# Symmetry in a multi-strain epidemiological model with distributed delay as a general cross-protection period and disease enhancement factor

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ABSTRACT

Important biological features of viral infectious diseases caused by multiple agents with interacting strain dynamics continue to pose challenges for mathematical modelling development. Motivated by dengue fever epidemiology, we study a system of Integro-Differential Equations (IDE) considering strain structure of pathogens. Knowing that complex dynamics observed in dengue models are driven by the combination of two biological features, the temporary cross-immunity (TCI) and disease enhancement via the antibody-dependent enhancement process (ADE), our IDE system incorporates the TCI with a general time delay term, and the ADE effect by a constant factor to differentiate the susceptibility of individuals experiencing a primary or a secondary infection. Aiming at analysing the effect of the symmetry on dengue serotypes in the IDE framework, a detailed qualitative analysis of the model is performed and the instability of the coexistence steady state is shown using the perturbation theory approach. Numerical simulations identify the bifurcation structures and confirm the stability analysis. Results for the symmetric and asymmetric models are discussed.

## 1. Introduction

Mathematical models have a long history in epidemiological research, used as an important tool to understand the dynamics of infectious disease spreading and control under different scenarios.

Dengue fever is a widespread viral disease transmitted by mosquitoes, with half of the world's population at risk of acquiring dengue infection [1, 2]. There are four distinct serotypes that are antigenically related. Thus, infection with one serotype confers short cross-immunity protection (TCI) to all serotypes and long-immunity protection to that serotype. Secondary infection with a heterologous serotype has been associated with the severity of illness symptoms and dengue hemorrhagic fever due to a biological process known as ADE [3, 4, 5] . This process occurs when antibodies produced by an immune response after a first infection recognize the first related serotype, attempt to bind to the virus but are unable to do so, instead increasing the virus's ability and enhancing the new infection [6, 7, 8, 9].

There is no specific treatment for dengue infection. Most people have mild or no symptoms that will require only supportive care. However, severe dengue cases will require hospitalization and can eventually lead do death due to the disease. Due to the dengue-specific complexities described above, vaccine development focuses on the production of a tetravalent vaccine aimed at providing long-term protection against all dengue virus serotype. the Dengvaxia, developed by Sanofi Pasteur [10], and the Qdenga (TAK-003) vaccine, developed by Takeda Pharmaceutical Company [11, 12] have both completed phase 3 clinical trials. The Dengvaxia vaccine has resulted in serious adverse events in seronegative individuals in a study comparing the age-matched seronegative controls [13, 14, 15, 16, 17, 18], whereas serotype specific negative vaccine efficacy was observed for vaccinated seronegative individuals who have received the Qdenga vaccine [19], resulting that long-term surveillance involving prudent and careful observation of people receiving Qdenga is necessary [20, 21, 22].

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To explain the irregular behavior of dengue epidemics, mathematical models that investigated dengue dynamics and focused on the interplay between strains have been proposed [23].

Using an extension of the SIR models, the multi-strain dengue dynamics have been studied by adding biological features of the disease such as ADE process [24, 25, 26, 27, 28, 29, 30], successfully describing the large fluctuations observed in empirical outbreak data. The combination of TCI and ADE features in these models has shown to be the most important drivers for the complex dynamics found in the models [31]. The combination of these biological features have been modeled in different ways. The ADE effect can be introduced to act either on individual transmissibility [28, 32, 33, 34, 35, 36] or on individual susceptibility [37, 38, 39], whereas the TCI can either be included using a constant waning immunity period (thus the mathematical model is the typical Ordinary Differential Equations (ODEs) system) [24] or can be represented by including a general time protection period (leading to an Integro-differential equations (IDEs) system) [37, 40].

Regarding models that considering asymmetry between serotypes have been studied in both the general ODE framework [32] and in the IDE framework [37, 40]. In the last one [37, 40], the authors have shown that the ODE system that consider constant immunity period (exponential distributed function) and the IDE system that consider a general immunity period (distributed delay using polynomial function) present the same qualitative behavior. However, quantitative behaviour depends on the choice of the function affecting the behaviour of the steady state regarding the coexistence of different strains. On the other hand, models considering symmetry between dengue serotypes have been studied in the general ODE framework [32, 41], whereas in the IDE framework the symmetry effect have been not been fully studied and understood [40].

Motivated by the study of disease transmission, we study a system of integro-differential equations describing the disease transmission dynamics considering strain structure of pathogens, ADE effect differentiating the susceptibility rate in a primary and secondary infection and TCI as a general time protection period. Differently from previous work, here we assume symmetry between dengue serotypes, that is, considering same virulence between serotypes. The main purpose of this study is to assess and analyse the impact of the symmetry between biological parameters and variables of the model where TCI is introduced as distributed delay. While it is recognized that the serological relationship between pairs of virus strains might not always be symmetrical, with one strain potentially dominating over another, this study focuses on the symmetric case. This approach is taken to simplify the system and derive theoretical insights from the model that wouldn't have been attainable with an assumption of asymmetry.

The outcomes presented in this work offer a deeper understanding of potential disease spread scenarios. This is achieved through an approximation of the general model, using the assumption of symmetry in the force of infection.

This paper is organized as follows. The proposed model framework is described in the qualitative analysis is discussed in Section 2. The associated limiting system is defined in Section 3, where we look for the equilibria and analyse the local stability determined by an important threshold value. In Section 4, numerical simulations are performed to describe the bifurcation structures appearing in the system and to study the stability of the coexistence equilibrium. In Section 5, perturbation theory is used to demonstrate that the Hopf bifurcation occurs out of a symmetric manifold, showing the instability of the coexistence steady state. In Section 6, the findings of the asymmetric and symmetric cases are discussed, followed by final considerations and conclusions.

## 2. Model structure

The system of integro-differential equations (IDE) proposed by Steindorf et al. [37] studied the propagation of multi-serotype infectious diseases. Motivated by dengue fever epidemiology, the model assumes asymmetry of serotypes and includes important biological features of the disease epidemiology, the temporary cross-immunity period (TCI) and the disease enhancement via the antibody-dependent enhancement (ADE) process to describe disease transmission dynamics in endemic scenarios.

As proposed in Steindorf et al. [37], the total population $N$ of individuals at time $t$ is stratified into 10 classes, $S(t)$, $I_i(t)$, $C_i(t)$, $R_i(t)$, $I_{ij}(t)$ and $R(t)$, with $i, j = 1, 2$ and $i \neq j$, representing all possible disease stages. Susceptible to all serotypes, $S(t)$, become infected for the first time with one of the dengue serotype, $I_i(t)$. After recovering from the first infection, individuals are temporarily immune to all serotypes, $C_i(t)$. After immunity wanes, individuals are life long immune to that specific serotype, $R_i(t)$, but susceptible to a secondary infection with a heterologous serotype, moving to the class $I_{ij}(t)$. Finally, individuals are recovered and fully immune after two infections, $R(t)$.

The constants, $d$ is the natural mortality rate for the population, $\beta$ is the transmission rate of primarily infected individuals, while $\alpha$ is the transmission rate of individuals experiencing a secondary infection with an heterologous

strain. With the assumption of a general length of cross-immunity protection, $P(t)$ denotes the proportion of people who, after recovering from the serotype $i$, remain temporarily protected against all serotypes during $t$ units assuming

$$P(0) = 1 \quad and \quad P(\infty) = 0, \tag{1}$$

$P(t)$ is non-increasing and

$$\int_0^\infty P(s)ds = \frac{1}{\omega} < \infty. \tag{2}$$

Moreover, $\gamma$ is the recovery rate, and, $\phi$ is the disease enhancement factor representing the disease severity due to the ADE process occurring during a secondary infection. The ADE effect is introduced as a constant rate that can increase or decrease the probability of a primarily infected recovered individual, to become infected for the second time, assuming that these individuals have a certain level of cross-reactive antibodies able to neutralize or enhance the new infection [9]. Hence, while $\phi < 1$ decreases the probability of a secondary infection to occur, $\phi > 1$ increases the probability of individuals to experience a secondary infection. Thus, here we assume that a previous exposure to one serotype results will increase the susceptibility to reinfection [9, 42]. The model does not consider the rare occurrence of co-infection of different strains [43], or the possibility of reinfection with same strain.

