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Article

Modeling Dengue Immune Responses Mediated by Antibodies: a Qualitative Study

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Abstract: Dengue fever is a viral mosquito-borne infection, a major international public health concern. With 2.5 billion people at risk of acquiring the infection around the world, disease severity is influenced by the immunological status of the individual, seronegative or seropositive, prior to natural infection. Caused by four antigenically related but distinct serotypes, DENV-1 to DENV-4, infection by one serotype confers life-long immunity to that serotype and a period of temporary cross-immunity (TCI) to other serotypes. The clinical response on exposure to a second serotype is complex with the so-called Antibody-Dependent enhancement (ADE) process, a disease augmentation phenomenon when pre-existing antibodies to previous dengue infection do not neutralize but rather enhance the new infection, used to explain the etiology of severe disease. In this paper, we present a minimalistic mathematical model framework developed to describe qualitatively the dengue immunological response mediated by antibodies. Three models are analyzed and compared: i) primary dengue infection, ii) secondary dengue infection with the same (homologous) dengue virus and iii) secondary dengue infection with a different (heterologous) dengue virus. We explore the features of viral replication, antibody production and infection clearance over time. The model is developed based on body cells and free virus interactions resulting in infected cells activating antibody production. Our mathematical results are qualitatively similar to the ones described in the empiric immunology literature, providing insights on the immunopathogenesis of severe disease. Results presented here are of use for future research directions to evaluate the impact of dengue vaccines.

Keywords: Within-host modeling; Dengue fever; immune response; antibodies; viral load; Antibody-Dependent Enhancement

1. Introduction

Dengue fever is a viral mosquito-borne infection affecting a large percentage of the population living in the tropics and subtropics. Caused by four antigenically related but distinct viruses, DENV1, DENV2, DENV3, and DENV4, it is estimated that around 400 million dengue infections occur every [1] year, with disease severity being influenced by the immunological status of the individual, seronegative or seropositive, prior to natural infection. While a primary dengue infection is usually asymptomatic or results in mild disease manifestation, the clinical response on exposure to a heterologous dengue serotype is complex, recognized to be a risk factor of progressing to severe disease [2–5].

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Early dengue diagnosis is important for the clinical management of the patient [6,7]. 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 rate of immunoglobulins M and G from the blood sample, the so-called IgM and IgG antibodies respectively [8–10].

From the basic immunology literature, it is known that the IgM is the first antibody secreted by the adaptive immune system in response to a foreign antigen, followed by the production of IgG antibody with increased affinity for the pathogen causing the infection [11]. Likewise, in a primary dengue infection the IgM antibody type is produced more quickly 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 [12–14]. Instead of neutralizing the new dengue serotype, the pre-existing 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) [3,15,16] and its occurrence in dengue has been used to explain the etiology of severe disease [17,18], which has been shown to be correlated with higher viral loads [19–22].

Treatment of uncomplicated dengue cases is only supportive, and severe dengue cases require careful attention to fluid management and proactive treatment of hemorrhagic symptoms. Two tetravalent dengue vaccines have completed phase 3 clinical trial: Dengvaxia, a product developed by Sanofi Pasteur that is now licensed in several countries [23], and the DenVax vaccine, developed by Takeda Pharmaceutical Company [24,25]. While Dengvaxia has resulted in serious adverse events in seronegative individuals compared with age-matched seronegative controls [26–29], long-term surveillance consisting of prudent and careful observation of DenVax vaccine recipients is required, since negative vaccine efficacy was estimated for vaccinated seronegative individuals who were infected with serotype 3, as opposed to an intermediate efficacy for seropositive [30,31].

In recent years, mathematical modeling became an important tool for the understanding of infectious disease epidemiology and dynamics, at both macroscopic and microscopic levels, addressing ideas about the components of host-pathogen interactions. Dengue models are often used to understand infectious disease dynamics and to evaluate the introduction of intervention strategies like vector control and vaccination. At the population level, multi-strain dengue dynamics have been modeled with extended (Susceptible-Infected-Recovered) SIR-type models including immunological aspects of the disease such as temporary cross-immunity and ADE phenomenology [32–39]. However, within-host host dengue modeling are restricted to a small number of studies so far [40–43]. Within-host models consider the dynamic interaction between free virus and susceptible target cells [40–42], differing on the functional form used to model viral infectivity, immune response, and viral clearance dynamics. However, the role of pre-existing DENV-serotype specific IgG antibody in a secondary dengue infection with an explicit mechanism to explain its protective or enhancing effect has not deeply being explored yet.

In this paper, we present a mathematical model framework developed to describe the dengue immunological response mediated by antibodies. Three models are analyzed and compared: i) primary dengue infection, ii) secondary dengue infection with the same (homologous) serotype and iii) secondary dengue infection with a heterologous dengue virus. The model is a refined version to that proposed in [40], and can describe qualitatively the dynamics of viral load and antibody production and decay for scenarios of primary and secondary infections as found in the empirical immunology literature. Giving insights on the immunopathogenesis of severe diseases, the results presented here are of use for future research directions to evaluate the impact of dengue vaccines.

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2. Modeling within-host dengue infections

In this section, we present the models developed to describe dengue immunological responses mediated by antibodies. The models are based on body cells and free viral particle interactions that result in infected cells and subsequently trigger to activate the immune response. We explore the feature of viral replication, viral load, antibody production and decay, and infection clearance over time for primary infection, secondary infection with the same serotype (homologous serotype), and secondary infection with different serotype (heterologous serotype), where the role of the ADE process is evaluated. The differences in viral load levels and the occurrence of clinical symptoms are discussed.

2.1. Primary dengue infection model

Dengue viruses are transmitted to a human host by an infected female *Aedes* mosquito bite. It is called a primary dengue infection if it occurs in seronegative hosts, i.e., individuals with no history of previous dengue infections. In its simplicity, the interaction between target cells, infected cell, virus, and immunological response mediated by antibodies is represented in Figure 1

