Virus antibody dynamics in primary and secondary dengue infections

Tanvi P. Gujarati · G. Ambika

Received: 2 February 2012 / Revised: 12 October 2013 / Published online: 4 January 2014
© Springer-Verlag Berlin Heidelberg 2014

Abstract Dengue viral infections show unique infection patterns arising from its four serotypes, (DENV-1,2,3,4). Its effects range from simple fever in primary infections to potentially fatal secondary infections. We analytically and numerically analyse virus dynamics and humoral response in a host during primary and secondary dengue infection for long periods using micro-epidemic models. The models presented here incorporate time delays, antibody dependent enhancement, a dynamic switch and a correlation factor between different DENV serotypes. We find that the viral load goes down to undetectable levels within 7–14 days as is observed for dengue infection, in both cases. For primary infection, the stability analysis of steady states shows interesting dependence on the time delay involved in the production of antibodies from plasma cells. We demonstrate the existence of a critical value for the immune response parameter, beyond which the infection gets completely cured. For secondary infections with a different serotype, the homologous antibody production is enhanced due to the influence of heterologous antibodies. The antibody production is also controlled by the correlation factor, which is a measure of similarities between the different DENV serotypes involved. Our results agree with clinically observed humoral responses for primary and secondary infections.

Keywords Humoral immune response · Antibody dependent enhancement · Correlation factor among serotypes · Time delay · Stability analysis

T. P. Gujarati
Indian Institute of Science Education and Research, TVM, Thiruvananthapuram 695016, Kerala, India
e-mail: tanvi@iisertvm.ac.in

G. Ambika (✉)
Indian Institute of Science Education and Research, Pune, Pune 411021, Maharashtra, India
e-mail: g.ambika@iiserpune.ac.in
1 Introduction

Dengue is one of the most serious diseases infecting humans. According to WHO estimates, 50–100 million infections occur every year leading to 500,000 hospitalizations and around 12,500 deaths (WHO 2013). Until recently dengue was considered to be a disease of the tropics, but it has spread its domain of infection to temperate regions as well, primarily due to global warming (Science Daily 1998). Dengue is transmitted to humans through the bite of infected *Aedes aegypti* and *A. albopictus* mosquitoes. It is understood that four closely related serotypes of DENV exist viz. DENV-1, DENV-2, DENV-3 and DENV-4 (Halstead 1988; Lindenbach and Rice 2001) and these four serotypes cause infections of varying severity in humans. The infected individual usually suffers from acute febrile illness called Dengue Fever (DF) which is cleared by a complex immune response in a short time of approximately 7 days after onset of fever. There are more severe manifestations of this disease like dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Often without immediate and necessary proper treatment DHF/DSS can be fatal (Gibbons and Vaughn 2002; Halstead 2007; Rigau-Perez et al. 1998). WHO has recently proposed a new classification for dengue based on disease severity (World Health Organisation (WHO) and Special programme for Research and Training in Tropical Diseases (TDR) 2009). We note that, though there is a huge effort going on to develop an effective vaccine against dengue infections, commercial dengue vaccines are not yet available (Kinney and Huang 2001; Murphy and Whitehead 2011). In this context it is important to understand the biological mechanisms and dynamical processes involved during this infection. Also these complex non-linear biological processes lead to dynamic models that are interesting for their varied and rich dynamics.

The epidemiology of dengue in different populations have been studied previously using improved or extended versions of the basic SIR model (Derouich and Boutayeb 2006; Dietz 1975; Esteva and Vargas 1998, 1999, 2003; Feng and Velasco-Hernandez 1997; Garba et al. 2008; Nuraini et al. 2007). Here we present a mathematical model on a cellular scale that incorporates time delays arising from multistage complex processes in immune response. Similar models describing the cell–virus interaction dynamics have been studied in other contexts like HIV, hepatitis or influenza A (Ambika and Dahanukar 2009; Beauchamin and Handel 2011; Nowak and May 2000). However, we note that micro-epidemiological studies concerning DENV are very few, one such study reported recently involves the T-cell immune response (Nuraini et al. 2009). Here we report a detailed dynamic model that incorporates antibody mediated immune response.

To develop a model for dengue infection at the micro-epidemic level, the multistage cellular processes that occur during the infection are to be considered in detail. It is understood that once virions enter into the body, they infect macrophages, monocytes, dendritic cells, mast cells and hepatocytes (Jindadamrongwech et al. 2004; Kliks et al. 1989; Tassaneentrithep et al. 2003; Wu et al. 2000). The virions start multiplying in the infected cells and burst out of them in large numbers, thus aggravating the infec-
tion. The immune response of the body tries to curb this infection. Generally, adaptive immune response is composed of the cell-mediated immune response and humoral immune response, both of which are responsible to clear infection and provide immunity (Janeway et al. 2001; Murphy and Whitehead 2011; Bielefeldt-Ohmann 1997). However in the case of dengue, among the different complex immune response mechanisms, the humoral immune response has been shown to play a more prominent role (Chaturvedi et al. 1978; Halstead 1988, 2007, 2009; Kyle et al. 2008; Murphy and Whitehead 2011; Run Tao et al. 1995). In this mechanism, the B-cells that come into contact with the antigens present on the virus particles start the process of producing antibodies. The antibodies thus produced complement the viral antigens and neutralise them, making them non-infectious. These virus–antibody aggregates are then chemically degraded and destroyed in the macrophages (note that macrophages are also DENV targets). The external manifestations of this whole process is the acute febrile illness that gets cured within 7–14 days even in the absence of medication (Murphy and Whitehead 2011; Scott and Morrison 2010). If a person is exposed to DENV of any serotype for the first time, it is termed as primary infection. It is observed that infection with a serotype provides long-term immunity against that serotype, i.e. recurrence of dengue infection with the same serotype is not observed (Murphy and Whitehead 2011). This is because the “memory” of the previous infection suppresses the spread of virions without much delay (Halstead 2007; Janeway et al. 2001; Marchuk 1997).

In this work we propose a within-host dynamical model that involves humoral or antibody mediated immune response to describe primary dengue infection based on the above described biological processes. We also introduce intra-cellular time delays that come from the various steps involved during antibody production (Chaturvedi et al. 1978; Run Tao et al. 1995). We carry out a detailed stability analysis followed by numerical analysis to identify the relevant range of parameters that correspond to several possible outcomes of the infection. Our results indicate that there exists a critical value for the immune response parameter, above which the disease free state is always stable. However, large time delay in antibody production can upset this and lead to recurring spikes of virus counts.

Further, if an individual who has already undergone primary infection is again exposed to DENV of a different serotype, it is called secondary infection. It is generally observed that in such patients complicated and fatal conditions of DSS/DHF occur. Since the new DENV serotype is structurally similar to the old one, it leads to production of antibodies that complement the old serotype (i.e. cross immunity) along with new antibodies that are made to combat the new serotype. Thus, there are mainly two relevant antibodies now, one from the old infection which are heterologous to the new serotype and the new homologous antibodies from the present infection. Both these antibodies have the capacity to bind to virions and neutralise them. Once neutralised the antibody–virus complex is taken to the macrophages. But on entering the macrophage, the heterologous antibodies are released from the virus due to their low affinity for this new serotype. This makes a fraction of the virus particles bare and ready for infecting the macrophage. Thus, the antibodies produced against the new serotype protects as well as carries the virus to their targets depending on the affinity between the antigen and antibody. This process is called the Anti-
body Dependent Enhancement (ADE) of infection (Murphy and Whitehead 2011; Porterfield 1986). ADE has been the most dominant hypothesis for decades that could explain the enhanced severity in secondary infections (Halstead 1970; Murphy and Whitehead 2011; Bielefeldt-Ohmann 1997). It must be mentioned that there are other proposed theories like the theory of original antigenic sin for the same (Julander et al. 2011; Noisakran and Perng 2008; Rotham 2011), but we focus on the modelling of ADE mechanism in the present work. Clinically it is observed that during the secondary infection the viral counts are higher than that of the primary infection but the virus gets cleared from the body in about the same time (Halstead 1970, 2007; Murphy and Whitehead 2011; Vaughn et al. 2000). The other important feature of secondary infections is a very high concentration of antibodies in the bodies of patients. It is postulated that this high load of antibodies could further lead to severe conditions described by DSS/DHF (Halstead 2007; Murphy and Whitehead 2011; Bielefeldt-Ohmann 1997). We thus see that it is the immune response which is responsible for controlling the infection and providing immunity as well as for stimulating reactions in the body leading to severe symptoms as seen in DHF/DSS (Halstead 2007; Murphy and Whitehead 2011). Thus a model for secondary infection should capture the observed features of ADE of infection and the enhanced antibody production.