Differently from the assumptions in [37], here we investigate the IDE framework considering serotype symmetry in transmission and immunity, that is, $\beta_1 = \beta_2 = \beta$, $\alpha_1 = \alpha_2 = \alpha$ and $P_1 = P_2 = P$, respectively. These assumptions lead to a system reduction allowing us to obtain theoretical results on the stability of coexistence equilibrium that were not possible for the asymmetric case. The refined system is shown in Equation System (3).

$$\begin{aligned}
\frac{dS(t)}{dt} &= dN(t) - dS(t) - \beta\frac{S(t)}{N(t)}\left(I_1(t) + I_2(t) + I_{12}(t) + I_{21}(t)\right)\\
\frac{dI_1(t)}{dt} &= -dI_1(t) + \beta\frac{S(t)}{N(t)}I_1(t) + \beta\frac{S(t)}{N(t)}I_{21}(t) - \gamma I_1(t)\\
\frac{dI_2(t)}{dt} &= -dI_2(t) + \beta\frac{S(t)}{N(t)}I_2(t) + \beta\frac{S(t)}{N(t)}I_{12}(t) - \gamma I_2(t)\\
\frac{dC_1(t)}{dt} &= \gamma I_1(t) - dC_1(t) + \int_0^t \gamma I_1(s)P'(t-s)e^{-d(t-s)}ds\\
\frac{dC_2(t)}{dt} &= \gamma I_2(t) - dC_2(t) + \int_0^t \gamma I_2(s)P'(t-s)e^{-d(t-s)}ds\\
\frac{dR_1(t)}{dt} &= -dR_1(t) - \alpha\phi\frac{R_1(t)}{N(t)}I_{12}(t) - \alpha\phi\frac{R_1(t)}{N(t)}I_2(t) - \int_0^t \gamma I_1(s)P'(t-s)e^{-d(t-s)}ds\\
\frac{dR_2(t)}{dt} &= -dR_2(t) - \alpha\phi\frac{R_2(t)}{N(t)}I_{21}(t) - \alpha\phi\frac{R_2(t)}{N(t)}I_1(t) - \int_0^t \gamma I_2(s)P'(t-s)e^{-d(t-s)}ds\\
\frac{dI_{12}(t)}{dt} &= -dI_{12}(t) - \gamma I_{12}(t) + \alpha\phi\frac{R_1(t)}{N(t)}I_2(t) + \alpha\phi\frac{R_1(t)}{N(t)}I_{12}(t)\\
\frac{dI_{21}(t)}{dt} &= -dI_{21}(t) - \gamma I_{21}(t) + \alpha\phi\frac{R_2(t)}{N(t)}I_1(t) + \alpha\phi\frac{R_2(t)}{N(t)}I_{21}(t)\\
\frac{dR(t)}{dt} &= -dR(t) + \gamma I_{12}(t) + \gamma I_{21}(t).
\end{aligned} \tag{3}$$

The total population dynamics is determined by

$$N = S(t) + I_1(t) + I_2(t) + C_1(t) + C_2(t) + I_{12}(t) + I_{21}(t) + R_1(t) + R_2(t) + R(t).$$

Thus, we redefined the fractions of each sub-population by writing: $\frac{S}{N} = S$, $\frac{I_{ij}}{N} = I_{ij}$, $\frac{C_i}{N} = C_i$ and $\frac{R_i}{N} = R_i$. In addition, the dynamics for the recovered and cross immunity classes are decoupled (that is, the solution of $C_i$ and $R$ can be obtained by integrating its differential equation, after solving and substituting the solution of $I_i$), hence the original system can be studied by analysing the following seven dimensional equation system:

$$
\begin{aligned}
\frac{dS(t)}{dt} &= d - dS(t) - \beta S(t)\left(I_1(t) + I_{21}(t) + I_2(t) + I_{12}(t)\right)\\
\frac{dI_1(t)}{dt} &= -(d+\gamma)I_1(t) + \beta S(t)(I_1(t) + I_{21}(t))\\
\frac{dI_2(t)}{dt} &= -(d+\gamma)I_2(t) + \beta S(t)(I_2(t) + I_{12}(t))\\
\frac{dR_1(t)}{dt} &= -dR_1(t) - \alpha\phi R_1(t)(I_{12}(t) + I_2(t)) - \int_0^t \gamma I_1(s)P'(t-s)e^{-d(t-s)}ds\\
\frac{dR_2(t)}{dt} &= -dR_2(t) - \alpha\phi R_2(t)(I_{21}(t) + I_1(t)) - \int_0^t \gamma I_2(s)P'(t-s)e^{-d(t-s)}ds\\
\frac{dI_{12}(t)}{dt} &= -(d+\gamma)I_{12}(t) + \alpha\phi R_1(t)(I_2(t) + I_{12}(t))\\
\frac{dI_{21}(t)}{dt} &= -(d+\gamma)I_{21}(t) + \alpha\phi R_2(t)(I_1(t) + I_{21}(t)).
\end{aligned}
\tag{4}
$$

## 3. Qualitative analysis

Following the idea proposed in [44, 37], we will examine the system (4) as a perturbation of the limiting system:

$$
\begin{aligned}
\frac{dS(t)}{dt} &= d - dS(t) - \beta S(t)\left(I_1(t) + I_{21}(t) + I_2(t) + I_{12}(t)\right)\\
\frac{dI_1(t)}{dt} &= -(d+\gamma)I_1(t) + \beta S(t)(I_1(t) + I_{21}(t))\\
\frac{dI_2(t)}{dt} &= -(d+\gamma)I_2(t) + \beta S(t)(I_2(t) + I_{12}(t))\\
\frac{dR_1(t)}{dt} &= -dR_1(t) - \alpha\phi R_1(t)(I_{12}(t) + I_2(t)) - \int_0^\infty \gamma I_1(t-s)P'(s)e^{-ds}ds\\
\frac{dR_2(t)}{dt} &= -dR_2(t) - \alpha\phi R_2(t)(I_{21}(t) + I_1(t)) - \int_0^\infty \gamma I_2(t-s)P'(s)e^{-ds}ds\\
\frac{dI_{12}(t)}{dt} &= -(d+\gamma)I_{12}(t) + \alpha\phi R_1(t)(I_2(t) + I_{12}(t))\\
\frac{dI_{21}(t)}{dt} &= -(d+\gamma)I_{21}(t) + \alpha\phi R_2(t)(I_1(t) + I_{21}(t)).
\end{aligned}
\tag{5}
$$

The system is well posed having solutions in the Banach space $\Omega_X$ as defined in [37]. Thus, the trivial equilibrium $D_0 = (1,0,0,0,0,0,0,0,0,0)$ is always in the invariant set $\Omega_X$.

Defining

$$
M := -\int_0^\infty P'(s)e^{-d(s)}ds, \tag{6}
$$

we look for the steady states of the system. Note that $0 < M < 1$.

After some algebraic computation, we are able to find the equilibrium of the system. The values at equilibrium for the susceptible population are the roots of the cubic polynomial $O(S) = Q(S)(bS + a)$, where

$$
\begin{aligned}
a &= -\alpha\phi(d+\gamma)^2\\
b &= \alpha\phi\beta(d + \gamma(1-M)),
\end{aligned}
$$

and $Q(S) = a_2S^2 + a_1S + a_0$, where

$$
\begin{aligned}
a_2 &= \beta[(d+\gamma)(\alpha\phi - 2\beta) + \gamma M\alpha\phi]\\
a_1 &= (d+\gamma)^2(2\beta - \alpha\phi) - \alpha\phi\beta(d + \gamma + \gamma M)\\
a_0 &= \alpha\phi(d+\gamma)^2.
\end{aligned}
$$

Since $S^* = \frac{-a}{b} = \frac{(d+\gamma)^2}{\beta(d+\gamma(1-M))}$ gives a negative value for $I_{12}^*$ and $I_{21}^*$, we look for the roots of the $Q(S)$ polynomial. While searching for the roots, note that it is necessary that $S^* > 0$, being root of $Q(S)$ polynomial, and $S^* < \frac{d+\gamma}{\beta}$, in order to have an equilibrium in the positive region. All these information give us the following theorem.

**Theorem 1.** *If $\mathcal{R}_0 = \frac{\beta}{d+\gamma} > 1$ the system of equations (5) always have two boundary equilibria in $\Omega_X$, namely,*

$$D_1 = \left(\frac{d+\gamma}{\beta}, \frac{d}{\beta}\left[\frac{\beta}{d+\gamma} - 1\right], 0, \frac{\gamma}{d}(1-M)I_1^*, 0, M\frac{\gamma}{\beta}\left[\frac{\beta}{d+\gamma} - 1\right], 0, 0, 0, 0\right),$$

$$D_2 = \left(\frac{d+\gamma}{\beta}, 0, \frac{d}{\beta}\left[\frac{\beta}{d+\gamma} - 1\right], 0, \frac{\gamma}{d}(1-M)I_2^*, 0, M\frac{\gamma}{\beta}\left[\frac{\beta}{d+\gamma} - 1\right], 0, 0, 0\right)$$

*and, a unique positive equilibrium, $D_3$, in $\Omega_X$, with coexistence of the two strains, where*

$$S^* = \frac{-a_1}{2a_2} - \frac{\sqrt{a_1^2 - 4a_0a_2}}{2a_2}, \tag{7}$$

*with $a_i$ being the coefficients of polynomial $Q(S)$ and, satisfies*

$$\begin{aligned}
I_1^* &= I_2^* = \frac{d(1-S^*)}{2(d+\gamma)},\\
C_1^* &= C_2^* = \frac{\gamma(1-M)}{d}I_1^*,\\
R_1^* &= R_2^* = \frac{d+\gamma-\beta S^*}{\alpha\phi},\\
I_{12}^* &= I_{21}^* = \frac{(d+\gamma)I_1^* - \beta S^* I_1^*}{\beta S^*},\\
R^* &= 1 - S^* - I_1^* - I_2^* - C_1^* - C_2^* - R_1^* - R_1^* - I_{12}^* - I_{21}^*.
\end{aligned} \tag{8}$$

PROOF. If $\frac{\beta}{d+\gamma} > 1$ then, it is easy to see that $D_i$ is in $\Omega$, for $i = 1, 2$. In addition, since the searched root $S^*$ needs to be smaller than $\frac{d+\gamma}{\beta}$, let $S_{max}$ be

$$S_{max} = \frac{d+\gamma}{\beta}.$$

Then, the quadratic polynomial evaluated in $S_{max}$ is

$$Q(S_{max}) = Q(\frac{d+\gamma}{\beta}) = (d+\gamma)\gamma M\alpha\phi\left(\frac{d+\gamma}{\beta} - 1\right) < 0,$$

because $\frac{\beta}{d+\gamma} > 1$.