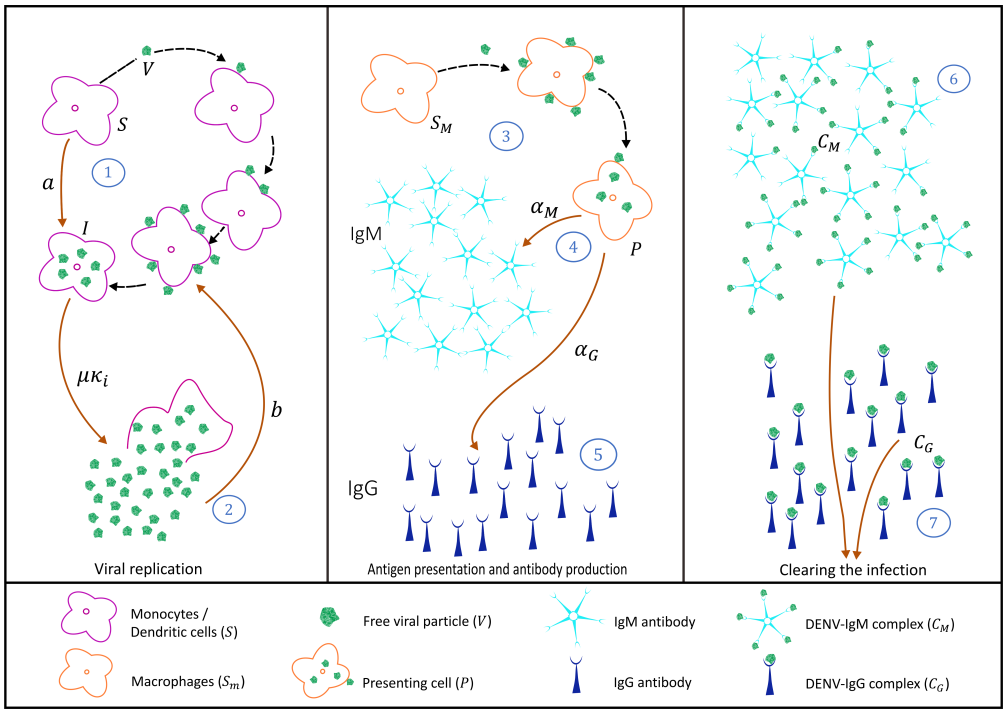

Figure 1. Schematic in-host dengue immunological responses mediated by antibodies: primary infection. Three blocks are used to describe 7 steps during the infection, from viral replication up to infection clearance.

Briefly, susceptible target cells, monocytes, and dendritic cells (S) are produced by the body at a constant rate (π_S) and have a natural mortality rate μ_S, where $\frac{1}{\mu_S}$ is the expected lifetime of the uninfected target cell. Free dengue virus V infect susceptible target cells S at rate a, producing infected cells I (see step 1 in Figure 1) [44]. It is assumed that infected cells have an infection-induced mortality rate $\mu_i \geq \mu_S$, releasing free virus κ to the system (see process 2 in Figure 1). We assume that several free virus particle are needed to infect a single susceptible cell and therefore, while the number of susceptible cells decreases with aSV rate, the number of free viruses decreases with a bSV rate.

Macrophages are also considered in the system as a target susceptible cell S_m. Upon infection, those cells differentiate to become presenting cells (P), shown in process 3 in Figure 1. Presenting cells are assumed to trigger, via antigen presentation, the production

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of antibodies IgM (M) and IgG (G) with rates γ_M and γ_G respectively (see process 4 and 5 in Figure 1. Presenting cells can eventually die with antigen presentation induced mortality rate μ_P.

While in a primary infection IgM antibodies are produced first and to higher levels than IgG, the reverse is true in a secondary infection. Antibodies IgM, a pentameter molecule and antibodies IgG, a monomer molecule, bind into the free virus with rates $\gamma_M d_M$ and $\gamma_G d_G$, generating virus-antibody complexes IgM-DENV (C_M) and IgG-DENV (C_G), respectively (see process 6 and 7 in Figure 1) [15,45]. Those complexes are assumed to clear the ongoing infection after being recognized by killing cells.

In order to understand the individual dynamics of viral replication, viral load, antibodies production, and decay, and finally the clearance of infection, our model is constructed in blocks of equations which are coupled gradually until we obtain the complete model framework able to describe a primary dengue infection and its immunological response mediated by antibodies.

2.1.1. Virus replication dynamics

With susceptible target cells (monocytes and dendritic cells) S, infected cells I, and the virus V, the process of viral replication can be analyzed with a basic SIV model as follows

$$\begin{aligned} \frac{dS}{dt} &= \pi_S - \mu_S S - aSV \\ \frac{dI}{dt} &= aSV - (\mu_i + \mu_S)I \\ \frac{dV}{dt} &= \kappa\mu_i I - bSV, \end{aligned} \tag{1}$$

where all parameters are described in Table 1.

The model described in Equation System (1) shows an exponential growth of viral particles in the absence of any immunological response. The free viral growth depends on the virus replication factor κ, as well as by the infection rate of susceptible cells a and the removal rate of viral particles during the infection of susceptible cells b. As the value of parameters in Table 1, the numerical simulations are shown in Figures 2, with free virus detected around day 2 of the infection process.

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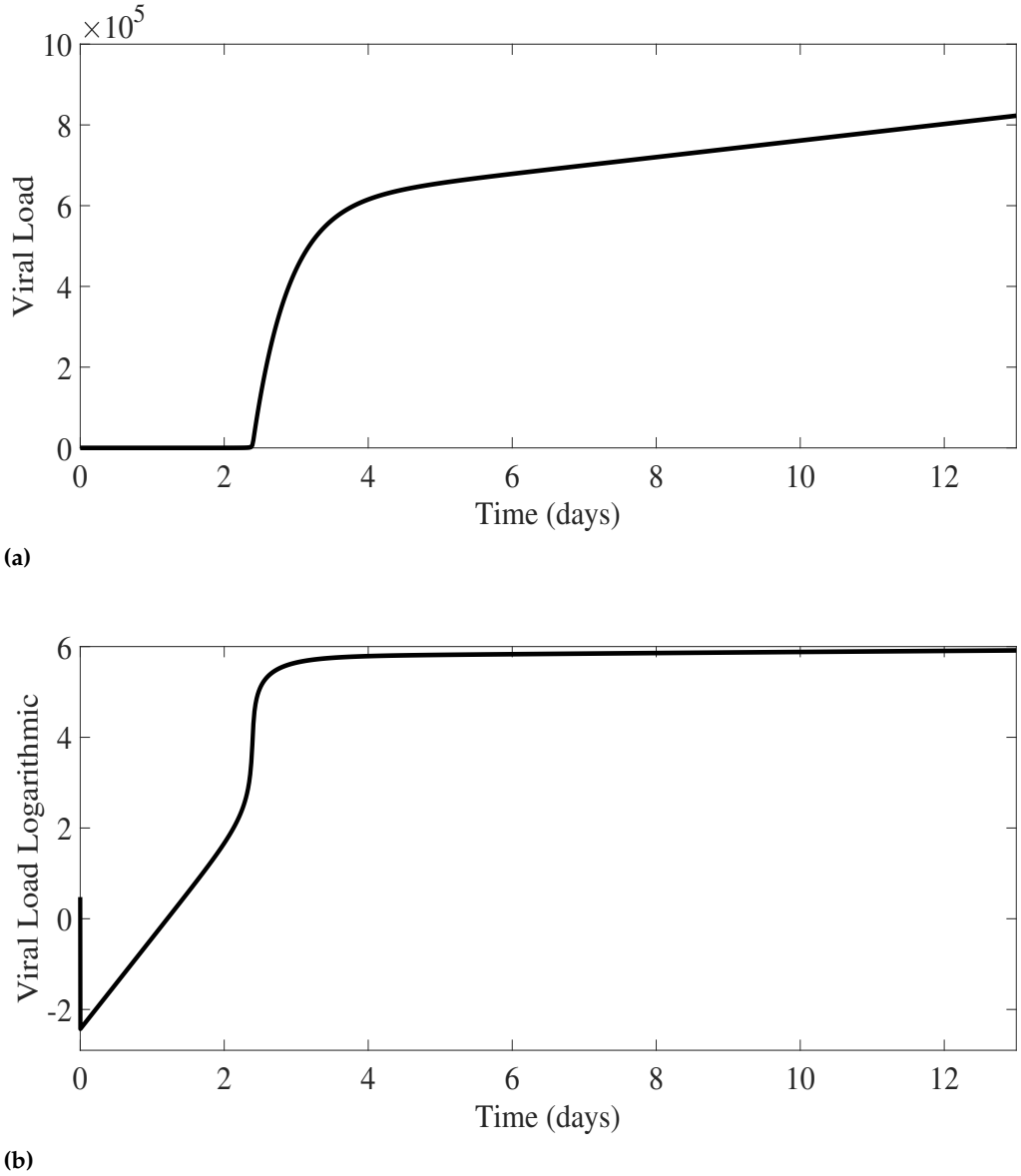