We extend the primary infection model to a six-dimensional secondary infection model with heterologous and homologous antibodies based on the above described mechanism. To the best of our knowledge, it is the first attempt at modelling the within-host processes during a secondary dengue infection. In addition to time delays, our model introduces a correlation factor between the viral serotypes to bring in the effect of relatedness of the different DENV serotypes (due to their antigenic similarities) into the dynamics, which is very important in the context of secondary infection. Also the dynamical switch introduced in the model takes care of the influence of homologous antibody concentrations present in the body from the primary infection. With these additional parameters, our model accounts for the ADE of virus as well as the increased antibody counts observed clinically during secondary dengue infection.

We present the model for primary infection in Sect. 2 and its analytical treatment in Sect. 3. The model for the secondary infection is introduced in Sect. 4 followed by its numerical analysis in Sect. 5. The discussion on our model and concluding remarks are given in the last section.

2 Model describing primary dengue infection

In this section, we present the mathematical model describing the primary infection as a 5-D model that takes into consideration the viral dynamics and humoral immune response as described in the introduction. It is built on the basic 3-D model with healthy cells, infected cells and virus particles proposed by Nowak and May (2000) with humoral response involving B cells and antibodies added to it. The pictorial representation of the B-cell dependent humoral response is given in Fig. 1a and a schematic representation of the model described below is shown in Fig. 1b.
Fig. 1  Humoral immune response in primary dengue infection. a Cartoon representation of virus–antibody interactions. b Schematic of the mathematical model. Dashed black arrows stand for intrinsic growth rate. Solid black arrows depict conversion and infection. Solid straight grey arrow shows activation rate. Curved grey arrows show intrinsic death rates and dashed grey arrows show elimination rates.

The equations describing the model are given by:

\[
\begin{align*}
\dot{S} &= \mu - \alpha S - a SV \\
\dot{I} &= a SV - \beta I \\
\dot{V} &= k I - \gamma V - p AV \\
\dot{B} &= \eta - \delta B + c BV \\
\dot{A} &= f H(t - \tau_1) B(t - \tau_2) - q AV - \kappa A
\end{align*}
\]

where the relevant variables are: \( S \)—healthy cells (e.g. among monocytes, macrophages, dendritic cells, mast cells or hepatocytes), \( I \)—infected cells, \( V \)—dengue virus particles, \( B \)—B lymphocytes and \( A \)—neutralizing antibodies. The description of the parameters controlling the dynamics are given in Table 1.

The concept of Heaviside step function, \( H \), and delay in antibody production is similar to the ones used earlier in immune response models (Dibrov et al. 1977; Fowler 1981). Our model includes two time delays \( \tau_1 \) and \( \tau_2 \). For an infection beginning at time \( t = 0 \), the total time delay \( \tau_1 \), introduced through the Heaviside step function, is the time period that is required for the first production of antibodies after the virus and B-lymphocytes interact. This process involves two significant biological steps: conversion of B-cells to plasma cells and production of antibodies from plasma cells. On coming in contact with the virions for the first time, the B-cells have to undergo multiple differentiations before they can be transformed into the plasma cells or B-cells capable of producing antibodies specific to the attacking viral antigen (Janeway et al. 2001). This delay is biologically significant since production of plasma cells (denoted by the same variable as B-cells in our model, Klein 1980) after the virions have interacted with the B-lymphocytes is a complex process involving multiple steps. The second part of the total delay, more specifically, time delay \( \tau_2 \) introduced in our model, takes into consideration the time required to produce antibodies from the plasma cells. This would mean that at any time \( t \), the model will consider the plasma
cell concentration present at time \((t - \tau_2)\) for the production of antibodies. It must be noted that the time delay \(\tau_1\) includes the time delay \(\tau_2\).

For this model the reproduction ratio, \(R_0\), calculated by using the next generation method (Diekmann and Heesterbeek 2000) is:

\[
R_0 = \frac{a \mu k}{\alpha \beta \gamma}
\]  

(2)

The detailed analysis of the possible steady states based on the model described by Eq. (1) is given in the next section.

3 Analysis of equilibrium states and their stability

Primary dengue infection is known to clear from the host completely with the virus getting totally removed from the body after infection and the antibodies to the primary infection persist in the body for a long time (Murphy and Whitehead 2011). Hence we are interested in looking for infection free solutions and their stability over a long time. For this we solve the modelling equations for all the equilibrium values. Then a detailed analysis of their stability is carried out to identify the relevant parameter values that lead to infection free steady states or infectious states after a long time.

The equilibrium values denoted with ‘\(\ast\)’ are obtained from Eq. (1) as:

\[
S^\ast = \frac{\mu}{(\alpha + aV^\ast)}
\]  

(3a)

\[
I^\ast = \frac{aS^\ast V^\ast}{\beta}
\]  

(3b)
\[ B^* = \frac{\eta}{(\delta - cV^*)} \]  
\[ A^* = \frac{f B^*}{(qV^* + \kappa)} \]

and

\[ V^*(p_3V^*^3 + p_2V^*^2 + p_1V^* + p_0) = 0 \]  
\[ (4) \]

where

\[ p_3 = qca\gamma \]  
\[ (5a) \]
\[ p_2 = [a\gamma(c\kappa - q\delta) - qca\gamma(R_0 - 1)] \]  
\[ (5b) \]
\[ p_1 = [a\gamma(q\delta - \kappa c)(R_0 - 1) - \kappa\gamma\delta a - apf\eta] \]  
\[ (5c) \]
\[ p_0 = \alpha[\kappa\delta\gamma(R_0 - 1) - f\eta] \]  
\[ (5d) \]

We find Eq. (4) has one solution \( V^* = 0 \) another \( V^* \neq 0 \) which can be obtained from the equation

\[ p_3V^*^3 + p_2V^*^2 + p_1V^* + p_0 = 0 \]  
\[ (6) \]

The existence of a positive solution for this equation will depend on the values of the parameters.

To study the stability of the equilibrium state, we linearise the system about the equilibrium points and the corresponding Jacobian matrix is given as the following (Lakshmanan and Senthilkumar 2010)

\[
J = \begin{bmatrix}
-(\alpha + aV^*) & 0 & -aS^* & 0 & 0 \\
aV^* & -\beta & aS^* & 0 & 0 \\
0 & k & -(c\gamma + pA^*) & 0 & -pV^* \\
0 & 0 & cB^* & -(\delta - cV^*) & 0 \\
0 & 0 & -qA^* & f e^{-\lambda \tau_2} & -(\kappa + qV^*)
\end{bmatrix}
\]  
\[ (7) \]

Here \( \lambda \) stands for the eigenvalues of the Jacobian matrix \( J \) given above. If the real parts of all the eigenvalues obtained by solving the characteristic equation of \( J \) are negative, it implies that the system is stable in that equilibrium state.

On substituting the equilibrium values of \( S^* \), \( B^* \) and \( A^* \) in terms of \( V^* \) from Eq. (3), the characteristic equation for the \( J \) can be written as

\[
G(\lambda) = \lambda^5 + G_4\lambda^4 + G_3\lambda^3 + G_2\lambda^2 + G_1\lambda + G_0 \\
+ H_2 e^{-\lambda \tau_2} \lambda^2 + H_1 e^{-\lambda \tau_2} \lambda + H_0 e^{-\lambda \tau_2}
\]

\[ = 0 \]  
\[ (8) \]

The details of all the coefficients in terms of the parameters are given in Appendix.
3.1 Infection free equilibrium state

We start by discussing the most interesting case i.e. \( V^* = 0 \), the infection free equilibrium state. In this case the characteristic equation in Eq. (8) can be simplified as (details in Appendix)

\[
G(\lambda) = (\alpha + \lambda)(\kappa + \lambda)(\delta + \lambda) \left( \lambda^2 + \lambda \left( \gamma \left( 1 + \frac{fp}{\delta \gamma \kappa} \right) + \beta \right) + \beta \gamma \left( 1 + \frac{fp}{\delta \gamma \kappa} - R_0 \right) \right)
\]

(9)