Moreover, the independent term, $a_0$, of the polynomial $Q(S)$ is positive. This proves that we have a positive root satisfying $S^* < \frac{d+\gamma}{\beta}$, and it is given by

$$\begin{aligned}
S^* = {} & \frac{(d+\gamma)^2(-2\beta+\alpha\phi) + \alpha\phi\beta(d+\gamma+\gamma M)}{2\beta[(d+\gamma)(\alpha\phi-2\beta) + \gamma M\alpha\phi]}\\
& - \frac{\sqrt{((d+\gamma)^2(2\beta-\alpha\phi) + \alpha\phi\beta(d+\gamma+\gamma M))^2 - 8\alpha\phi\beta^2\gamma M(d+\gamma)^2}}{2\beta[(d+\gamma)(\alpha\phi-2\beta) + \gamma M\alpha\phi]}
\end{aligned} \tag{9}$$

Therefore, the equilibrium $D_3 = (S^*, I_1^*, I_2^*, C_1^*, C_2^*, R_1^*, R_2^*, I_{12}^*, I_{21}^*, R^*)$ is in $\Omega_X$, where $S^*$ is given by (9), and satisfies (8).

### 3.1. Stability of the equilibrium

In the previous subsection (3) we calculated the equilibria of the limiting system in order to know the equilibria of system with time delay. Following the results from Brauer et al. [44] and Steindorf et al. [37], here we show the results regarding the stability of the limiting system and, thus, the local stability of the system with delay.

The stability of the equilibria of the limiting system (5) is a consequence of stability of the zero solution of the linearised system. And, the asymptotic stability of the zero solution of the linear system $X'(t) = AX(t) + \int_0^\infty B(s)X(t-s)ds$ is equivalent to find no solutions in the right half plane $Re\lambda \geq 0$ of $det(\lambda I - A - \hat{B}(\lambda)) = 0$, where $I$ is the identity matrix, $A$ is a matrix and $\hat{B}(\lambda)$ denote the Laplace transform of $B$ [45, 46]. Therefore, with the results of stability, we have the necessary assumptions to use Theorem 2 in [44].

For the analysis of the stability of the equilibria on the symmetric case, we need to solve the characteristic equation,

$$det(\lambda I - H_0 - \hat{G}(\lambda)) = 0,$$

of the linear associated system.

Solving this equation, we find the following eigenvalues of the linear associated system at $D_0$,

$$\begin{aligned}
\lambda_1 &= -d, & \lambda_6 &= -(d+\gamma)\\
\lambda_2 &= -d, & \lambda_7 &= -(d+\gamma)\\
\lambda_3 &= -d, & \lambda_8 &= -(d+\gamma)+\beta\\
\lambda_4 &= -d, & \lambda_9 &= -(d+\gamma)+\beta\\
\lambda_5 &= -d.
\end{aligned} \tag{10}$$

In the same way, we have the characteristic equations

$$det(\lambda I - H_i - \hat{G}(\lambda)) = 0,$$

for $i = 1, 2$. Thus, the eigenvalues of the linear associated system at

$$D_1 = \left(\frac{d+\gamma}{\beta}, \frac{d}{\beta}(\mathcal{R}_0 - 1), 0, \frac{\gamma}{d}(1-M)I_1^*, 0, M\frac{\gamma}{\beta}(\mathcal{R}_0 - 1), 0, 0, 0\right), \tag{11}$$

and, at

$$D_2 = \left(\frac{d+\gamma}{\beta}, 0, \frac{d}{\beta}(\mathcal{R}_0 - 1), 0, \frac{\gamma}{d}(1-M)I_2^*, 0, M\frac{\gamma}{\beta}(\mathcal{R}_0 - 1), 0, 0\right), \tag{12}$$

are the same, and given by

$$\begin{aligned}
\lambda_1 &= -d\\
\lambda_2 &= -d\\
\lambda_3 &= -d\\
\lambda_4 &= -(d+\gamma)\\
\lambda_5 &= -(d+\gamma)\\
\lambda_6 &= -d\left(1 + \frac{\alpha\phi}{\beta}(\mathcal{R}_0 - 1)\right)\\
\lambda_7 &= \frac{1}{2}\left(-d\mathcal{R}_0 - \sqrt{(d\mathcal{R}_0)^2 - 4d(d+\gamma)(\mathcal{R}_0 - 1)}\right)\\
\lambda_8 &= \frac{1}{2}\left(-d\mathcal{R}_0 + \sqrt{(d\mathcal{R}_0)^2 - 4d(d+\gamma)(\mathcal{R}_0 - 1)}\right)\\
\lambda_9 &= \frac{\alpha\phi}{\beta}\gamma M(\mathcal{R}_0 - 1),
\end{aligned} \tag{13}$$

giving the following theorem about the stability of the equilibria.

**Theorem 2.** *If $\mathcal{R}_0 < 1$ then the Disease Free Equilibrium (DFE) of the system (5) is locally asymptotically stable. It is unstable if $\mathcal{R}_0 > 1$. In addition, the boundary equilibria, $D_1$ and $D_2$, given in (11) and (12) respectively, are always unstable in the $\Omega_X$ region, when $\mathcal{R}_0 > 1$.*

PROOF. If $\mathcal{R}_0 < 1$, then, $\beta < d + \gamma$. Therefore, the eigenvalues $\lambda_8$ and $\lambda_9$ in (10) are negative. It proves the local asymptotic stability of DFE. If $\mathcal{R}_0 > 1$, then $\beta > d + \gamma$. And, the eigenvalues $\lambda_8$ and $\lambda_9$ in (10) are positive, what proves the instability of the DFE.

According to the previous theorem, if $\mathcal{R}_0 > 1$, $D_1$ and $D_2$ are in the positive region $\Omega_X$, then, $\beta > d + \gamma$ and the eigenvalue $\lambda_6$, given in (13), is negative. Also, the eigenvalues $\lambda_7$ and $\lambda_8$ have a negative real part. On the other hand, $\lambda_9$ is positive, since $\mathcal{R}_0 > 1$. In this way, the boundary equilibrium are always unstable.

It is important to note that, when $\mathcal{R}_0 = 1$, we have $\dfrac{d+\gamma}{\beta} = 1$. Therefore, the only equilibrium of the system is the disease-free equilibrium in this case. Biologically speaking, these results mean that if disease invades a disease-free population, both strains will coexist.

#### *3.1.1. Stability of the solutions of the system with time delay*

In the previous section, we showed the equilibria of the unperturbed (limiting) system (5) and the stability of the equilibria. In addition, having all the assumptions needed to use Theorem 2 in [44], the following results hold.

**Corollary 1.** *If $\mathcal{R}_0 < 1$ then the disease-free equilibrium of the system (3) is locally asymptotically stable. And, it is unstable if $\mathcal{R}_0 > 1$. In addition, the boundary equilibria, $D_1$ and $D_2$, given in (11) and (12) respectively, are always unstable when $\mathcal{R}_0 > 1$.*

**Remark 1.** As seen for the asymmetric case studied by Steindorf et al. [37], one strain can protects the population from another strain when one of the strains would have higher transmission rate. As we just proved above, for symmetric case, either the disease dies out or both strains coexist.

**Remark 2.** The analysis of the local stability of the coexistence endemic equilibrium (CEE) using this theory was not successful, since we have to deal with a characteristic transcendental equation having an infinite number of roots. Thus, in the following section, we will study the stability of the CEE numerically and, using as well, the perturbation theory.