Figure 2. Free viral load dynamics for primary infection prior to antibody production. The viral replication dynamics are shown in natural scale (a) and in semi-logarithmic scale (b). Model parameters are shown in Table 1.

To investigate the sensitivity of viral level related to the model parameters in Equation System (1), Figure 3 presents the numerical result of viral load related to κ, a, and b. Sensitivity analysis is performed by varying one of the parameters and fixing the others. The result shows that the variation of the number of free viral particles released by an infected cell plays a major role in viral load peak, reaching very high values in a short period of time as κ increases (see Figure 3(a)).

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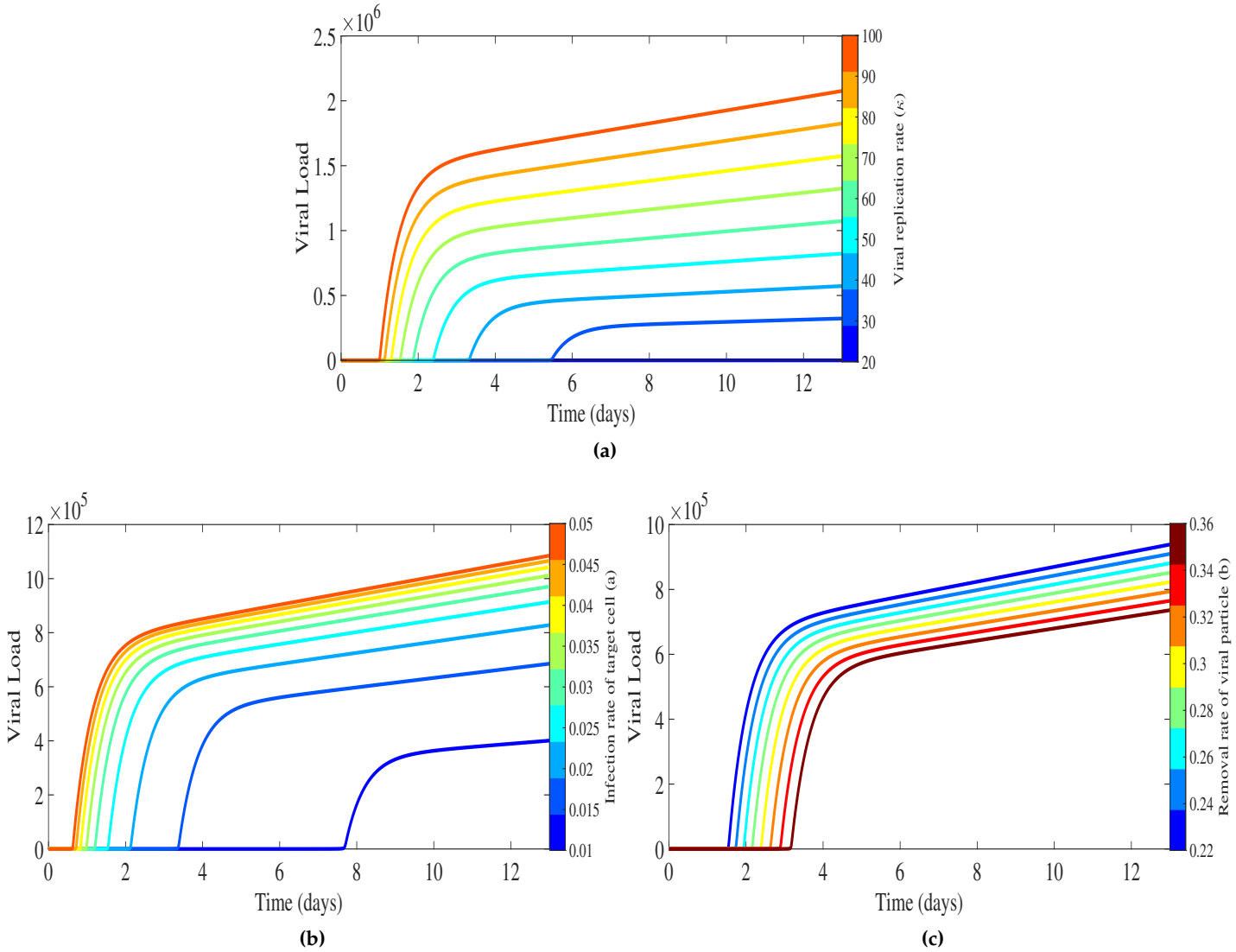

Figure 3. Sensitivity analysis for the parameters involved on free virus dynamics. (**a**) For fixed $a = 0.02$ and $b = 15a$ parameters, we vary the viral replication factor κ between $[20, 100]$. (**b**) For fixed $\kappa = 50$ and $b = 0.3$, we vary the infection rate of susceptible cells parameter a between $[0.01, 0.05]$. (**c**) The removal rate of viral particles b is varied between $[11a, 18a]$ with of fixed $\kappa = 50$ and $a = 0.02$.

As for the infection rate of susceptible cells a, free viral particle levels increases as the parameter value increases, since a higher infection rate generates more infected cells that will release more viral particles. The biological time for free viral particles detection also decreases as parameter a increases (see Figure 3(b)). On the other hand, only a small variation of free viral load particles is observed when changing the rate b, at which the viral particles are lost due to the infection process, see Figure 3(c))).

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Table 1. The biological meaning of the parameters and parameter values used for the numerical simulation.

