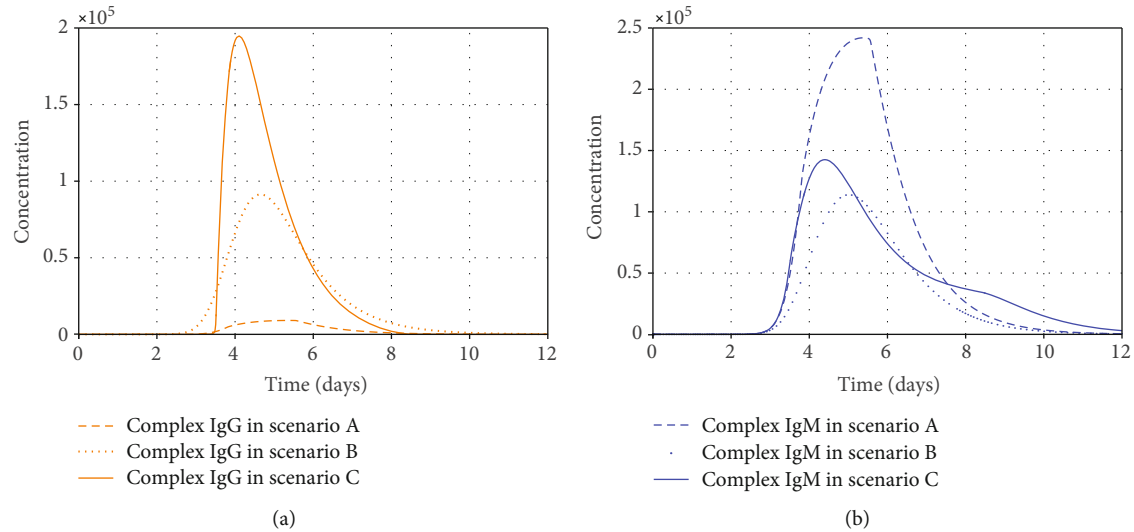


FIGURE 10: Dynamics of complex antibodies in (a) we have dynamics for 12 days where we have a production of complex IgM-antibody for primary dengue infection (A), secondary dengue infection with same (B) and different virus (C) in blue and in (b) we have dynamics for 12 days where we have a production of complex IgG-antibody for Primary dengue infection (A) secondary dengue infection with same (B) and different virus (C) in orange.

In a secondary infection with a heterologous serotype, the preexisting IgG antibody type (Figure 10(b), in orange) immediately responds to the new serotype, reaching very high levels. These antibodies are able to bind to the heterologous dengue serotype but instead of neutralizing the virus, it enhances the infection. This process is called antibody-dependent enhancement (ADE), well described by our framework, model C, leading to a much higher viral load level than in a primary infection or in a secondary infection with homologous serotype. The faster and much higher viral load observed here are assumed to cause the disease augmentation with hemorrhagic symptoms that without proper treatment will eventually evolve to death.

4. Conclusions

In this paper, we performed a detailed analysis of the within-host modeling framework recently proposed by Sebayang et al. [24]. Within-host dengue modeling is restricted to a small number of studies and although the proposed modeling framework is able to describe qualitatively well the dynamics of dengue infections, the understanding of the effects of different parameter combinations are unexplored and indeed of major importance to understand the effect of vaccine administration [17, 18].

Using a different parameter set, we have evaluated the dynamics for the three possible scenarios of primary dengue infection, secondary dengue infection with a homologous serotype and secondary dengue infection with a heterologous serotype. Our results support the notion that severity of dengue illness is influenced by the level of the adaptive humoral responses, with the preexisting IgG antibodies playing a major role during a secondary infection caused by a homologous serotype as well as for the disease enhancement during a secondary infection cause by a heterologous serotype (ADE process). Regarding the initial conditions and

assumptions used for the modeling simulations, an important threshold for the viral replication factor was found, giving insights on the biological parameters describing the immunopathogenesis of the severe disease. Regarding the dynamics of the immune response mediated by antibodies, we have shown a window of time where the free antibody IgM is not detectable—although acting for clearing the ongoing infection, consistent with the current dengue serologic test recommendation. This result was never discussed by any modeling exercise and validates the best use of diagnostic tests used during an epidemic.

Our models are under refinement, and the current system studied here is used as a baseline to understand the results of a more complex system. The results presented here are of use beyond the state of the art, to be used in future research directions to evaluate the impact of imperfect vaccines [27].

Data Availability

This is a qualitative study and no real data is used while writing up this manuscript. For parameter esteems we have given references from where we pick them.

Conflicts of Interest

The authors declare no potential conflict of interests.

Authors' Contributions

M. A supervised the development of this study. V. A conceived and performed the numerical simulations. All authors contributed to the to the development of the modeling framework, analysis of the results, and to the writing of the manuscript.

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