## 4. Numerical experiments

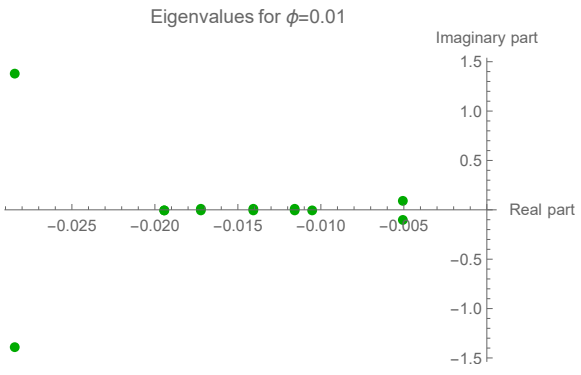
Although it was possible to describe analytically the equilibrium with coexistence of two strains, the expression for the value of $S^*$ shows a complexity of dependency of the parameters. In this section, we will perform numerical experiments to analyse the sign of the eigenvalues of the characteristic equation at the endemic equilibrium, exploring the effect of different values of the parameter $\phi$ used as a bifurcation parameter. The parameters values used for the numerical computation are listed in Table 1 from [37] (see also in Appendix B for convenience), as well as, the function that represent the general immunity period is also chosen as proposed in [37].

In Figure 1, we show the eigenvalues of the endemic equilibrium in the complex plane for different $\phi$ values. A pair of conjugated complex eigenvalues change the sign of the real part as $\phi$ increases. Therefore, a Hopf bifurcation occurs when the parameters $\phi$ is $\approx 0.032$.

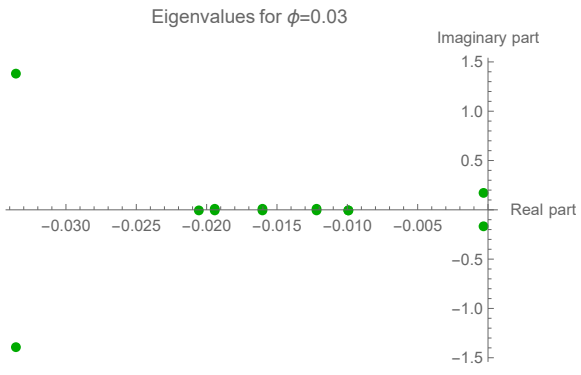
To complete the analysis, Figure 2 shows the maximum of the real part of eigenvalues varying all the values of the parameter $\phi$. It is also possible to observe that as $\phi$ approaches the value 0.032, the biggest real part of the eigenvalues crosses the x-axis, remaining positive, verifying the occurrence of Hopf bifurcation. Therefore, coexistence equilibria is stable for $\phi < 0.032$, periodic solutions are found close to this critical value, and after the Hopf bifurcation, the endemic equilibrium is unstable.

### 4.1. Bifurcation structure

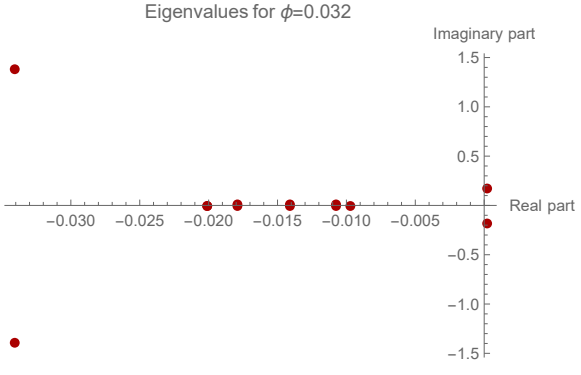
We have shown numerically that the coexistence endemic equilibrium changes the stability as the parameter $\phi$ changes. In detail, as $\phi$ increases from small values to the critical value $\phi_c$, the steady state changes from a stable focus to an unstable focus. Figure 3 (a) and (b) shows the bifurcation diagrams for the total infected population, with $\phi$ as the bifurcation parameter. We can observe a a Hopf bifurcation occurring at $\phi_c = 0.032$ (see Fig. 3 (b)). The solution



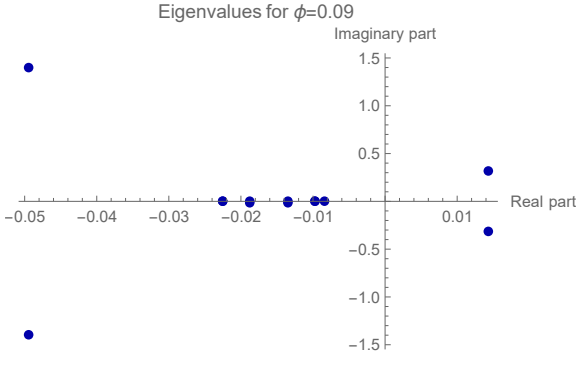

(a) $\phi = 0.01$



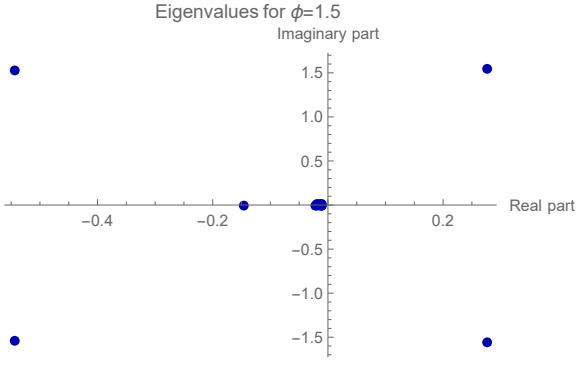

(b) $\phi = 0.03$



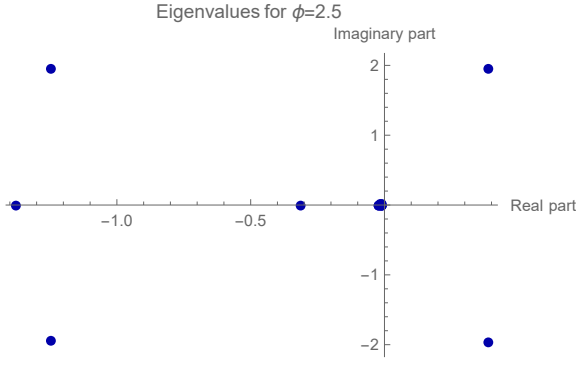

(c) $\phi = 0.032$




(d) $\phi = 0.09$




(e) $\phi = 1.5$




(f) $\phi = 2.5$

**Figure 1:** Eigenvalues of the endemic equilibrium (symmetric case) in the complex plane, for various values of $\phi$. For $\beta = 180$, a purely imaginary eigenvalue appears for $\phi \approx 0.032$. Parameter values used in the simulations are listed in Table 1 from [37] (also in Appendix B for convenience).

exhibits a small amplitude limit cycle around the endemic equilibrium and a stable limit cycle arises and goes away from the equilibrium point. Thus, it is possible to conclude that a supercritical Hopf bifurcation occurred.

Different bifurcation structures are identified as $\phi$ increases (see Fig. 3 (a)). Coexistence of strains is only possible for $\phi \in (0, 0.032)$, while periodic outbreaks appear for medium and high values of $\phi$ ($\phi \in (0.032, 0.4)$ and $\phi > 1.2$). Complex dynamics with short term predictability and long term predictability is restricted to $\phi \in (0.4, 1.2)$, where complicated attractors up to chaotic behaviour are observed.

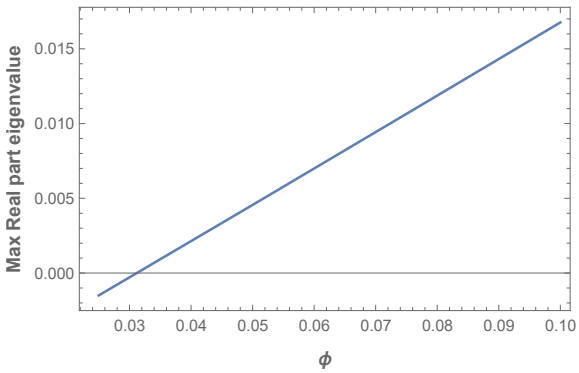
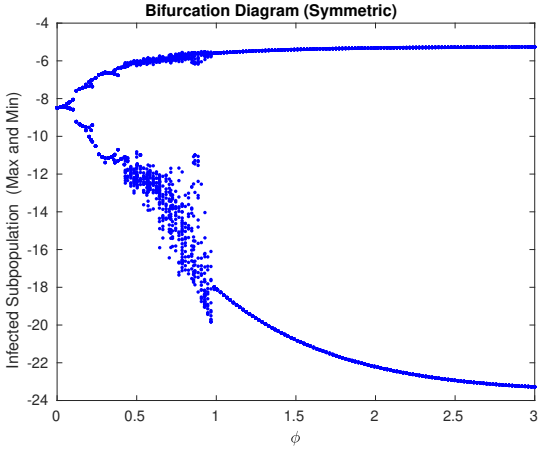
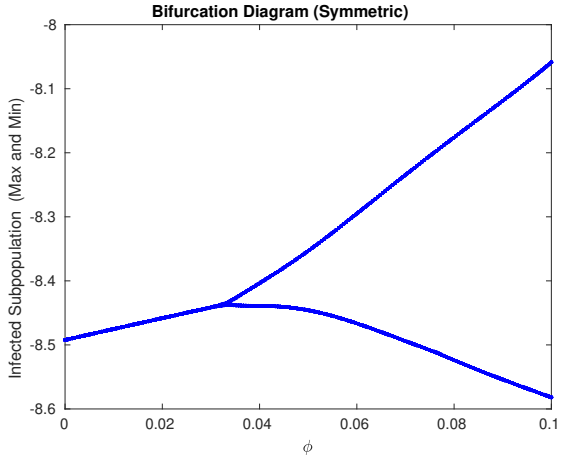



**Figure 2:** Maximum value of the real part of the eigenvalues of the endemic equilibrium for values of $\phi$ close to the Hopf Bifurcation ($\phi = 0.032$).