Dengue modeling framework parameters			
Parameters	**Parameter values**	**Biological meaning**	**Reference**
π_S	600	constant target cell production (monocytes/dendritic cells) per day	[42,46]
π_M	300	constant target cell production (macrophages) per day	[42,46]
μ_S	$1/30$	lifespan of susceptible target cells in days	[47]
μ_i	2	lifespan of infected cells (monocytes/dendritic cells) per day	estimated
μ_P	$0.1 \cdot \mu_1$	lifespan of presenting cells per day	estimated
$a = a_m$	0.02	infection rate of susceptible target cells per viral particle per day	estimated
$b = b_m$	$15 \cdot a$	removal rate of viral particles during the infection of target cells	estimated
κ	50	viral replication factor	[48]
α_M	10	reproduction rate of IgM antibody per day	estimated
α_G	1.5	reproduction rate of IgG antibody per day	estimated
α_{G_sec}	2000	reproduction rate of pre-existing IgG antibody per day	estimated
$\gamma_M = \gamma_G$	0.06	antibodies binding rate per day	estimated
d_M	$4 \cdot \gamma_M$	binding rate of free virus with IgM antibody per day	estimated
d_G	γ_G	binding rate of free virus with IgG antibody per day	estimated
μ_M	0.03	decay rate of IgM per day	[29]
μ_G	$1/365$	decay rate of IgG per day	[29]
$\mu_{CM} = \mu_{CG}$	1	decay rate of virus-antibody complexes per day	estimated
$S(t_0)$	π_S/μ_S	initial value for target cells (monocytes/dendritic cells)	[47]
$S_m(t_0)$	π_M/μ_S	initial value for target cells (macrophages)	[47]
$V(t_0)$	10	initial value for free viral particles upon infection (mosquito bite)	estimated

2.1.2. IgM and IgG antibody production and decay and free viral load dynamics

To understand the process of antibody production via antigen presentation, we now extend the Equation System (3) to include another susceptible target cell type, the macrophages (S_m). Upon infection, macrophages will differentiate to become antigen-presenting cells P, triggering the production of free IgM and free IgG antibodies types [11,29,49]. In a primary infection, IgM antibodies, a pentamer molecule, are produced first and to higher levels than IgG antibodies, a monomer molecule. Free IgM and free IgG binds into the free viral particles with $d_M\gamma_M$ and $d_G\gamma_G$ biding rates, respectively.

The extended model to describe the IgM and IgG production is given by

$$\begin{aligned}
\frac{dS}{dt} &= \pi_S - \mu_S S - aSV \\
\frac{dI}{dt} &= aSV - (\mu_i + \mu_S)I \\
\frac{dV}{dt} &= \kappa\mu I - bSV - b_m S_m V - d_M MV \\
\frac{S_m}{dt} &= \pi_m - \mu_S S_m - a_m S_m V \\
\frac{dP}{dt} &= a_m S_m V - (\mu_P + \mu_S)P \\
\frac{dM}{dt} &= \alpha_M P - \gamma_M MV - \mu_M M \\
\frac{dG}{dt} &= \alpha_G P - \gamma_G GV - \mu_G G,
\end{aligned} \tag{2}$$

including a natural removal rate for IgM, $\mu_M M$, and IgG, $\mu_G G$.

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Free IgM antibody production is observed to start between day 2 and day 3 of the infection process (see Figure 4(a)), lasting for about three months (see Figure 4(b)). Free IgG antibody type appears shortly after IgM antibodies (see Figure 4(a)), with lower concentration levels, but lasting much longer than free IgM (see Figure 4(b)), reaching eventually a constant "life-long immunity" level. Viral load dynamics, (see Figure 4(c)), is influenced by the antibodies production, with a peak between day 5 and day 6 of the infection process. The complete process of free virus dynamics in the presence of antibodies is shown. Figure 4(d).

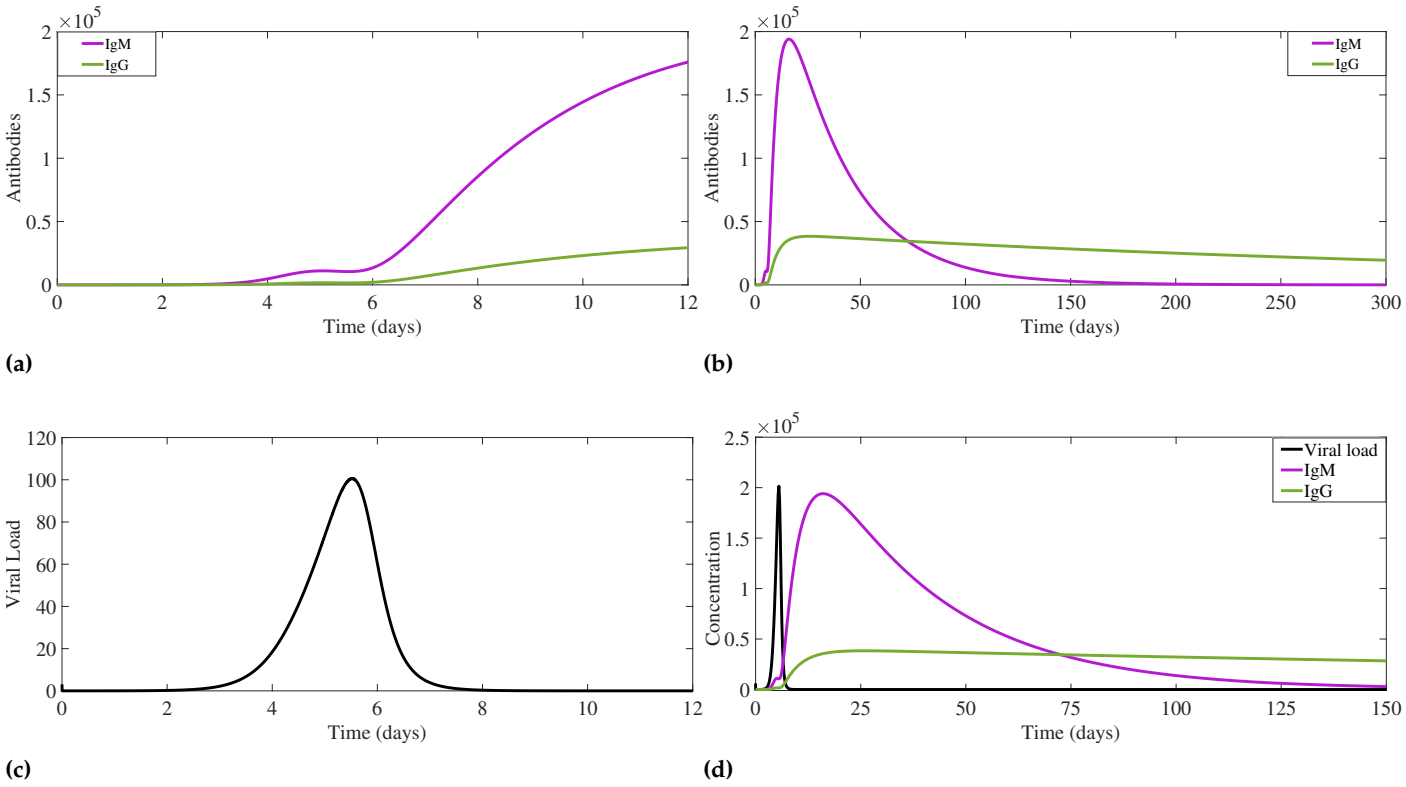

Figure 4. For a primary dengue infection, antibodies IgM (in violet) and IgG (in green) production dynamics are shown for a 10 days period (a) and for a 300 days period (b). Free virus particle dynamics for a 12 days period is shown in (c). The complete process of viral load in the presence of antibodies is shown in (d). Here, for better visualization, free viruses were scaled to 2000.