On analysing the Eq. (9) we find that it is independent of \( \tau_2 \). The eigenvalues have negative real parts when \( R_0 > 1 \) and \( f > f_c \) given as:

\[
f_c = (R_0 - 1) \frac{\kappa \delta \gamma}{p \eta}
\]

(10)

We consider the two parameters, \( k \), the burst rate of virus (\( k \) is directly proportional to the reproduction ratio \( R_0 \)) and \( f \), the production rate of antibodies as the relevant parameters controlling the dynamics and identify regions of stability in the parameter plane \( f-k \). For this, the parameter plane is scanned in the steps of 0.01 and colour coded using the maximum value of the real parts of the eigenvalues as index. This is shown in Fig. 2. In this analysis the values of other parameters used are \( \mu = 10, \alpha = 0.05, a = 0.001, \beta = 0.5, \kappa = 0.051, \gamma = 0.5, p = 0.001, \eta = 10, \delta = 0.049, c = 0.001 \), \( q = 0.001 \) (colour figure online)

![Fig. 2 The parameter plane \( f-k \) indicating stability regions as indexed by the maximum of the real parts of eigenvalues obtained from the characteristic Eq. (9) for \( V^* = 0 \). Blackish blue (grey) end of the spectrum denotes negative values and hence implies that the system is in stable equilibrium in those regions. Similarly the yellow (white) end of the spectrum denotes positive values, implying that the system is unstable in those regions. The numerical values of the parameters used are: \( \mu = 10, \alpha = 0.05, a = 0.001, \beta = 0.5, \kappa = 0.051, \gamma = 0.5, p = 0.001, \eta = 10, \delta = 0.049, c = 0.001 \), \( q = 0.001 \) (colour figure online)](image-url)
0.001. \( q = 0.001 \) adapted from models in similar contexts (Ambika and Dahanukar 2009; Beauchamin and Handel 2011).

The line separating the blackish blue (dark grey)–blue (whitish-grey) regions in Fig. 2 corresponds to the stability boundary of the infection free equilibrium state \( V^* = 0 \). Thus for a given \( k \), this line gives the critical value of immune response parameter, \( f > f_c \) required for eliminating the infection.

In the next section, we discuss the conditions under which nonzero solution exists for (6) and the stability of this equilibrium.

### 3.2 Infectious equilibrium \( V^* \neq 0 \)

On numerically solving the Eq. (6) in the parameter plane \((f–k)\) with the same parameter values used in Sect. 3.1, we find that \( V^* \neq 0 \) equilibrium does not exist in the region where \( V^* = 0 \) is stable as is seen in Fig. 3. The region that corresponds to negative \( V^* \) values is shown in black and the region where positive \( V^* \) values exist are colour coded as per their values. We mention that the other solutions \( V^* \geq \frac{\delta}{c} \) are ignored as they would give unrealistic values for \( B^* \) as per Eq. (3c). Thus from our numerical analysis, we find multiple positive and biologically relevant equilibria do not exist in the parameter plane studied.

For \( V^* \neq 0 \) the characteristic equation is given by Eq. (8). It is clear that the presence of time delay in the dynamics makes the characteristic equation transcendental. Hence the derivation of stability criteria is not straight forward. However, we can continue with the analysis by assuming that the eigenvalues are continuous functions of the time delay \( \tau_2 \). Thus we can write \( \lambda(\tau_2) = \epsilon(\tau_2) + i\omega(\tau_2) \) where \( \epsilon \) and \( \omega \) are the real

![Fig. 3](color figure online)
The parameter plane $f-k$, indicating stability regions for $V^* \neq 0$ as indexed by the maximum of the real parts of eigenvalues obtained from the characteristic Eq. (11) where $\tau_2 = 0$. Blue (black) end of the spectrum denotes negative values and hence implies that the system is in stable equilibrium in those regions. Similarly, the orange (grey) end of the spectrum denotes positive values, implying that the system is unstable in those regions. The region where $V^* < 0$ corresponding to biologically irrelevant equilibrium give the yellow (white) region. The numerical values of the parameters used are same as in Fig. 2 (colour figure online)

and imaginary parts of $\lambda$ respectively. We analyse the stability in this case in two steps (Lakshmanan and Senthilkumar 2010). First we check the stability for $\tau_2 = 0$ and if the state is stable it means that $\varepsilon(\tau_2) < 0$. As $\tau_2$ increases, if $\varepsilon(\tau_2)$ crosses zero at some value of $\tau_2$, say $\tau_2^0$, then it means that the stable state would become unstable at $\tau_2^0$ and $\lambda(\tau_2^0) = i \omega_0$. If no such value of $\tau_2$ exists, then the state will remain stable for all values of $\tau_2$ if it was stable for $\tau_2 = 0$. Hence we start our analysis by considering the stable regions for $\tau_2 = 0$ and then continue to find out the conditions where changes in stability occur when $\tau_2$ is non-zero.

For $\tau_2 = 0$, the characteristic Eq. (8) becomes:

$$G(\lambda) = \lambda^5 + G_4\lambda^4 + G_3\lambda^3 + (G_2 + H_2)\lambda^2 + (G_1 + H_1)\lambda + (G_0 + H_0) = 0$$

(11)

For $\tau_2 = 0$, the stability regions for $V^* \neq 0$ in the parameter plane $(f-k)$ is given in Fig. 4. The colour coded regions gives the maximum of the real parts of eigenvalues obtained from the Eq. (11) for the corresponding relevant value of $V^*$ given in Fig. 3. We see that regions with blue (black) have negative values and hence are stable regions whereas regions orange (grey) in colour with positive values are unstable. The yellow region corresponds to the region where relevant $V^* \neq 0$ does not exist. We also note that the line separating the yellow region from the other regions is similar to the line corresponding to $f_c$ observed in Fig. 2.

A direct numerical simulation of the equations of the model for illustrative sets of parameter values support the conclusions from the stability analysis given above. The time series of virus particles corresponding to typical regions in the parameter
Fig. 5 Asymptotic dynamics of virus count for specific chosen values of the parameters $f$ and $k$ for $\tau_2 = 0$. a For $f = 0.8$ and $k = 2$ corresponds to a point in the stable region with $V^* = 0$. The time series for the virus particles tend to zero asymptotically. b For $f = 0.01$ and $k = 2$ from the stable region for $V^* \neq 0$ in Fig. 4, time series for the virus particles settles to non-zero value asymptotically. c For $f = 0.1$ and $k = 5$ from the unstable region, the virus particles show oscillatory behaviour. The parameter values used in the numerical simulations are $\mu = 10$, $\alpha = 0.05$, $a = 0.001$, $\beta = 0.5$, $\kappa = 0.051$, $\gamma = 0.5$, $p = 0.001$, $\eta = 10$, $\delta = 0.049$, $c = 0.001$, $q = 0.001$, $\tau_1 = 3$ days along with the initial conditions $(S, I, V, B, A) = (200, 20, 80, 200, 0)$

plane showing different asymptotic dynamics are obtained by numerically solving the modelling Eq. (1) for $\tau_2 = 0$ using the Runge–Kutta method. Here we use initial conditions $(S, I, V, B, A) = (200, 20, 80, 200, 0)$ along with $\tau_1 = 3$ days (Agur and Mehr 1992) and the other parameter values as mentioned above. We find that for $f = 0.8$ and $k = 2$, the virus count goes down to zero within 14 days and remains so asymptotically as given in Fig. 5a. For $f = 0.01$ and $k = 2$, a point from the stable region of $V^* \neq 0$ (Fig. 4), the numerical analysis gives that the virus count goes to a steady non-zero value (Fig. 5b). For $f = 0.1$ and $k = 5$ from the unstable region of both the steady states, we see oscillatory behaviour for virus count (Fig. 5c).

Thus, we find that for sufficiently high $f$ values, the infection gets cleared and does not recur as is observed in primary dengue infections. Also, the infectious steady state with $V^* \neq 0$ can occur when $f$ is small enough, corresponding to the case of very low immune response with high burst rate for virus. Moreover, we also observe the possibility of oscillatory solutions that consist of spikes separated by long intervals of
very low count. This would correspond to the recurrence of infection after an interval.

In this context, we add that in the case of HIV, oscillations and recurrence of infection are clinically reported (Kitchen et al. 2011). In the case of dengue, lack of diagnostic measurements of viremia in patients along with the fact that a natural human system has many other intertwined processes simultaneously functional, not just reaction to dengue, hampers the detection of possible oscillatory solution or infectious steady state which may be present in immunocompromised individuals. Hence detailed clinical measurements are required for establishing their existence.