(a) $\phi \in (0, 3)$




(b) $\phi \in (0, 0.1)$

**Figure 3:** Bifurcation diagram where in (a) the bifurcation parameter $\phi$ varies between 0 and 3 and in (b) $\phi$ varies in the vicinity of $\phi_c = 0.032$. The vertical axis shows the maximum and minimum values for the the total infected population $log(I_1 + I_2 + I_{12} + I_{21})$ in logarithmic scale.

## 5. Stability analysis of the endemic equilibrium

Using perturbation theory, we perform the stability analysis of the symmetric system, where the endemic equilibrium and its eigenvalues can be directly calculated. We use the method proposed by Domoshnitsky el al. [50], that reduces a class of IDE to the corresponding ODE system as follows. If the elements of the kernel function in the integral are constant matrices or have the form

$$(t-s)^k e^{-A(t-s)} sin(B(t-s)), \tag{14}$$

where $k$ is an integer non-negative number, and $A$, $B$ real numbers, then a new corresponding autonomous ODE system can be written. The generalization of this method is proved in [50] where the authors use Cauchy functions and using kernel functions for the construction of the Cauchy matrix of an auxiliary ODE system.

Aiming at proving analytically that the endemic equilibrium is unstable after the bifurcation critical value $\phi_c$, we select for the kernel function $P(s)$, functions of the form (14) and we demonstrate for two particular cases.

### 5.1. Case (i): $P(s) = cos(As)e^{-\omega s}$, $A > 0$

With the function $P(s) = cos(As)e^{-\omega s}$ satisfying the necessary assumptions of the model, i.e., with $P(0) = 1$, $P(\infty) = 0$ and $\int_0^\infty e^{-ds}P(s)ds < \infty$, then,

$$C_i(t) = \int_0^t \gamma I_i(s) cos(A(t-s)) e^{-(\omega+d)(t-s)} ds,$$

and,

$$C_i'(t) = \gamma I_i(t) - (d+\omega)C_i(t) - A\int_0^t \gamma I_i(s) sen(A(t-s)) e^{-(\omega+d)(t-s)} ds. \tag{15}$$

Defining

$$E_i(t) = \int_0^t \gamma I_i(s) sen(A(t-s)) e^{-(\omega+d)(t-s)} ds,$$

then,

$$E_i'(t) = -(\omega+d)E_i(t) + AC_i(t). \tag{16}$$

Therefore, using the method in [50] the IDE system (4) can be reduced to the corresponding ODE system, as shown in the system of equations (17).

$$\begin{aligned}
S'(t) &= d - dS - \beta S(I_1 + I_2 + I_{12} + I_{21}) \\
{I_1}'(t) &= -(d+\gamma)I_1 + \beta S(I_1 + I_{21}) \\
{I_2}'(t) &= -(d+\gamma)I_2 + \beta S(I_2 + I_{12}) \\
{C_1}'(t) &= -(d+\omega)C_1 + \gamma I_1 - AE_1 \\
{C_2}'(t) &= -(d+\omega)C_2 + \gamma I_2 - AE_2 \\
{E_1}'(t) &= -(\omega+d)E_1 + AC_1 \\
{E_2}'(t) &= -(\omega+d)E_2 + AC_2 \\
{R_1}'(t) &= -dR_1 - \alpha\phi R_1(I_2 + I_{12}) + \omega C_1 + AE_1 \\
{R_2}'(t) &= -dR_2 - \alpha\phi R_2(I_1 + I_{21}) + \omega C_2 + AE_2 \\
{I_{12}}'(t) &= -(d+\gamma)I_{12} + \alpha\phi R_1(I_2 + I_{12}) \\
{I_{21}}'(t) &= -(d+\gamma)I_{21} + \alpha\phi R_2(I_1 + I_{21}).
\end{aligned} \tag{17}$$

### *5.1.1. Symmetric manifold - Symmetry in the variables*

Since the parameters are symmetric, the dynamic of the model will be also symmetric for symmetric initial conditions. Thus the variables that represent the sub-populations will be equal for the respective class for different serotypes. Using the symmetry among the serotypes, we reduce the whole system defining new variables as follow.

$$\begin{aligned} s &= S \\ x &= I_1 = I_2 \\ c &= C_1 = C_2 \\ e &= E_1 = E_2 \\ r &= R_1 = R_2 \\ y &= I_{12} = I_{21}. \end{aligned} \tag{18}$$

Thus, the endemic equilibrium of the system will be the same equilibrium of the following associated reduced model

$$\begin{aligned} s'(t) &= d - ds - \beta s 2(x+y) \\ x'(t) &= -(d+\gamma)x + \beta s(x+y) \\ c'(t) &= -(d+\omega)c + \gamma x - Ae \\ e'(t) &= -(d+\omega)e + Ac \\ r'(t) &= -\alpha\phi r(x+y) + \omega c - dr + Ae \\ y'(t) &= -(d+\gamma)y + \alpha\phi r(x+y). \end{aligned} \tag{19}$$

There is still a complexity of the direct calculation of the endemic equilibrium and its eigenvalues due to the parameter dependency. Hence, we will use perturbation theory as an attempt to deal with this complexity as proposed by Billings et al. [41].

It is important to note that the mortality rate $d$ is small compared to the other parameters. Thus, we introduce another small parameter $\mu$, with $\mu$ being slightly larger than $d$, but still small enough to keep the other parameters of the system in order of $\frac{1}{\mu}$. However, $d$ is of $\mathcal{O}(\mu)$.

Upon defining the birth rate $\mu$ and the mortality rate $d$, the other parameters are re-scaled in relation to $\mu$, letting $\beta = \frac{\beta_0}{\mu}$, $\alpha = \frac{\alpha_0}{\mu}$, $\omega = \frac{\omega_0}{\mu}$, $\gamma = \frac{\gamma_0}{\mu}$, and hence, close enough to the original system (19). By setting the mortality parameter $d = 0$ (since $d$ is of $\mathcal{O}(\mu)$, having a negligible effect on the steady state) the model can be simplified, see equation system (20), and the endemic equilibrium can be calculated analytically (in terms of the parameters) and the stability analysis can be carried out.

$$\begin{aligned} s' &= \mu - \beta s 2(x+y) \\ x' &= -\gamma x + \beta s(x+y) \\ c' &= \gamma x - \omega c - Ae \\ e' &= -\omega e + Ac \\ r' &= -\alpha\phi r(x+y) + \omega c + Ae \\ y' &= -\gamma y + \alpha\phi r(x+y). \end{aligned} \tag{20}$$

The qualitative analysis of this model is an interesting approach to our original system, but it is only valid for small values of the mortality and birth rate birth rate. With this constraint, considering, $x \neq 0$ and $y \neq 0$, the endemic equilibrium of the system (20) is given by

$$E_S = \left(\frac{\gamma_0}{2\beta_0}, \frac{\mu^2}{2\gamma_0}, \frac{\mu^2\omega_0}{2(\omega_0^2 + A^2\mu^2)}, \frac{\gamma_0}{2\alpha_0\phi}, \frac{\mu^2}{2\gamma_0}\right). \tag{21}$$