2.1.3. Antibody-virus complexes and infection clearance

Following the antibody production process described above, the model framework is extended to include the antibody-virus complex production, IgM-DENV (C_M) and IgG-DENV (C_G), which are assumed to be responsible for clearing the ongoing infection after being recognized by killing cells. With constant target cells production π_S, for monocytes and dendritic cells, and π_m for macrophages, the complete modeling framework including each step presented in Figure 1 is written as a system of ordinary differential equations (ODEs) as follows

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$$
\begin{aligned}
\frac{dS}{dt} &= \pi_S - aSV - \mu_S S \\
\frac{dI}{dt} &= aSV - (\mu_i + \mu_S)I \\
\frac{dV}{dt} &= \kappa\mu_i I - bSV - b_m S_m V - d_M VM - d_G VG \\
\frac{dS_m}{dt} &= \pi_m - a_m S_m V - \mu_S S_m \\
\frac{dP}{dt} &= a_m S_m V - (\mu_P + \mu_S)P \\
\frac{dM}{dt} &= \alpha_M P - \gamma_M MV - \mu_M M \\
\frac{dG}{dt} &= \alpha_G P - \mu_G G - \gamma_G VG \\
\frac{dC_M}{dt} &= \gamma_M VM - \mu_{C_M} C_M \\
\frac{dC_G}{dt} &= \gamma_G VG - \mu_{C_G} C_G.
\end{aligned} \tag{3}
$$

The complete model output describing the immunological response mediated by IgM and IgG antibodies during a primary dengue infection is shown in Figure 5.

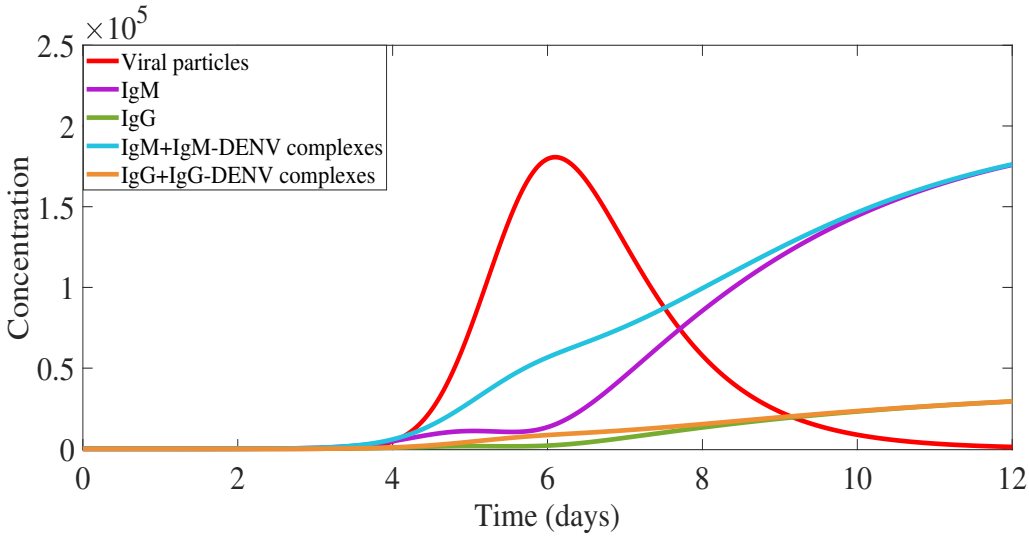

Figure 5. Model simulation: primary dengue infection immunological responses mediated by antibodies. Viral particles encountered as free virus and complexes ($V + 4\cdot$ DENV-IgM + DENV-IgG). Free IgM is shown in violet and free IgG in green. Virus-antibodies complexes DENV-IgM and DENV-IgG are shown in blue and orange respectively.

In Figure 5, the overall viral load curve (in red) includes not only free viral particles, as shown in Figure 4(c), but also the viral particles bound into antibody-virus complexes. Free IgM (in violet) are observed at very low levels until day 5 of infection since the majority of the molecules are bound to free virus, the so-called IgM-DENV complexes (in blue). Note that for each IgM, 4 viral particles must be counted on average. Free IgM appears to be detectable on day 9 after the infection is cleared, i.e, removal of all C_M complexes, lasting for about three months. Free IgG (in green) and IgG-DENV complex (in orange) are appearing around day 4, and eventually do not play a significant role in the primary infection clearance. Free IgG reaches very small levels in comparison with the free IgM, lasting much longer than IgM, and are assumed to confer lifelong immunity against that specific serotype.

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2.2. Secondary dengue infection model with a homologous serotype

After a period of temporary cross-immunity, the human host is considered to be susceptible again, able to acquire a secondary dengue infection [32]. In this section, we investigate a secondary infection with the same (homologous) serotype, represented in Figure 6. The difference here lies in the order of antibody production triggered by antigen presentation, shown in steps 4 to 7. Immunological response initiates with IgG antibody type increasing quicker than the IgM type and reaching much higher levels than in primary infection.