3.3 Effect of time delay

The analysis given in Sect. (3.1) establishes the stability regions of \( V^* = 0 \) for any \( \tau_2 \). However, the stability for \( V^* \neq 0 \) states is to be further analysed to take care of the case \( \tau_2 \neq 0 \).

We proceed to get the conditions under which it will remain stable for all values of \( \tau_2 \), i.e. conditions under which \( \lambda = i \omega \) is not possible. On substituting \( \lambda = i \omega \) in the characteristic Eq. (8) we get;

\[
G(i \omega) = i \omega^5 + G_4 \omega^4 - i G_3 \omega^3 - G_2 \omega^2 + i G_1 \omega + G_0 - H_2 \omega^2 (\cos(\omega \tau_2) - i \sin(\omega \tau_2)) + i H_1 \omega (\cos(\omega \tau_2) - i \sin(\omega \tau_2)) + H_0 (\cos(\omega \tau_2) - i \sin(\omega \tau_2)) = 0
\]

(12)

We follow the graphical way of finding dependence of stability on time delay by analysing Eq. (8) geometrically for \( \lambda = i \omega \). We write Eq. (8) as shown below:

\[
e^{-i \omega \tau_2} = \frac{((G_4 \omega^4 - G_2 \omega^2 + G_0) + i(\omega^5 - G_3 \omega^3 + G_1 \omega))}{((H_2 \omega^2 - H_0) - i H_1 \omega)} \]

(13)

The left hand side of the Eq. (13) defines a unit circle on the Argand plane. The right hand side is called the ratio curve. If the ratio curve intersects the unit circle there is a change of stability. By plotting the real and imaginary parts of both sides of Eq. (13) simultaneously we can check for the change in stability of the equilibrium point. The point of intersection, if any, is given by Eq. (14) which is derived from Eq. (13)

\[
\tau_2^p = \pm \frac{1}{\omega_0} \arccos \left[ \frac{((H_2 \omega_0^2 - H_0) (G_4 \omega_0^4 - G_2 \omega_0^2 + G_0) - H_1 \omega_0 (\omega_0^5 - G_3 \omega_0^3 + G_1 \omega_0))}{((H_0 - H_2 \omega_0^2)^2 + \omega_0^2 H_1^2)} \right] + \frac{2p \pi}{\omega_0}, \quad p = 0, 1, 2 \ldots
\]

(14)

We illustrate this analysis by taking the following specific cases:

Case 1 For \( f = 0.01 \) and \( k = 2 \), which is a point of stable equilibrium for \( \tau_2 = 0 \), the plots of the unit circle and ratio curve are shown in Fig. 6a. As the curves do not intersect, the equilibrium point will be stable for all \( \tau_2 \) values. The time series for virus particles obtained by direct numerical analysis with \( \tau_2 \neq 0 \) shown in Fig. 6b also supports this.
Dengue virus and antibody dynamics

Fig. 6  a Real and imaginary parts of both sides of Eq. (13) indicating that stability does not change as unit circle and ratio curve do not intersect, i.e. the equilibrium state \( f = 0.01 \) and \( k = 2 \) remains stable for \( \tau_2 \neq 0 \). b Time series for virus particles obtained by numerical simulations for \( \tau_2 = 1 \) day (dashed curve) and \( \tau_2 = 15 \) days (solid curve). We see that the virus count stabilises to non-zero counts asymptotically, i.e. the equilibrium point retains its stability for non-zero \( \tau_2 \) values. The \( \tau_1 \) value used is 16 days and all other parameter values with initial conditions are given in the text.

Case 2 For \( f = 0.1 \) and \( k = 3.5 \), corresponding to a steady state for \( \tau_2 = 0 \), the plots of the unit circle and ratio curve intersect each other as shown in Fig. 7a. Thus, the equilibrium point changes its stability. The time series for the virus particles obtained in Fig. 7b from a direct numerical analysis shows that the solution becomes oscillatory for higher values of \( \tau_2 \).

The analysis mentioned so far is applicable to the steady states only and does not therefore include the unstable regions shown in Figs. 2 and 4. Hence for understanding the nature of the dynamics in this region, we numerically analyse the system in Eq. (1) and find that the dynamic state corresponding to that region is oscillatory. Thus the oscillatory nature of the state which was observed for \( \tau_2 = 0 \) for \( f = 0.1 \) and \( k = 5 \) persists for \( \tau_2 \neq 0 \). We also study the change in the dynamics with increase in \( \tau_2 \) as shown in Fig. 8. It is clear that as delay increases, the amplitude of the oscillations increases. This would mean that, large delay in production of antibodies could lead to conditions where the infection recurs periodically as spaced out spikes.

We know that the actual biological processes considered here occur with some inherent non-zero value of time delay. The analysis given above for three specific
Fig. 7  

a Real and imaginary parts of both sides of Eq. (13) indicating that stability changes as unit circle and ratio curve intersect, i.e. the equilibrium state $f = 0.1$ and $k = 3.5$ becomes unstable for $\tau_2 \neq 0$.  
b Time series for virus particles obtained by numerical simulations for $\tau_2 = 1$ day (dashed curve) and $\tau_2 = 15$ days (solid curve). We see that the virus count stabilises asymptotically for smaller values of $\tau_2 \neq 0$ but becomes oscillatory for higher values of $\tau_2$. The $\tau_1$ value used is 16 days and all other parameter values with initial conditions are given in the text.

Fig. 8  

Time series corresponding to virus particles with $\tau_2 = 0$ days (dotted curve), $\tau_2 = 0.3$ days (dashed curve) and $\tau_2 = 4$ days (solid curve) for $f = 0.1$ and $k = 5$. The oscillatory behaviour persists for higher $\tau_2$ values with increasing amplitude. We choose $\tau_1 = 5$ days and other parameter values same as for Fig. 7b.
cases indicates that the steady states that are stable for $\tau_2 = 0$, can become unstable for a finite time delay $\tau_2$ and this method can be applied to all values of parameters to understand the change in stability for each case.

4 Model describing secondary infection

The model for secondary infection introduced here is an extension of the primary infection model given in the previous sections. Added to the primary model is a sixth variable which describes the level of antibody formed in the previous dengue infection that still circulate in the body but are heterologous to the new virus serotype.

In this case the heterologous antibodies can bind to the virions, but the extent of binding not only depends on the complementarity between the antigen and antibody but also on the concentrations of the heterologous antibodies. It is found that different serotypes of virus in the primary and secondary infections have antigenic similarities in their protein coat (Halstead 2009; Murphy and Whitehead 2011). As a result, the intensity with which a particular virus stimulates a response for heterologous or homologous antibodies will depend on this degree of similarity (Zhou and Deem 2006). Our model introduces two features, correlation factor and dynamic switch, that can take care of the specific dynamical processes in secondary infection.

We introduce a parameter $w$ to specifically take care of the relatedness between the various virus serotypes of primary and secondary infection. This correlation factor $w$ can vary from 0 to 1 and it quantifies the similarity between the individual serotypes.

For very low concentrations of the heterologous antibodies in the body, the probability of its interaction with virus particles is almost zero. Lack of infection at low heterologous antibody concentrations has been reported (Chen et al. 2013; Halstead 2003; Murphy and Whitehead 2011). At high concentrations of the heterologous antibodies there is a good probability of the virus undergoing complete opsonization with these antibodies. In this case it is very probable that the macrophages succeed in destroying the neutralised virions. Hence at very high concentrations the heterologous antibodies actually help in curbing the infection (Chan et al. 2011; Wahala and de Silva 2011). Therefore, the mechanism of ADE is at work only within a certain range in the concentration of heterologous antibodies which corresponds to sub-neutralising concentrations of these antibodies (Halstead 1970, 1988, 2009; Murphy and Whitehead 2011). This means when heterologous antibodies are present in the body between a certain minimum and maximum value ($A_{min}, A_{max}$) they actually help in virion production. This is incorporated in our model by introducing a dynamic, smooth switch function ‘$y$’ which is a function of antibody concentration. We note that, the switch function is phenomenological in nature and serves to mathematically model the hypothesized cellular mechanism. The new set of non-linear equations describing secondary dengue infection can then be written as:

\[
\begin{align*}
\dot{S} &= \mu - aS - aSV \\
\dot{I} &= aSV - \beta I \\
\dot{V} &= kI - \gamma V - yrA_1V - pA_2V
\end{align*}
\]
Fig. 9 Comparison of the switch function $y$ for $\nu_1 = 0.05, \nu_2 = 0.1$ and $\nu_1 = 0.005, \nu_2 = 0.01$ for $A_{min} = 50$ and $A_{max} = 1,500$. With smaller values of $\nu_1$ and $\nu_2$ the switching action of function $y$ extends over larger range of antibodies $A$.