The stability analysis of the endemic equilibrium is performed with the linearisation theory. The Jacobian matrix of the reduced associated system (20) at the steady state $E_S$ is given by

$$J(E_S) = \begin{bmatrix} -\frac{2\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{\mu} & 0 & 0 & 0 & -\frac{\gamma_0}{\mu} \\ \frac{\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & 0 & 0 & 0 & \frac{\gamma_0}{2\mu} \\ 0 & \frac{\gamma_0}{\mu} & -\frac{\omega_0}{\mu} & -A & 0 & 0 \\ 0 & 0 & A & -\frac{\omega_0}{\mu} & 0 & 0 \\ 0 & -\frac{\gamma_0}{2\mu} & \frac{\omega_0}{\mu} & A & -\frac{\alpha_0\phi\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} \\ 0 & \frac{\gamma_0}{2\mu} & 0 & 0 & \frac{\alpha_0\phi\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} \end{bmatrix} \tag{22}$$

with the characteristic polynomial $m(\lambda) = m_0 + m_1\lambda + m_2\lambda^2 + m_3\lambda^3 + m_4\lambda^4 + m_5\lambda^5 + m_6\lambda^6$ with the coefficients given by

$$\begin{aligned}
m_0 &= \frac{2\alpha_0\phi\beta_0(\omega_0^2 + A^2\mu^2)}{\mu^2} \\
m_1 &= \frac{4A^2\alpha_0\phi\beta_0\mu}{\gamma_0} + \frac{\beta_0\gamma\omega_0^2}{\mu^3} + \frac{\beta_0(A^2\gamma_0^2 + 4\alpha_0\phi\omega_0(\gamma_0 + \omega_0))}{\gamma_0\mu} \\
m_2 &= \frac{2A^2\alpha_0\phi\beta_0\mu^2}{\gamma_0^2} + \frac{\gamma_0^2\omega_0\alpha\phi(\gamma_0 + 3\omega_0) + 2\beta_0\omega_0\gamma_0^2(2\gamma_0 + 3\omega_0)}{2\gamma_0^2\mu^2} \\
&\quad + \frac{6A^2\beta_0\gamma_0^2 + 3A^2\alpha_0\phi\gamma_0^2 + 4\alpha_0\phi\beta_0(\gamma_0^2 + 4\gamma_0\omega_0 + \omega_0^2)}{2\gamma_0^2} \\
m_3 &= \frac{\gamma_0\omega_0^2}{\mu^3} + \frac{\mu(8\alpha_0\phi\beta_0\gamma_0 + 2A^2\gamma_0(2\beta_0 + \alpha_0\phi) + 8\alpha_0\phi\beta_0\omega_0)}{2\gamma_0^2} \\
&\quad + \frac{2A^2\gamma_0^3 + 2\beta_0\gamma_0^3 + 12\beta_0\gamma_0^2\omega_0 + 4\beta_0\gamma_0\omega_0^2 + \alpha_0\phi\gamma_0(\gamma_0^2 + 6\gamma_0\omega_0 + 2\omega_0^2)}{2\gamma_0^2\mu} \\
m_4 &= \frac{2\alpha_0\beta_0}{\gamma_0^2} + \frac{\omega_0(2\gamma_0 + \omega_0)}{\mu^2} + \frac{2A^2\gamma_0^2 + 6\beta_0\gamma_0^2 + 8\beta_0\gamma_0\omega_0 + \alpha_0\phi\gamma_0(3\gamma_0 + 4\omega_0)}{2\gamma_0^2} \\
m_5 &= \frac{2\gamma_0^3\mu^2 + 4\beta_0\gamma_0\mu^4 + 2\alpha_0\phi\gamma_0\mu^4 + 4\gamma^2\omega_0\mu^2}{2\gamma_0^2\mu^3} \\
m_6 &= 1.
\end{aligned}$$

Since the coefficients of the polynomial are of order $\mathcal{O}(1/\mu^3)$ we redefine a polynomial $M(\lambda) = \mu^3 m(\lambda)$. Thus, we apply the regular perturbation theory, assuming that the solutions of the polynomial $M(\lambda)$ are of the form $\lambda = z_0 + z_1\mu + z_2\mu^2 + \mathcal{O}(\mu^3)$.

Substituting the solutions $\lambda$ in the polynomial $M(\lambda) = \mu^3 m(\lambda)$ and equalising the terms of the same order, we have

$$\begin{aligned}
z_0 &= 0 \\
z_1 &= -2\frac{\alpha_0\phi}{\gamma_0} \\
z_2 &= 0
\end{aligned} \tag{23}$$

and,

$$\begin{aligned}
z_0^2 &= -\beta_0 \\
z_1 &= -\frac{1}{4\gamma_0\omega_0}[\alpha_0\phi(\gamma_0 - \omega_0) + 4\beta_0\omega_0]
\end{aligned} \tag{24}$$

$$z_2 = \pm v_0\sqrt{\beta_0}i,$$

where $v_0 = \frac{1}{32\beta\gamma^2\omega^2}[16A^2\beta(\gamma-1)\gamma^2 - 16\beta^2\omega^2 - (\alpha\phi)^2(\gamma^2+14\gamma\omega-15\omega^2) + 8\beta\alpha\phi(\gamma^2-\omega^2))]$.

Thus, the $\mathcal{O}(\mu^3)$ approximation of the eigenvalues gives

$$\lambda_1 = -2\frac{\alpha_0\phi}{\gamma_0}\mu < 0 \tag{25}$$

and,

$$\lambda_{2,3} = -\frac{1}{4\gamma_0\omega_0}[\alpha_0\phi(\gamma_0-\omega_0) + 4\beta_0\omega_0]\mu \pm (1+v_0\mu^2)\sqrt{\beta_0}i \tag{26}$$

with the negative real part for $\omega \leq \gamma$ (using biological assumption).

The magnitude of the other eigenvalues can be determined by analysing the coefficients of the characteristic polynomial. Performing this analysis, it is possible to verify that the other solutions of the polynomial $m(\lambda)$ are of the order $\mathcal{O}(\frac{1}{\mu})$. Dividing $m(\lambda)$ by the roots found $\lambda_{1,2,3}$ (see equations 25 and 26), we find that the real root $\lambda_4$ has the form

$$-\frac{1}{3\mu}(\gamma+2\omega) + \frac{\alpha\phi}{3}(\gamma+\omega)\mu + \mathcal{O}(u) \tag{27}$$

while, the real part of the complex roots has the form

$$\frac{-1}{3\mu}(\gamma+2\omega) + \frac{\alpha\phi}{3}(\gamma+\omega)\mu + \frac{\sqrt[3]{2}\mu}{2\gamma} + \mathcal{O}(u^2). \tag{28}$$

Thus, the real part of the eigenvalue is negative since the term of order $\mathcal{O}(\frac{1}{\mu})$ is negative.

While the assumption of symmetry of the parameters and variables lead to a significant system reduction, the bifurcation structure can not be seen in the symmetric manifold as shown numerically for the initial system. For that, the whole symmetric system must be considered, without the assumption of symmetric variables, since the symmetry among the variables does not reflect the stability of the whole system. In fact, it is the assumption of symmetric variables rather than the perturbation in the mortality term that leads the stable dynamic to appear in the system. This statement is proved with numerical experiments for the symmetric system (19), without the perturbation in the mortality term, where the eigenvalues of Jacobian matrix at the endemic equilibrium of the system have always negative real part, independent of the value of the parameter $\phi$, see Figures 4a to 4f in the A.

#### *5.1.2. Symmetric system - Symmetry only in the parameters*

By using perturbation theory in the system (17), the new variables are defined as

$$\begin{aligned} s &= S \\ x_i &= I_i \\ c_i &= C_i \\ e_i &= E_i \\ r_i &= R_i \\ y_1 &= I_{21} \\ y_2 &= I_{12}, \end{aligned} \tag{29}$$

with the endemic equilibrium of initial system being the same as the equilibrium of the associated system

$$
\begin{aligned}
s'(t) &= d - ds - \beta s(x_1 + x_2 + y_1 + y_2)\\
x_1'(t) &= -(d+\gamma)x_1 + \beta s(x_1 + y_1)\\
x_2'(t) &= -(d+\gamma)x_2 + \beta s(x_2 + y_2)\\
c_1'(t) &= -(d+\omega)c_1 + \gamma x_1 - Ae_1\\
c_2'(t) &= -(d+\omega)c_2 + \gamma x_2 - Ae_2\\
e_1'(t) &= -(d+\omega)e_1 + Ac_1\\
e_2'(t) &= -(d+\omega)e_2 + Ac_2\\
r_1'(t) &= -\alpha\phi r_1(x_2 + y_2) + \omega c_1 - dr_1 + Ae_1\\
r_2'(t) &= -\alpha\phi r_2(x_1 + y_1) + \omega c_2 - dr_2 + Ae_2\\
y_1'(t) &= -(d+\gamma)y_1 + \alpha\phi r_2(x_1 + y_1)\\
y_2'(t) &= -(d+\gamma)y_2 + \alpha\phi r_1(x_2 + y_2).
\end{aligned}
\tag{30}
$$

Using the same re-scaling approach described above, we introduce the small parameter $\mu$, with $d$ of $\mathcal{O}(\mu)$ and, the other parameters of the system re-scaled in order of $\frac{1}{\mu}$, letting $\beta = \frac{\beta_0}{\mu}$, $\alpha = \frac{\alpha_0}{\mu}$, $\omega = \frac{\omega_0}{\mu}$, $\gamma = \frac{\gamma_0}{\mu}$. We are again close enough to our original system at the steady state point, with the mortality parameter $d = 0$ (since $d$ is of $\mathcal{O}(\mu)$), simplifying the model near to the equilibrium. The resulting local dynamics can be described by the following system

$$
\begin{aligned}
s'(t) &= \mu - \beta s(x_1 + x_2 + y_1 + y_2)\\
x_1'(t) &= -\gamma x_1 + \beta s(x_1 + y_1)\\
x_2'(t) &= -\gamma x_2 + \beta s(x_2 + y_2)\\
c_1'(t) &= -\omega c_1 + \gamma x_1 - Ae_1\\
c_2'(t) &= -\omega c_2 + \gamma x_2 - Ae_2\\
e_1'(t) &= -\omega_1 e_1 + Ac_1\\
e_2'(t) &= -\omega_2 e_2 + Ac_2\\
r_1'(t) &= -\alpha\phi r_1(x_2 + y_2) + \omega c_1 + Ae_1\\
r_2'(t) &= -\alpha\phi r_2(x_1 + y_1) + \omega c_2 + Ae_2\\
y_1'(t) &= -\gamma y_1 + \alpha\phi r_2(x_1 + y_1)\\
y_2'(t) &= -\gamma y_2 + \alpha\phi r_1(x_2 + y_2).
\end{aligned}
\tag{31}
$$

Again, while the qualitatively analysis of this model is an interesting approximation of our original system, it is only valid for small values of the mortality rate and different values of the birth rate, suggesting an attempt to the approximation of the value of the endemic equilibrium, not including the mortality in the long time dynamic and, a possible estimation analysis of the Hopf bifurcation structure for values of $\phi$.