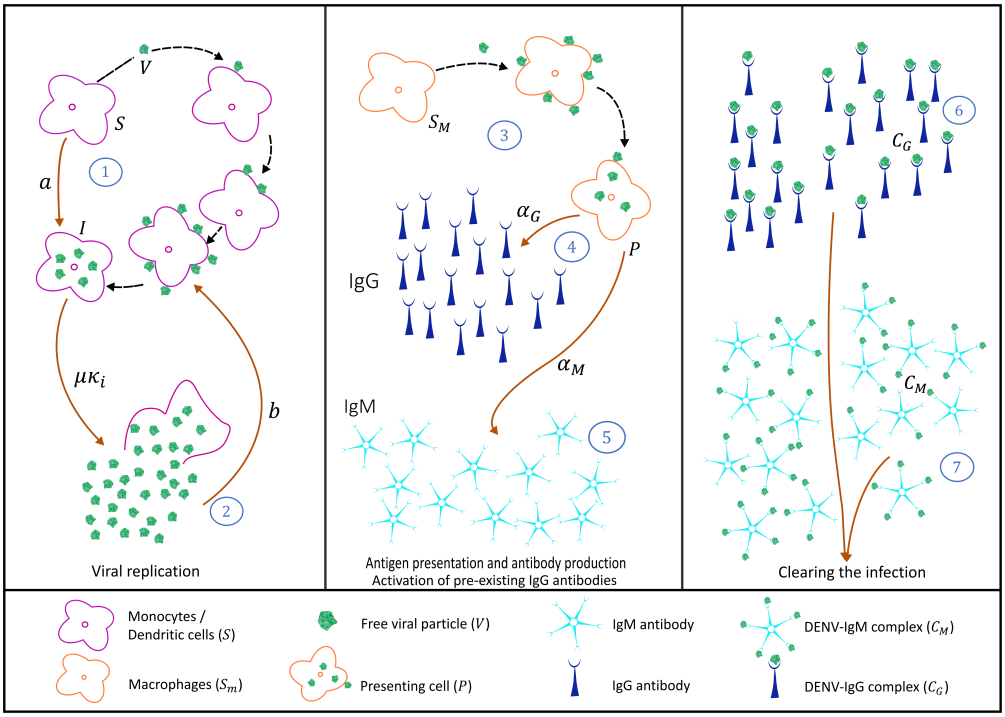

Figure 6. Schematic in-host dengue immunological responses mediated by antibodies: secondary infection with the same dengue serotype. Three blocks are used to describe 7 steps during the infection, from viral replication up to infection clearance.

We use the same modeling framework described in Equation System (4), only including an extra term $\alpha_{G,sec} V$ (shown in blue), representing the pre-existing IgG antibodies that were produced during the primary dengue infection. The complete model for the secondary dengue infection with the homologous can be written as follows

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$$
\begin{aligned}
\frac{dS}{dt} &= \pi_S - aSV - \mu_S S \\
\frac{dI}{dt} &= aSV - (\mu_i + \mu_S)I \\
\frac{dV}{dt} &= \kappa\mu_i I - bSV - b_m S_m V - d_M VM - d_G VG \\
\frac{dS_m}{dt} &= \pi_m - a_m S_m V - \mu_S S_m \\
\frac{dP}{dt} &= a_m S_m V - (\mu_P + \mu_S)P \\
\frac{dM}{dt} &= \alpha_M P - \gamma_M MV - \mu_M M \\
\frac{dG}{dt} &= \alpha_G P - \mu_G G - \gamma_G VG + \alpha_{G_{sec}} V \\
\frac{dC_M}{dt} &= \gamma_M VM - \mu_{C_M} C_M \\
\frac{dC_G}{dt} &= \gamma_G VG - \mu_{C_G} C_G,
\end{aligned}
\tag{4}
$$

with now the immunological response initiated by the pre-existing IgG antibodies, specific to that serotype. These pre-existing specific IgG antibodies are able to bind and neutralize the homologous dengue serotype causing this new infection.

Figure 7 shows a numerical simulation of the model for the immune response during a secondary infection with the homologous serotype with $\alpha_{G_{sec}} V$ =2000. With a lower overall viral load (in red), the immunological response mediated by antibodies is reversed to the response described for the primary infection.

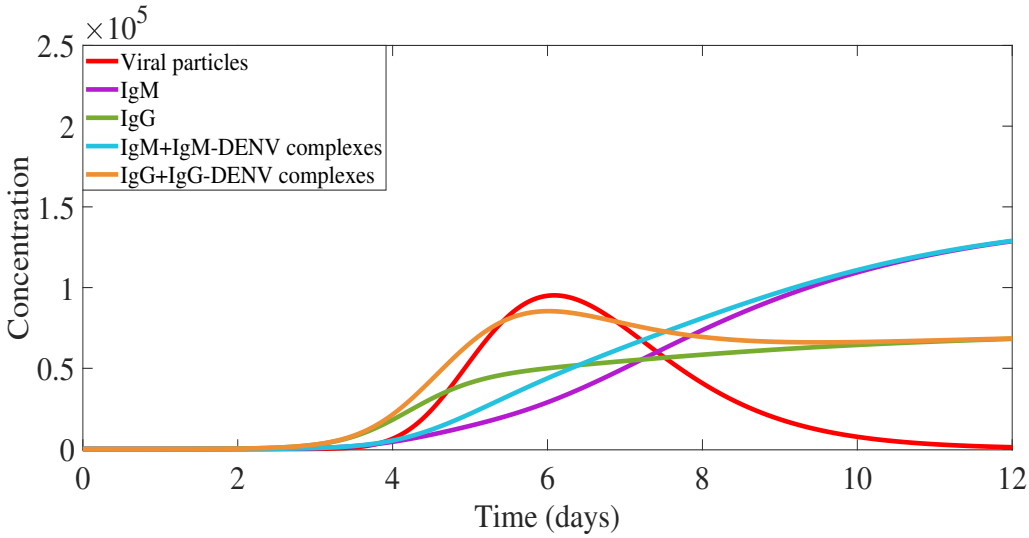

Figure 7. Model simulation: secondary dengue infection with a homologous serotype. Viral particles encountered as free virus and complexes ($(V + 4\cdot$ DENV-IgM + DENV-IgG)). Free IgM is shown in violet and free IgG in green. Virus-antibodies complexes DENV-IgM and DENV-IgG are shown in blue and orange respectively.

In this scenario, the IgG-DENV complexes (in orange) play a major role in viral clearance (see step 3 in Figure 6, appearing already on day 2 of the infection process. The free IgG (in orange) binds into the free viral particles and the high concentrations of IgG-DENV complexes are responsible for clearing the ongoing infection.

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2.3. Secondary infection with a heterologous serotype

Similar to the process described in Section 2.2, we now investigate the dynamics of a secondary infection caused by a heterologous dengue serotype, recognized to be a risk factor of progressing to severe disease. The difference here lies in the ability of pre-existing IgG antibodies to bind into the new viral particles (see step 6 in Figure 8) and enhance viral replication due to the antibody-dependent enhancement (ADE) phenomenon (see step 7 in Figure 8) since these pre-existing IgG antibodies are not able to neutralize the new virus.