\[
\begin{align*}
\dot{B} &= \eta - \delta B + c B V \\
\dot{A}_1 &= w f H(t - \tau_2)B(t - \tau_2) - q A_1 V - \kappa A_1 \\
\dot{A}_2 &= f H(t - \tau_1)B(t - \tau_2) - q' A_2 V - \kappa A_2
\end{align*}
\] (15)

with,

\[
y(A_1) = \frac{\tanh(\nu_1(A_1 - A_{max}))}{1 + e^{-\nu_2(A_1-A_{min})}}
\] (16)

The variable $A_1$ stands for the heterologous antibody previously formed on primary infection and $A_2$ for the homologous antibody against the new virus serotype of the secondary infection. $A_2$ follows a dynamics similar to primary infection. The parameters $\nu_1$ and $\nu_2$ are chosen such that the switch function $y(A_1)$ changes its value smoothly from 0 to $-1$ as $A_1$ becomes greater than $A_{min}$ and to $+1$ as $A_1$ rises above $A_{max}$. The nature of $y$ as a function of antibody count for two different sets of parameters $\nu_1$ and $\nu_2$ is shown in Fig. 9. We observe that for smaller values of $\nu_1$ and $\nu_2$, the function $y$ shows a smooth transition over larger range of antibody counts $A$.

The Heaviside step function corresponding to a time lag of $\tau_1$ is not associated with the antibody $A_1$ as corresponding plasma cells are already present in the form of memory B-cells. On infection with a different serotype virus at $t = 0$, it takes at least $\tau_2$ amount of time for the antibodies to get produced for the first time from the B-cells (memory cells) present at $t = 0$. To take care of this we introduce the Heaviside step function $H(t - \tau_2)$. The new parameters are, ‘$r$’, the rate at which virus particles are neutralised by $A_1$ antibodies and ‘$q’$, the rate at which $A_2$ antibody–virus complex is neutralised and degraded. All the other parameters in this model are analogous to the primary model.

We first present the analysis of the dynamics of secondary infection by numerical simulations of the above set of equations. Then we study the effect of the parameters of the dynamic switch and the correlation factor on the outcome of the infection.
5 Numerical analysis for the secondary infection model

For the numerical analysis of the secondary infection model, we take \( q = q' \) and \( r = p \), with values of \( A_{\text{max}} = 1500 \), \( A_{\text{min}} = 50 \) and \( A_1(0) = 800 \). The initial value of \( A_1 \) has been chosen to be less than the equilibrium value of antibodies obtained after primary infection because, the antibodies decay with time long after the infection. The values of \( \nu_1 \) and \( \nu_2 \) have been chosen to be 0.05 and 0.1 respectively. Here the correlation factor \( w \) is taken as 0.5 for secondary infection with \( \tau_1 = 3 \) days and \( \tau_2 = 0.3 \) days. We choose the initial value of \( A_2 \) to be zero. For all the other parameters and initial values we take the same values as in the primary model given in Sect 3. This system of Eq. (15) is numerically solved by using the Runge–Kutta method for delay differential equations (Lakshmanan and Senthilkumar 2010).

The viral count in the primary and secondary models obtained from numerical analysis are shown together for comparison in Fig. 10. This indicates that the viral load is cleared from the body within 7 days even for secondary infection and it is faster than the primary infection. This is supported by the reports of observed data, that the viral load is not detected in patients affected by secondary infection when they are suffering from severe conditions like DSS or DHF (Halstead 1970, 1988). Moreover, from this figure we observe that the maximum value of viral load is higher in secondary infection as compared to primary infection. Also, clinical data on higher viral loads and faster clearance of viremia in secondary infections has been reported (Vaughn et al. 2000).

One of the important results from the numerical analysis of our secondary infection model is that the total antibody count for secondary infection is much higher than the antibody count in the primary infection. This is shown in Fig. 11. Such a stronger immune response caused by higher antibody levels can lead to complex and fatal manifestations resulting in DSS or DHF when infected by a different serotype of DENV as observed in patients with secondary dengue infections (Fink et al. 2006; Halstead 1970, 1988; Lei et al. 2001; Rothman and Ennis 1999; Rothman 2004). Supporting this, we present the clinical data of the total antibody counts (ELISA counts) taken from a sample set of 34 patients suffering from primary dengue infection.
Fig. 11 Total antibody counts during primary (dashed curve) and secondary (solid curve) dengue infections for $f = 0.8$ and $k = 2$. The total antibody count in secondary infection is more than that in the primary infection.

Fig. 12 Clinical data giving total antibodies counts (ELISA count) of 34 patients suffering from primary infection and a separate set of 34 patients suffering from secondary infections. We see that observed antibody counts are higher in the case of secondary infections.

and a separate set of 34 patients suffering from secondary infection, supplied by Hedgewar Hospital in Aurangabad, Maharashtra, India (Dr. Ravi Patwadkar and Dr. Manjusha Kulkarni, manju-kulkarni@hedgewar.org) in Fig. 12. The data clearly shows that the total antibody counts are higher in secondary dengue infections when compared to primary dengue infection.

Another interesting aspect due to the non-linearity of our model is that the production of heterologous antibodies in the secondary infection enhances the production of homologous antibodies. Therefore we observe higher values of homologous antibodies in the secondary infection in comparison to homologous antibodies of the primary infection as is clear from Fig. 13. This leads us to conclude that the higher values of total antibody counts in secondary infection are not only because of the presence of heterologous antibodies but also because of the enhancement in homologous antibody production.

We will now have a look at the effect of various parameters of the switch function $y(A)$ on the outcome of secondary dengue infection in terms of its severity and duration. For values of $\nu_1$ and $\nu_2$ chosen as 0.05 and 0.1 respectively, the maximum
Fig. 13 Comparison of homologous antibody count in primary (dashed curve) and secondary (solid curve) infections for $f = 0.8$ and $k = 2$. The homologous antibody count in the secondary infection is higher compared to that in the primary infection.

The value of virus count ($V$) is plotted for different values of $A_{\text{max}}$ with $A_{\text{min}} = 50$ (Fig. 14a). The other parameter values are the same as taken for numerical analysis of the secondary infection mentioned above. We observe that when the initial value of heterologous antibody $A_1(0)$ is much lower than $A_{\text{min}}$, the infection is not very severe and it saturates with increasing $A_{\text{max}}$. Such values of maximum virus counts are what we typically get in primary dengue infections. For values of $A_1(0)$ larger than $A_{\text{max}}$ the infection gets cleared exponentially and the maximum value of the virus count is just the initial $V(0)$ value. For values of $A_1(0)$ considerably higher than $A_{\text{min}}$ and around $A_{\text{max}}$, the maximum value of $V$ increases with increasing $A_{\text{max}}$. With further increase in $A_{\text{max}}$ the maximum of virus count saturates eventually. Exactly similar observations are made with respect to the maximum of total antibody count ($A_1 + A_2$) plotted for different values of $A_{\text{bmax}}$ as is shown in Fig. 14b. Thus, we see that the infection aggravates in the range where the ADE mechanism is active as is expected.

Similarly, results for the time taken for the virus count to go below undetectable levels, i.e. the time taken for clearance of infection with varying $A_{\text{max}}$ is shown in Fig. 14c. We have defined the virus clearance threshold to be fixed at $V = 10$. For really small values of $A_1(0)$, the time taken for the virus to clear is 7–14 days and saturates with increasing $A_{\text{max}}$. Again, the values observed are similar to that of what we get in primary dengue infections. For values of $A_1(0)$ which are relatively higher than $A_{\text{max}}$, the viral clearance is exponential and is cleared in 2–4 days. When $A_1(0)$ is around or below $A_{\text{max}}$, time taken for viral clearance increases. These values are smaller than the values observed in the case of primary dengue infection as is expected since ADE mechanism is active.