The endemic equilibrium of the system (31), considering, $x_i \neq 0$ and $y_i \neq 0$, is given by

$$
E_A = \left(\frac{\gamma_0}{2\beta_0}, \frac{\mu^2}{2\gamma_0}, \frac{\mu^2}{2\gamma_0}, \frac{\omega_0\mu^2}{2(\omega_0^2 + A^2\mu^2)}, \frac{\omega_0\mu^2}{2(\omega_0^2 + A^2\mu^2)}, \frac{\gamma_0}{2\alpha_0\phi}, \frac{\gamma_0}{2\alpha_0\phi}, \frac{\mu^2}{2\gamma_0}, \frac{\mu^2}{2\gamma_0}\right).
\tag{32}
$$

The stability of the endemic equilibrium is analysed with the linearisation theory, and the Jacobian matrix of the reduced associated system (31) at the steady state $E_A$ is given by

$$J(E_A) = \begin{bmatrix} -\frac{2\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & -\frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{\gamma_0}{2\mu} & -\frac{\gamma_0}{2\mu} \\ \frac{\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\gamma_0}{2\mu} & 0 \\ \frac{\beta_0\mu}{\gamma_0} & 0 & -\frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\gamma_0}{2\mu} \\ 0 & \frac{\gamma_0}{\mu} & 0 & -\frac{\omega_0}{\mu} & 0 & -A & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\gamma_0}{\mu} & 0 & -\frac{\omega_0}{\mu} & 0 & -A & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & A & 0 & -\frac{\omega_0}{\mu} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & A & 0 & -\frac{\omega_0}{\mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & -\frac{\gamma_0}{2\mu} & \frac{\omega_0}{\mu} & 0 & A & 0 & -\frac{\alpha_0\phi\mu}{\gamma_0} & 0 & 0 & -\frac{\gamma_0}{2\mu} \\ 0 & -\frac{\gamma_0}{2\mu} & 0 & 0 & \frac{\omega_0}{\mu} & 0 & A & 0 & -\frac{\alpha_0\phi\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & 0 \\ 0 & \frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\alpha_0\phi\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & 0 \\ 0 & 0 & \frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & \frac{\alpha_0\phi\mu}{\gamma_0} & 0 & 0 & -\frac{\gamma_0}{2\mu} \end{bmatrix}. \tag{33}$$

The characteristic polynomial $n(\lambda)$ is of order 11, which is very difficult to find all the roots. On the other hand, the characteristic polynomial $m(\lambda)$ of the reduced model obtained through the assumption of symmetric variables is a particular case of the model (31). Since in the reduced model there is no bifurcation structure, we will only consider the quotient polynomial $\frac{m(\lambda)}{n(\lambda)} = r(\lambda)$. Hence, if a bifurcation structure exists, thus, it can be only found in the quotient polynomial $r(\lambda) = r_0 + r_1\lambda + r_2\lambda^2 + r_3\lambda^3 + r_4\lambda^4 + r_5\lambda^5$, where

$$\begin{aligned} r_0 &= -\alpha_0\phi\gamma_0\left(\frac{\omega_0^2}{\mu^3} + \frac{A^2}{\mu}\right) \\ r_1 &= -\frac{3\alpha_0\phi\omega(\gamma_0+\omega_0)}{2\mu^2} - \frac{3\alpha\phi A^2}{2} \\ r_2 &= -\alpha_0\phi A^2\frac{\mu}{\gamma_0} - \frac{\gamma_0\omega_0^2}{\mu^3} - \frac{A^2\gamma_0 + 3\alpha_0\phi\omega_0}{\mu} - \frac{\alpha_0\phi(\gamma_0^2+2\omega_0^2)}{2\gamma_0\mu} \\ r_3 &= -A^2 - \frac{3\alpha_0\phi}{2} - \frac{2\alpha_0\phi\omega_0}{\gamma_0} - \frac{2\gamma_0\omega_0+\omega_0^2}{\mu^2} \\ r_4 &= -\frac{\alpha_0\phi\mu}{\gamma_0} - \frac{\gamma_0+2\omega_0}{\mu} \\ r_5 &= -1\,. \end{aligned}$$

With the coefficients of the polynomial being of order $\mathcal{O}(1/\mu^3)$, we redefine the polynomial $R(\lambda) = \mu^3 r(\lambda)$, and apply the regular perturbation theory, assuming that the solutions of the polynomial $R(\lambda)$ are of the form $\lambda = z_0 + z_1\mu + z_2\mu^2 + \mathcal{O}(\mu^3)$.

Substituting the solutions $\lambda$ in the polynomial $R(\lambda) = \mu^3 r(\lambda)$ and equalising the terms of the same order, we have

$$\begin{aligned} z_0^2 &= -\alpha_0\phi \\ z_1 &= \frac{\alpha_0\phi}{4\gamma_0\omega_0}[\gamma_0 - \omega_0] \\ z_2 &= \pm v_1\sqrt{\alpha_0\phi}i\,. \end{aligned} \tag{34}$$

where $v_1 = \alpha_0\phi\left(\frac{1}{4\omega_0^2} + \frac{1}{\gamma_0^2} + \frac{1}{4\gamma_0\omega_0}\right)$,

Thus, the approximation of the $\mathcal{O}(\mu^3)$ of the eigenvalues are given by

$$\lambda_{1,2} = \left(\frac{\alpha_0\phi}{4\gamma_0\omega_0}[\gamma_0 - \omega_0]\right)\mu \pm (1 + v_1\mu^2)\sqrt{\alpha_0\phi}i\,, \tag{35}$$

with the positive real part, because $\omega \leq \gamma$. Therefore, we showed that the endemic equilibrium is always unstable. That also can be numerically verified for all values of $\phi > 0$, with the eigenvalues of the whole system being always

negative, except for a pair of complex eigenvalues, which have positive real part, showing unstable dynamic near the endemic equilibrium.

Note that while the perturbation analysis allowed us to have an analytically result, it was not possible to show the bifurcation structure obtained numerically for the initial system. We could, however, prove analytically the instability of the endemic equilibrium, with the bifurcation only occurring outside of the symmetric manifold, while a small perturbation on the mortality term shows an unstable steady s, and, thus, complex dynamics for the system.

## 5.2. Case (ii): $P(t) = e^{-\omega t}$

Of course this function satisfies the necessary assumptions of the model, such as, $P(0) = 1$, $P(\infty) = 0$ and $\int_0^\infty e^{-ds} P(s)ds < \infty$. Now, the ODE can be rewritten as

$$\begin{aligned}
S'(t) &= d - dS - \beta S(I_1 + I_2 + I_{12} + I_{21}) \\
{I_1}'(t) &= -(d+\gamma)I_1 + \beta S(I_1 + I_{21}) \\
{I_2}'(t) &= -(d+\gamma)I_2 + \beta S(I_2 + I_{12}) \\
{C_1}'(t) &= -(d+\omega)C_1 + \gamma I_1 \\
{C_2}'(t) &= -(d+\omega)C_2 + \gamma I_2 \\
{R_1}'(t) &= -dR_1 - \alpha\phi R_1(I_2 + I_{12}) + \omega C_1 \\
{R_2}'(t) &= -dR_2 - \alpha\phi R_2(I_1 + I_{21}) + \omega C_2 \\
{I_{12}}'(t) &= -(d+\gamma)I_{12} + \alpha\phi R_1(I_2 + I_{12}) \\
{I_{21}}'(t) &= -(d+\gamma)I_{21} + \alpha\phi R_2(I_1 + I_{21}).
\end{aligned} \tag{36}$$