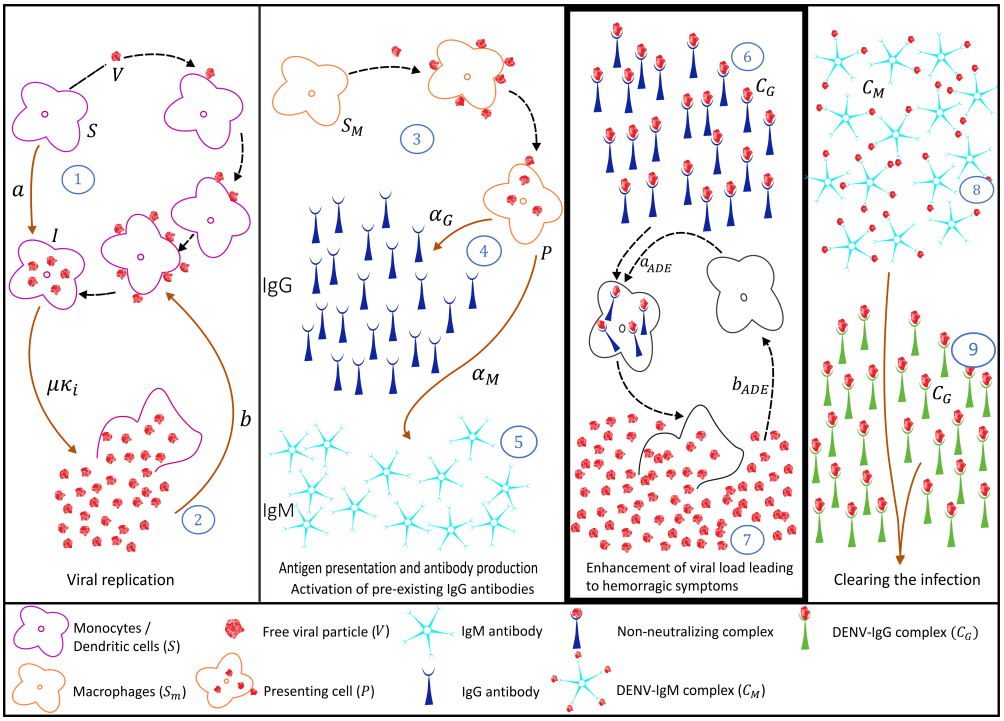

Figure 8. Schematic in-host dengue immunological responses mediated by antibodies: secondary infection with a different dengue serotype. Four blocks are used to describe 9 steps during the infection, from viral replication up to infection clearance, including disease augmentation via the ADE process (steps 6 and 7).

Again, we use the same modeling framework described in Equation System (5), now including extra terms $a_{ADE}SC_G$ and $b_{ADE}SC_G$ (shown in violet) affecting the viral replication of the system, with an enhancement mediated by the pre-existing IgG-DENV complexes. The complete model for the secondary dengue infection with a heterologous dengue serotype can be written as follows

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$$
\begin{aligned}
\frac{dS}{dt} &= \pi_S - aSV - \mu_S S - a_{ADE} S C_G \\
\frac{dI}{dt} &= aSV - (\mu_i + \mu_S) I + a_{ADE} S C_G \\
\frac{dV}{dt} &= \kappa \mu_i I - bSV - b_m S_m V - d_M V M - d_G V G \\
\frac{dS_m}{dt} &= \pi_m - a_m S_m V - \mu_S S_m \\
\frac{dP}{dt} &= a_m S_m V - (\mu_P + \mu_S) P \\
\frac{dM}{dt} &= \alpha_M P - \gamma_M M V - \mu_M M \\
\frac{dG}{dt} &= \alpha_G P - \mu_G G - \gamma_G V G + \alpha_{G_{sec}} V \\
\frac{dC_M}{dt} &= \gamma_M V M - \mu_{C_M} C_M \\
\frac{dC_G}{dt} &= \gamma_G V G - \mu_{C_G} C_G - b_{ADE} S C_G .
\end{aligned}
\tag{5}
$$

Figure 9 shows the simulation for the immune response during a secondary infection with a heterologous dengue serotype. With a much higher overall viral load (in red), the immunological response mediated by antibodies is similar to the described secondary response with the same virus. However, in this scenario, the pre-existing IgG-DENV complexes (in orange) play a major role in viral replication enhancement (see step 7 in Figure 8) via the ADE. The IgM levels (in violet and in blue) are needed for clearing the ongoing infection (see step 8 in Figure 8). The disease augmentation phenomenon will lead eventually to hemorrhagic symptoms that without proper treatment may lead to shock and death.

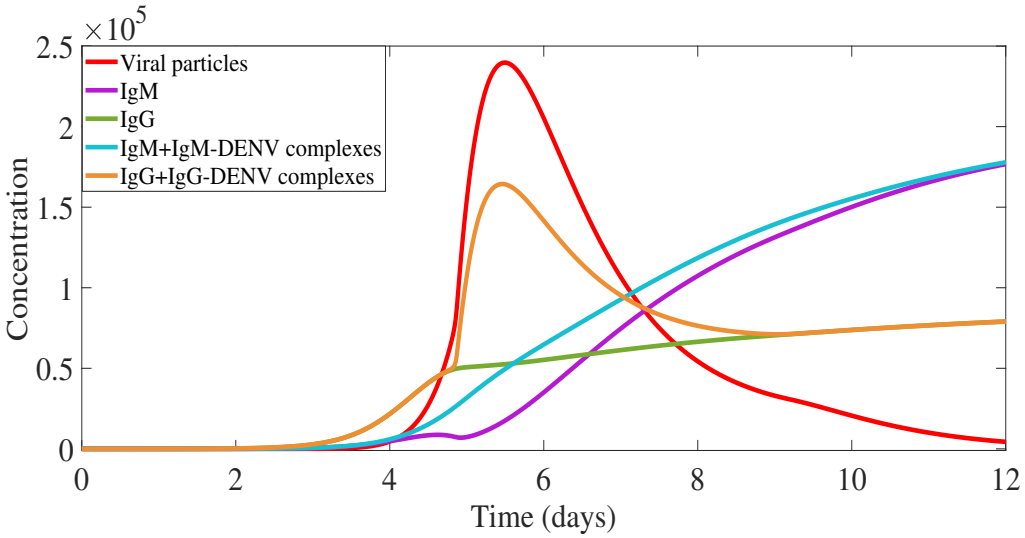

Figure 9. Model simulation: secondary dengue infection with a heterologous dengue serotype. Viral particles encountered as free viruses and complexes ($V + 4\cdot$ DENV-IgM+DENV-IgG). Free IgM is shown in violet and free IgG in green. Virus-antibodies complexes DENV-IgM and DENV-IgG are shown in blue and orange respectively.

Note that for this study we focus on the qualitative behavior of the dengue immunological responses. Concentrations of viral particles and antibodies are given as arbitrary but reasonable values. Model parameters are shown in Table 1, including the biological meaning and values used for the numerical simulations.

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3. Antibody responses and viral load levels to explain disease symptoms and severity

In our within-host modeling approach, we show different dengue immunological responses mediated by antibodies. For each infection process, the IgM-antibody and IgG-antibody dynamics are shown in Figure 10.