The above analysis is repeated for $\nu_1$ and $\nu_2$ as 0.005 and 0.01 respectively. The results obtained are qualitatively the same. The corresponding values of maximum virus count and maximum total antibody count are found to be slightly smaller (smaller by multiples of ten for virus count and by multiples of few hundreds for total antibody count) in this case.
It is known that the concentration of antibodies in the body decays with time (Imrie et al. 2007; Halstead 2003; Wahala and de Silva 2011). Therefore, the initial value of antibodies present from the primary infection would depend on the time interval between the primary and the consecutive secondary dengue infection. Thus, the dependence of the secondary infection severity on this time interval can be studied by looking at the effect of initial heterologous antibody concentration in secondary infection. This study based on the values of maximum viral count, maximum total antibody count and the time taken for viral clearance as discussed above, calculated for different sets of parameter $A_{\text{max}}$, is given in Fig. 15. We have chosen $A_{\text{min}}$ as 50 along with $\nu_1, \nu_2$ as 0.005 and 0.01 respectively. The other parameter values are kept the same as in the above discussion.

From the Fig. 15a we observe that as the initial concentration of heterologous antibody ($A_1(0)$) increases, the maximum viral count increases and peaks when the value of $A_1(0)$ is similar to the value of $A_{\text{max}}$. We also note that, higher the value of $A_{\text{max}}$ stronger is the peak for maximum viral count. With further increase in $A_1(0)$, the virus gets exponentially cleared from the body and the maximum viral count is
Dengue virus and antibody dynamics

Fig. 15  a The maximum value of virus count calculated for varying initial heterologous antibody count ($A_1(0)$) shown for two different values of $A_{\text{max}}$ namely 1,000 and 2,000. b The maximum value of total antibody count in the secondary infection plotted against $A_1(0)$ for $A_{\text{max}} = 1,000$ and 2,000. c The time taken for viral clearance in secondary infection plotted against $A_1(0)$ for $A_{\text{max}}$ =1,000 and 2,000. The parameter values are as given in the text.

just the initial viral count. Similar results are observed for the maximum value of the total antibody count as is shown in Fig. 15b. When time of viral clearance is calculated with increasing $A_1(0)$ values, we observe that the virus gets cleared faster with higher values of $A_1(0)$ as is shown in Fig. 15c. When the $A_1(0)$ values are around $A_{\text{max}}$, we observe a slight increase in viral clearance time. This is the region where ADE mechanism is most active. For really small values of $A_1(0)$, the time taken for viral clearance is as good as what we get in primary infections. Thus, we can conclude that when a host who had suffered from primary dengue infection a long time back, such that the antibodies from the primary infection are negligible in count, gets secondary infection, the infection will not be severe and will be comparable to the primary infection. Similarly, a person who contracts secondary infection just after he has suffered from primary dengue infection, will not face severe consequences as the infection will be exponentially cured. But, if the person were to contract secondary infection after a particular time duration from the primary infection, ADE mechanism would be strongly active and lead to severe infection. This conclusion matches with the observations made in studies based on dengue infection severity with changes in
The maximum homologous antibody count in secondary infection vs. the correlation factor $w$ for $f = 0.8$ and $k = 2$. This is found to increase with increasing $w$.

We now discuss how the correlation factor $w$ affects the outcome of secondary infection. In Fig. 16 we present the maximum value of homologous antibody count obtained from our numerical analysis as $w$ is varied from 0 to 0.9. This shows that the enhancement of homologous antibody production in the secondary infection depends on this factor. We note that there are studies that suggest the severity of secondary dengue infection varies depending on the two DENV serotypes involved (Halstead 1970; Vaughn et al. 2000).

We carry out detailed numerical exploration of the model to identify the regions of stability for possible steady states in the parameter plane $f-k$. This is shown in Fig. 17 for two values of $w$, 0.5 and 0.8. It is clear that in the case of secondary infection also, $V^* = 0$ state exists which implies that non-infectious steady state is reached. The stability region for this state is shown in green (light grey). We also find the existence of infectious steady state solutions in the region shown in red (dark grey) and oscillatory solutions in region shown in blue (black). Moreover, we note that, as the value of $w$ increases the region of stability with zero virus count shifts to lower values of $f$. This implies that even though the severity of the infection might increase with $w$ (because of enhanced antibody production) the infection free stability region in fact increases. Further biological studies are needed to understand the nature of this correlation or the degree of similarity between the different serotypes and the severity of infection.

6 Discussion

In the current global context, dengue forms a major concern due to its severity and complexity. Considered to be a tropical disease, it is spreading to higher latitudes
due to changes in climatic and human activities. Hence, it is of great importance to study the epidemiology of dengue infections on a global macro-epidemic scale. Here we emphasise the relevance of studying it on a micro-epidemic level to know the mechanism involved in the infection which will possibly help to eradicate it.

In this paper, we present a model based on several observed features of dengue infection. We consider the humoral or antibody mediated immune response as the main mechanism that is involved in viral clearance and subsequent development of immunity since this is reported as the relevant one in the context of dengue. It is known that host immune mechanism involves multiple cellular processes which are taken care of by introducing a delay time $\tau_1$ in the initial production of antibodies after maturation of naive B-cells to virus specific plasma cells (modified B-cells) and another delay $\tau_2$ for the production of antibodies from plasma cells once they are formed. The analysis presented here brings out the dependence of virus counts on delays and the specific range of parameters for which infection free state is stable.

Our results imply that in general the virus gets cleared in 7–14 days which is in agreement with clinical literature. An interesting outcome of the primary infection model is a critical value $f_c$ for the parameter $f$ representing immune response, such that when $f > f_c$ we always get infection free stable state which corresponds to what is observed in this context. However, for values of $f < f_c$, which means that immune response is weak and burst rate of virus is large, it is possible that the virus count will settle to a non-zero value, corresponding to infectious steady state. Our analysis also brings out the dependence of stability of solutions for the primary model on the delay parameter $\tau_2$. Specifically, if the delay in the immune response is considerable, infectious steady state can become recurring peaks of infection.

The dynamics of secondary infection with a different DENV serotype is modelled to take care of the ADE process. The consequent production of higher viremia and antibodies which can lead to severe manifestations of DHF and DSS are the obtained outcomes of the model. Since the mechanism is found to be dependent on the concentrations of heterologous antibodies present from previous primary infection, we have introduced a dynamic switch function which can take care of this dependence. The
effects of varying the parameters of the switch function on the severity and duration of the secondary infection are studied in detail. Our results also support the observed clinical data on increased antibody counts in secondary infection. The degree of similarity between the two virus serotypes involved is a crucial factor that decides the ability of the heterologous antibodies to neutralise viral particles. In our model the correlation factor $w$ is introduced as a measure of this similarity. Our results suggests that the antibody production and correspondingly the severity of secondary infection depends on this similarity.

In conclusion we note that this is the first attempt to model primary dengue infection along with the secondary infection on a micro-epidemic level using humoral immune response. The delay in the immune response, the correlation factor and the dynamic switch in the secondary infection model are the important features of this work. The results obtained so forth are very encouraging to further extend this work for the mathematical analysis of the secondary infection model and tune it to the finer details of the unusual virus–host interactions observed in dengue infections with biological data. Further work in this direction will surely help in understanding the complex mechanisms involved in dengue pathogenesis. It will also be helpful to formulate relevant schemes to develop a dengue vaccine which can provide immunity against all four serotypes in future.

**Acknowledgments** We would like to thank Dr. Hedgewar Hospital, Aurangabad, Maharashtra for providing the ELISA data on Dengue infections. We thank the anonymous reviewers for their valuable comments.