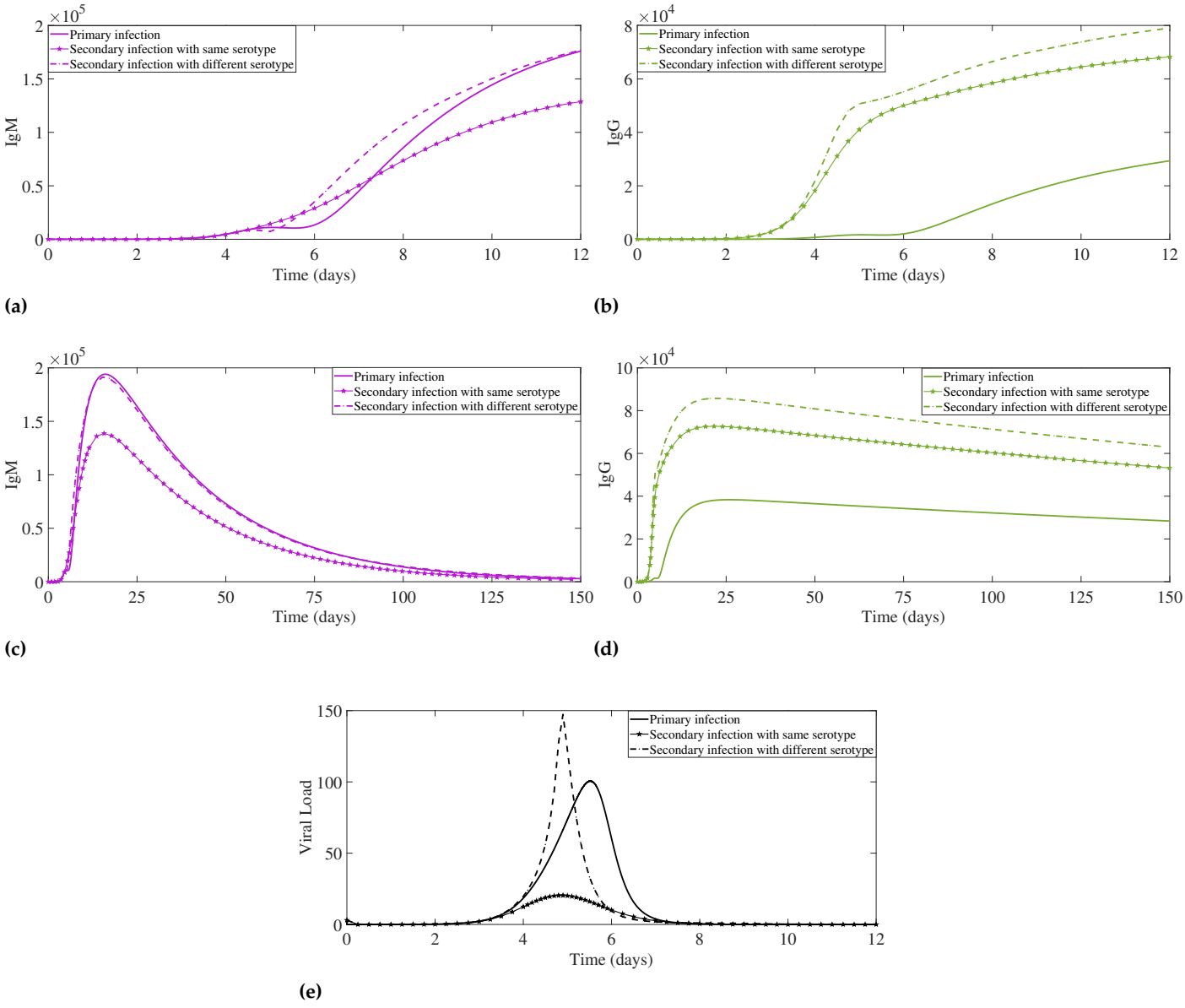

Figure 10. Antibody responses and free viral load comparison. For a primary dengue infection (full line), secondary infection with a homologous dengue serotype (line with pentagram marker), and secondary infection with heterologous dengue serotype (dashed line) we show the dynamics for IgM antibody type (in violet) and IgG antibody type (in green). In(a) and (b) we plot the antibodies dynamics over a 12 days period while in (c) and (d) over a 150 days period. Free viral load dynamics are shown in (e).

In a primary dengue infection, the antibody IgM type is the dominant antibody type. IgM binds into the free virus and generates the virus-antibody complexes in the early stage of the infection (see Figure 10(a)), reaching high levels and decaying after 3 months approximately (see Figure 10(b)). The specific antibody IgG is produced afterward and will provide the so-called long-life specific immunity. This specific antibody maintains an immunological memory and is able to bind and to neutralize a homologous dengue

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serotype (see Figure 10(c)-(d)). Free virus peaks around day 5-6 of the infection process, with a fast decay reaching undetectable levels after day 8 of the infection process (see Figure 10(e)). A primary infection is often asymptomatic and that is eventually correlated with the viral load levels generated during a primary dengue infection.

During a second infection with a homologous serotype, the pre-existing antibody IgG type is the dominant antibody type. These antibodies immediately respond to the new serotype (see Figure 10(c)), able to neutralize the virus, leading to a much faster clearing of the infection. These antibodies are lasting longer, boosting the immune system of the individual, assumed to confer lifelong immunity against that specific serotype (see Figure 10(d)). Free virus peaks around day 4-5 and reaches a much lower viral load level than in a primary infection (see Figure 10(e)). Here, we assume that individuals would have no symptoms at all and eventually will not be able to transmit the disease, given the observed viral load level.

In a second infection with a heterologous serotype, the pre-existing antibody IgG type immediately responds to the new serotype (see Fig. 10(c)), 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 (see Fig. 10(e)). This process is called Antibody-Dependent Enhancement (ADE), well reproduced by our system, leading to a much higher viral load level than in a primary infection. Free viral load peaks a bit earlier than in a secondary infection with a homologous virus. Here, we assume that individuals would have symptoms and eventually developing the severe form of the disease, the so-called dengue hemorrhagic fever that without proper treatment will evolve to shock syndrome and eventually death.

4. Conclusions

We have developed a within-host dengue modeling framework to describe the qualitatively dengue immunological response mediated by antibodies. Models for a primary dengue infection, a secondary dengue infection with the same virus, and for secondary dengue infection with a different dengue virus were analyzed and compared. We have explored the features of viral replication, antibody production, and infection clearance over time, including the path for disease severity via the ADE process.

Models were developed by adding gradually the steps of disease infection described in the immunology literature. We have analyzed each step individually, from viral replication up to clearance of the infection. Our models were able to reproduce qualitatively the features of different dengue infections, including the ADE process leading to the disease augmentation in a secondary heterologous dengue infection.

The modeling framework is the first one to describe qualitatively the dynamics of viral load and antibody production and decay for scenarios of primary and secondary infections as found in the empirical immunology literature. Giving insights on the immunopathogenesis of severe diseases via pre-existing antibodies and the ADE process, the results presented here are of use for future research directions to evaluate the impact of imperfect dengue vaccines.

Author Contributions: Conceptualization, E.S., M.A. and N.S.; A.S., H.F., V.Z. and D.K performed the numerical simulation with discussion with E.S., M.A. and N.S; M.A and H.F. prepared the dengue immunological processes schemes; A.S. performed the analysis with support from E.S., M.A. and N.S.; A.S., H.F., V.A and D.K. wrote the manuscript in consultation with E.S., M.A. and d N.S.; All authors have read and agreed to the published version of the manuscript.

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