**Appendix**

Details of the Jacobian and the characteristic equation

The Jacobian describing the primary infection in terms of $S^*$, $V^*$, $B^*$ and $A^*$ which are the equilibrium values of healthy cells, virus count, B-cells and antibody count respectively is given as,

$$
J = \begin{bmatrix}
-(\alpha + aV^*) & 0 & -aS^* & 0 & 0 \\
aV^* & -\beta & aS^* & 0 & 0 \\
0 & k & -(\gamma + pA^*) & 0 & -pV^* \\
0 & 0 & cB^* & -(\delta - cV^*) & 0 \\
0 & 0 & -qA^* & \beta^{-\lambda t_2} & -(\kappa + qV^*) \\
\end{bmatrix}
$$

(17)

where;

$$
S^* = \frac{\mu}{(\alpha + aV^*)}
$$

(18a)

$$
I^* = \frac{aS^*V^*}{\beta}
$$

(18b)
\[ B^* = \frac{\eta}{(\delta - c V^*)} \]  
\[ A^* = \frac{f B^*}{(q V^* + \kappa)} \]  

(18c)  

(18d)

The characteristic equation for the Jacobian \( J \) with eigenvalues \( \lambda \) can be written as:

\[ G(\lambda) = \lambda^5 + G_4 \lambda^4 + G_3 \lambda^3 + G_2 \lambda^2 + G_1 \lambda + G_0 + H_2 e^{-\lambda t_2} \lambda^2 \]

\[ + H_1 e^{-\lambda t_2} \lambda + H_0 e^{-\lambda t_2} = 0 \]  

(19)

where:

\[ G_4 = (\alpha + \beta + \gamma + \delta + \kappa + V^*(a + \kappa - c) + p A^*) \]

\[ G_3 = (\alpha \beta + \alpha \gamma + \beta \gamma + \beta \delta + \gamma \delta + \alpha \kappa + \beta \kappa + \gamma \kappa + \delta \kappa \]

\[ + V^*(\alpha \beta + \gamma + \delta + \kappa + q(\alpha + \beta + \gamma + \delta) - c(\alpha + \beta + \gamma + \kappa)) \]

\[ + V^*(q a - a c - c q) + A^* p(a - c) + A^* p(\alpha + \beta + \delta + \kappa - \alpha k S^*) \]

\[ G_2 = (\alpha \beta \gamma + \alpha \beta \delta + \alpha \gamma \delta + \beta \gamma \delta + \alpha \beta \kappa + \alpha \gamma \kappa + \beta \gamma \kappa + \alpha k \delta + \beta \delta \kappa + \gamma \delta \kappa \]

\[ + V^*(\alpha \beta \gamma + \beta \gamma + \gamma \delta + \beta k + \gamma k + \delta k) + q(\alpha \beta + \alpha \gamma + \beta \gamma + \alpha \delta + \beta \delta + \gamma \delta) \]

\[ - c(\alpha + \beta + \gamma + \kappa) - c q V^* \]

\[ + A^* p(\alpha \beta + \alpha \gamma + \beta \gamma + \alpha \kappa + \beta \kappa + \kappa) + A^* p(a + \beta + \delta + \kappa - c(\alpha + \beta + \kappa)) \]

\[ G_1 = (\alpha \beta \gamma \delta \kappa + \alpha \beta \gamma \kappa + \kappa \beta \gamma \delta - \alpha \beta \gamma \kappa) \]

\[ + V^*(\alpha \beta \gamma + \beta \gamma + \gamma \delta + \beta k + \gamma k + \delta k) + q(\alpha \beta + \alpha \gamma + \beta \gamma + \alpha \delta + \beta \delta + \gamma \delta) \]

\[ - c(\alpha + \beta + \gamma + \kappa) - c q V^* \]

\[ + A^* p(\alpha \beta + \alpha \delta \kappa + \beta \delta \kappa + \beta \kappa) + A^* p(a + \beta + \delta + \kappa - c(\alpha + \beta + \kappa)) \]

\[ - a p c A^* V^* - a k S^*(\kappa + \alpha + \delta + q V^* - c V^*) \]

\[ G_0 = (\alpha \beta \gamma \kappa + V^*(q a \beta \gamma + \kappa a \beta \gamma + \kappa \beta \gamma - \alpha \beta \gamma \kappa) \]

\[ + V^*(q a \beta \gamma + \kappa a \beta \gamma + \kappa \beta \gamma - \alpha \beta \gamma \kappa) - V^* a c q \beta \gamma + A^* p a \beta \kappa \delta \]

\[ + A^* p(q a \beta \delta + \alpha \beta \kappa - a a \beta \kappa - q a \beta \delta) - A^* p a c \beta \kappa \]

\[ - a k S^*(\alpha \delta \kappa + \alpha a \delta V^* - c a \kappa V^* - c q a V^* \]  

\[ H_2 = (c f p B^* V^*); \]

\[ H_1 = c f p(\alpha B^* V^* + \beta B^* V^* + a B^* V^*); \]

\[ H_0 = c f p B^*(\alpha B^* V^* + a B^* V^*) \]  

(20)

For \( V^* = 0 \), we get the coefficients of the characteristic Eq. (19) as:

\[ G_4 = (\alpha + \beta + \gamma + \delta + \kappa + p A^*) \]
\[ G_3 = (\alpha \beta + \alpha \gamma + \gamma \beta + \alpha \delta + \beta \delta + \gamma \delta + \alpha \kappa + \beta \kappa + \gamma \kappa + \delta \kappa + \ldots + A^* p(\alpha + \beta + \delta + \kappa) - akS^*); \]
\[ G_2 = (\alpha \beta \gamma + \alpha \beta \delta + \alpha \gamma \delta + \alpha \beta \kappa + \alpha \gamma \kappa + \beta \gamma \kappa + \alpha \delta \kappa + \beta \delta \kappa + \gamma \delta \kappa + \ldots + A^* p(\alpha \beta + \alpha \delta + \beta \delta + \gamma \delta + \alpha \kappa + \beta \kappa + \gamma \kappa + \ldots - akS^*(\kappa + \alpha + \delta)); \]
\[ G_1 = (\alpha \beta \gamma \delta + \alpha \beta \gamma \kappa + \alpha \beta \delta \kappa + \alpha \gamma \delta \kappa + \beta \gamma \delta \kappa + \alpha \beta \kappa \delta + \alpha \gamma \kappa \delta + \beta \gamma \kappa \delta + \alpha \kappa \delta \kappa + \beta \kappa \delta \kappa + \gamma \kappa \delta \kappa + \ldots + A^* p(\alpha \beta \delta + \alpha \beta \kappa + \alpha \delta \kappa + \beta \delta \kappa) - akS^*(\kappa + \alpha + \delta)); \]
\[ G_0 = (\alpha \beta \gamma \delta \kappa + A^* p\alpha \beta \kappa \delta - akS^*(\alpha \delta \kappa)); \]
\[ H_2 = 0; \]
\[ H_1 = 0; \]
\[ H_0 = 0 \quad (21) \]

On substituting the above coefficients in Eq. (19) and simplifying after using Eq. (18) we get the characteristic equation for \( V^* = 0 \) as
\[
G(\lambda) = (\alpha + \lambda)(\kappa + \lambda)(\delta + \lambda) \left( \lambda^2 + \lambda \left( \gamma \left( 1 + \frac{fp\eta}{\delta \gamma \kappa} \right) + \beta \right) + \beta \right)
\]
\[
+ \beta \gamma \left( 1 + \frac{fp\eta}{\delta \gamma \kappa} - R_0 \right) \quad (22)
\]
where;
\[
R_0 = \frac{a\mu k}{\alpha \beta \gamma}
\]

We carry out further analysis in the paper by considering the coefficient values given in this Appendix.

**References**

Agur Z, Mehr R (1992) Use of modelling for elucidating trypanotolerance: preliminary considerations. In: Perry BD, Hansen JW (eds) Modelling vector borne and other parasitic diseases. ILRAD, Nairobi
Ambika G, Dahanukar N (2009) Virus immune drug dynamics. In: Daniel M, Rajasekar S (eds) Nonlinear dynamics. Narosa Publication, New Delhi
Beauchamin CAA, Handel AA (2011) Review of mathematical models of influenza A infection within a host or cell culture: lessons learned and challenges ahead. BMC Public Health 11(suppl 1):S7
Bielefeldt-Ohmann H (1997) Pathogenesis of dengue virus disease: missing pieces in the jigsaw. Trends Microbiol 5:409–413
Chan KR, Zhang SLX, Tan HC, Chan YK, Chow A, Lim APC, Vasudevan SG, Hanson BJ, Ooib EE (2011) Ligation of Fc gamma receptor IIB inhibits antibody-dependent enhancement of dengue virus infection. Proc Natl Acad Sci USA 108(30):12479–12484
Chaturvedi UC, Tandon P, Mathur A, Kumar A (1978) Host defence mechanisms against dengue virus infection of mice. J Gen Virol 39:293–302
Chen IC, Wang SM, Yu CK, Liu CC (2013) Subneutralizing antibodies to enterovirus 71 induce antibody-dependent enhancement of infection in newborn mice. Med Microbiol Immunol 202(4):259–265
Derouich M, Boutayeb A (2006) Dengue fever: mathematical modelling and computer simulation. Appl Math Comput 177:528–544
Dengue virus and antibody dynamics

Dibrov BF, Livshits MA, Volkenstein MV (1977) Mathematical model of immune processes. J Theor Biol 65:609–631
Diekmann O, Heesterbeek JAP (2000) Mathematical epidemiology of infectious diseases, model building, analysis and interpretation. John Wiley, Chichester
Dietz K (1975) Transmission and control of arbovirus diseases. In: Ludwig D, Cooke KL (eds) Epidemiology. SIAM, Philadelphia, pp 104–121
Esteva L, Vargas C (1998) Analysis of a dengue disease transmission model. Math Biosci 15:131–151
Esteva L, Vargas C (1999) A model for dengue disease with variable human population. J Math Biol 38:220–240
Esteva L, Vargas C (2003) Coexistence of different serotypes of dengue virus. J Math Biol 46:31–47
Feng Z, Velasco-Hernandez JK (1997) Competitive exclusion in vector host-model for the dengue fever. J Math Biol 35:523–544
Fink J, Gu F, Vasudevan JK (2006) Role of T cells, cytokines and antibody in dengue fever and dengue haemorrhagic fever. Rev Med Virol 16:263–275
Fischer DB, Halstead SB (1970) Observations related to pathogenesis of dengue hemorrhagic fever. V. Examination of age specific sequential infection rates using a mathematical model. Yale J Biol Med 42:329–349
Fowler AC (1981) Approximate solution of a model of biological immune responses incorporating delay. J Math Biol 13:23–45
Garba SM, Gumel AB, Abu Baker MR (2008) Backward bifurcations in dengue transmission dynamics. Math Biosci 215:11–25
Gibbons RV, Vaughn DW (2002) Dengue: an escalating problem. Br Med J 324:1563–1566
Guzman MG, Kouri G, Valds L, Bravo J, Vzquez S, Halstead SB (2002) Enhanced severity of secondary dengue-2 infections: death rates in 1981 and 1997 Cuban outbreaks. Rev Panam Salud Publica 11(4):223–227
Halstead SB (1997) Observations related to pathogenesis of dengue haemorrhagic fever VI: hypothesis and discussion. Yale J Biol Med 42:350–362
Halstead SB (1988) Pathogenesis of dengue: challenges to molecular biology. Science 239:476–481
Halstead SB (2003) Neutralization and antibody-dependent enhancement of dengue viruses. Adv Virus Res 60:421–467
Halstead SB (2007) Dengue. Lancet 370:1644–1652
Halstead SB (2009) Antibodies determine virulence in dengue. Ann N Y Acad Sci 1171(Suppl. 1):E48–56
Imrie A, Meeks J, Gurary A, Sukhbaatar M, Truong TT, Cropp CB, Effler P (2007) Antibody to dengue 1 detected more than 60 years after infection. Viral Immunol 20(4):672–675
Janeway CA, Travers P, Walport M, Shlomchik MJ (2001) Immunobiology: the immune system in health and disease, 5th edn. Garland Science, New York
Jindadamrongwech S, Thepparit C, Smith DR (2004) Identification of GRP 78 (BiP) as a liver cell expressed receptor element for dengue virus serotype 2. Arch Virol 149:915–927
Julander J, Perry ST, Shresta S (2011) Important advances in the field of anti-dengue virus research. Antivir Chem Chemother 21:105–116
Kinney RM, Huang CY (2001) Development of new vaccines against dengue fever and Japanese encephalitis. Intervirology 44(2–3):176–197
Kitchen CMR, Yeghiazarian L, Hoh R, McCune JM, Sinclair E, Martin JN, Deeks SG (2011) Immune activation, Cdt4+T cell counts, and viremia exhibit oscillatory patterns over time in patients with highly resistant HIV infection. PLoS One 6:e21190
Klein P (1980) Mathematical models of antibody response. Folia Microbiol 25:430–438
Kliks SC, Nisalak A, Brandt WE, Wahl L, Burke DS (1989) Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue haemorrhagic fever. Am J Trop Med Hyg 40:444–451
Kyle JL, Balsitis SB, Zhang L, Beatty RP, Harris E (2008) Antibodies play a greater role than immune cells in heterologous protection against secondary dengue virus infection in mouse model. Virology 380(2):296–303
Lakshmanan M, Senthilkumar DV (2010) Dynamics of non-linear time delay systems. Springer-Verlag, Berlin
Lei HY, Yeh TM, Liu HS, Lin YS, Chen SH, Liu C (2001) Immunopathogenesis of dengue virus infection. J Biomed Sci 8:377–388
Lindenbach D, Rice CM (2001) Flaviviridae: the viruses and their replication. In: Knipe D, Howley P (eds) Fields virology. Lippincott, Philadelphia, pp 991–1041
Marchuk GM (1997) Mathematical modelling of immune response on infectious diseases. Kluwer Academic Publishers, Dordrecht
Murphy BR, Whitehead SS (2011) Immune response to dengue virus and prospects for a vaccine. Annu Rev Immunol 29:587–619
Noisakran S, Perng GC (2008) Alternate hypothesis on the pathogenesis of dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) in dengue virus infection. Exp Biol Med 233:401–408
Nowak MA, May RM (2000) Virus dynamics: mathematical principles of immunology and virology. Oxford University Press, New York
Nuraini N, Soewono E, Sidarto KA (2007) A mathematical model of dengue internal transmission process. J Indonesia Math Soc (MIHMI) 13–1:123–132
Nuraini N, Tasman H, Soewono E, Sidarto KA (2009) A with-in host dengue infection model with immune response. Math Comput Model 49:1148–1155
Porterfield JS (1986) Antibody-dependent enhancement of viral infectivity. In: Maramorosch K (ed) Advances in virus research, vol 31. Academic Press, London, pp 335–355
Rigau-Perez JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV (1998) Dengue and dengue haemorrhagic fever. Lancet 352:971–977
Rotham AL (2011) Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev 11:532–543
Rothman AL (2004) Dengue: defining protective versus pathologic immunity. J Clin Invest 113:946–951
Rothman AL, Ennis FA (1999) Immunopathogenesis of dengue haemorrhagic fever. Virology 257:1–6
Run Tao H, Innis BL, Nisalak A, Usawattanakul W, Wang S, Kalayanarooj S, Anderson R (1995) Antibodies that block virus attachment to vero cells are a major component of the human neutralizing antibody response against dengue virus type 2. J Med Virol 45:451–461
Sabin AB (1959) Dengue. In: Rivers TM, Horsfall F (eds) Viral and rickettsial infections of man, 3rd edn, vol 361. Lippincott, Philadelphia
Science Daily (1998) Global warming would foster spread of dengue fever into some temperate regions. http://www.sciencedaily.com/releases/1998/03/980310081157.htm/. Accessed 2 September 2013
Scott TW, Morrison AC (2010) Vector dynamics and transmission of dengue virus: implications for dengue surveillance and prevention strategies. In: Rotham AL (ed) Dengue virus. Current topics in microbiology and immunology, vol 338. Springer, Berlin, pp 115–125
Tassaneentrithep B, Burgess TH, Granelli-Piperno A, Trumpfheller C, Finke J, Sun W, Eller MA, Pattanapanatasat K, Saraporchant B, Brix DL, Steinman RM, Schlesinger S, Marovich MA (2003) DC SIGN (CD209) mediates dengue virus infection of human dendritic cells. J Exp Med 197:823–829
Vaughn DW, Green S, Kalayanarooj S, Innis BL, Nimmanntiya S, Sunayakorn S, Endy TP, Raengsakulrach B, Rothman AL, Ennis FA, Nisalak A (2000) Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis 181:2–9
Wahala WM, de Silva AM (2011) The human antibody response to dengue virus infection. Viruses 3(12):2374–2395
WHO (2013) Dengue and dengue haemorrhagic fever. http://www.who.int/mediacentre/factsheets/fs117/en/. Accessed 6 October 2013
World Health Organisation (WHO) and Special programme for Research and Training in Tropical Diseases (TDR) (2009) Dengue-guidelines for diagnosis, treatment, prevention and control (ISBN 9789241547871)
Wu SJ, Grouard-Vogel G, Sun W, Mascola JR, Brachtel E, Putvatanas T, Louder MK, Filgueira L, Marovich MA, Wong HK, Blauvelt A, Murphy GS, Robb ML, Innes BL, Brix DL, Hayes CG, Frankel SS (2000) Human skin Langerhans cells are targets of dengue virus infection. Nat Med 6:816–820
Zhou H, Deem MW (2006) Sculpting the immunological response to dengue fever by polytopic vaccination. Vaccine 24:2451–2459