### *5.2.1. Symmetric manifold - Symmetry in the variables*

Using the proposed approach in [41] and symmetry between the serotypes, we reduce the whole system by defining the new variables as

$$\begin{aligned}
s &= S = S \\
x &= I_1 = I_2 \\
c &= C_1 = C_2 \\
r &= R_1 = R_2 \\
y &= I_{12} = I_{21}.
\end{aligned} \tag{37}$$

Thus, the endemic equilibrium for the system will be the same equilibrium of the following associated reduced model

$$\begin{aligned}
s'(t) &= d - ds - \beta s2(x + y) \\
x'(t) &= -(d+\gamma)x + \beta s(x + y) \\
c'(t) &= -(d+\omega)c + \gamma x \\
r'(t) &= -\alpha\phi r(x + y) + \omega c - dr \\
y'(t) &= -(d+\gamma)y + \alpha\phi r(x + y).
\end{aligned} \tag{38}$$

We re-scale the parameters in relation to $\mu$, letting $\beta = \frac{\beta_0}{\mu}$, $\alpha = \frac{\alpha_0}{\mu}$, $\omega = \frac{\omega_0}{\mu}$, $\gamma = \frac{\gamma_0}{\mu}$, and in the sequence, we set the birth rate $\mu$ and the mortality rate $d$. Again, the assumption of $d = 0$ (because $d$ is of $\mathcal{O}(\mu)$) simplifies the model near the equilibrium point. Then, the resulting local dynamics can be reduced to the following associated system

$$\begin{aligned}
s' &= \mu - \beta s2(x + y) \\
x' &= -\gamma x + \beta s(x + y) \\
c' &= \gamma x - \omega c \\
r' &= -\alpha\phi r(x + y) + \omega c
\end{aligned} \tag{39}$$

$$y' = -\gamma y + \alpha\phi r(x+y).$$

The endemic equilibrium of the system (39), considering, $x \neq 0$ and $y \neq 0$, is giving by

$$E_S = (\frac{\gamma_0}{2\beta_0}, \frac{\mu^2}{2\gamma_0}, \frac{\mu^2}{2\omega_0}, \frac{\gamma_0}{2\alpha_0\phi}, \frac{\mu^2}{2\gamma_0}). \tag{40}$$

Using the linearisation theory to analyse the stability of the endemic equilibrium, the Jacobian matrix of the reduced associated system (39) at the steady state $E_S$ is given by

$$J(E_S) = \begin{bmatrix} -\frac{2\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{\mu} & 0 & 0 & -\frac{\gamma_0}{\mu} \\ \frac{\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & 0 & 0 & \frac{\gamma_0}{2\mu} \\ 0 & \frac{\gamma_0}{\mu} & -\frac{\omega_0}{\mu} & 0 & 0 \\ 0 & -\frac{\gamma_0}{2\mu} & \frac{\omega_0}{\mu} & -\frac{\alpha_0\phi\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} \\ 0 & \frac{\gamma_0}{2\mu} & 0 & \frac{\alpha_0\phi\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} \end{bmatrix} \tag{41}$$

.

And, the coefficients of the characteristic polynomial $m(\lambda) = m_0 + m_1\lambda + m_2\lambda^2 + m_3\lambda^3 + m_4\lambda^4 + m_5\lambda^5$ are given by

$$\begin{aligned}
m_0 &= -\frac{2\alpha_0\phi\beta_0\omega_0}{\mu} \\
m_1 &= -\frac{\beta_0\gamma_0^3\omega_0 + 2\alpha_0\phi\beta_0(\gamma_0^2 + 2\gamma_0\omega_0)\mu^2}{\gamma_0^2\mu^2} \\
m_2 &= -\frac{(2\beta_0 + \alpha_0\phi)\gamma_0^3\mu + 3(2\beta_0 + \alpha_0\phi)\gamma_0^2\omega\mu + 4\alpha_0\phi\beta_0(\omega_0 + 2\gamma_0)\mu^3}{2\gamma_0^2\mu^2} \\
m_3 &= -\frac{2\gamma_0^3\omega_0 + 4\alpha_0\phi\beta_0\mu^4 + (6\beta_0\gamma_0^2 + 4\beta_0\gamma_0\omega_0 + 3\alpha_0\phi\gamma_0^2 + 2\alpha_0\phi\gamma_0\omega_0)\mu^2}{2\gamma_0^2\mu^2} \\
m_4 &= -\frac{\gamma_0^2(\gamma_0 + \omega_0)\mu + (2\beta_0 + \alpha_0\phi)\gamma_0\mu^3}{\gamma_0^2\mu^2} \\
m_5 &= -1.
\end{aligned}$$

Since the coefficients of the polynomial are of order $\mathcal{O}(1/\mu^2)$, we redefine a polynomial $M(\lambda) = \mu^2 m(\lambda)$. Thus, we apply the regular perturbation theory, assuming that the solutions of the polynomial $M(\lambda)$ are of the form $\lambda = z_0 + z_1\mu + z_2\mu^2 + \mathcal{O}(\mu^3)$.

Substituting the solutions $\lambda$ in the polynomial $M(\lambda) = \mu^2 m(\lambda)$ and equalising the terms of the same order we have

$$\begin{aligned}
z_0 &= 0 \\
z_1 &= -2\frac{\alpha_0\phi}{\gamma_0} \\
z_2 &= 0
\end{aligned} \tag{42}$$

and,

$$\begin{aligned}
z_0^2 &= -\beta_0 \\
z_1 &= -\frac{1}{2\gamma_0\omega_0}[\beta_0\gamma_0\omega_0 + \alpha_0\phi(\gamma_0 - \omega_0)]
\end{aligned} \tag{43}$$

$$z_2 = \pm v_0\sqrt{\beta_0}i,$$

where $v_0 = z_1(2\beta_0(\gamma_0 - \omega_0) - \alpha_0\phi(3\omega_0 + \gamma_0)) - 3\gamma_0\omega_0 z_1^2 + \frac{\beta_0^2}{\gamma_0}(2\omega_0 + 2\gamma_0) - \frac{\beta_0\alpha_0\phi}{2\gamma_0}(\gamma_0 + 6\omega_0)$.

Thus, the approximation of the $\mathcal{O}(\mu^3)$ of the eigenvalues are

$$\lambda_1 = -2\frac{\alpha_0\phi}{\gamma_0}\mu < 0 \tag{44}$$

and,

$$\lambda_{2,3} = -\left(\frac{1}{2\gamma_0\omega_0}[\beta_0\gamma_0\omega_0 + \alpha_0\phi(\gamma_0 - \omega_0)]\right)\mu \pm (1 + v_0\mu^2)\sqrt{\beta_0}i \tag{45}$$

with the negative real part, since $\omega \leq \gamma$.

The other eigenvalues can be determined by verifying their magnitude, by analysing the coefficients of the characteristic polynomial. Performing this analysis, it is possible to verify that the other solutions of the polynomial $m(\lambda)$ are of the order $\mathcal{O}(\frac{1}{\mu})$ . By dividing $m(\lambda)$ by the roots found $\lambda_{1,2,3}$ (see equations 44 and 45), we see that the real part of the complex roots $\lambda_{4,5}$ is of the form

$$-\frac{(\gamma_0 + \omega_0)}{\mu} - \frac{2\beta_0\mu}{\gamma_0} + \frac{(\beta_0\omega_0 + \alpha_0\phi)\mu}{\omega_0}, \tag{46}$$

with the real part of the eigenvalue being negative, since the negative term is of order $\mathcal{O}(\frac{1}{\mu})$, the positive term is of the order $\mathcal{O}(\mu)$.

The symmetry of the parameters and variables lead to a reduced system from which it is not possible to find the bifurcation structure. We can, however, verify numerically that the eigenvalues of this reduced associated model are always negative, showing a stable dynamic near the endemic equilibrium, that does not necessarily occur as previously seen numerically. Therefore, we have to work with the whole system, without the assumption of symmetric variables (since the symmetry among the variables does not reflect the stability of the whole system), but only with symmetry in the parameters.

As mentioned above, it is the assumption of the symmetry in the variables and not the perturbation in the mortality term that makes the stable dynamic appear in the system. We can confirm this statement with numerical experiments of the stability of the system (38), with symmetry in the variables and without the perturbation of the mortality term. It is possible to see that the eigenvalues of Jacobian matrix at the endemic equilibrium of the system (38) have always negative real part, independent of the size of the parameter $\phi$, see Figures 5a to 5f in A.

#### *5.2.2. Symmetric system - Symmetry only in the parameters*

By using perturbation theory in the system (36), the new variables are defined as,

$$\begin{aligned} s &= S \\ x_i &= I_i \\ c_i &= C_i \\ r_i &= R_i \\ y_1 &= I_{21} \\ y_2 &= I_{12}. \end{aligned} \tag{47}$$

The endemic equilibrium in the initial system will be the same as of the following associated system

$$\begin{aligned} s'(t) &= d - ds - \beta s(x_1 + x_2 + y_1 + y_2) \\ x_1'(t) &= -(d + \gamma)x_1 + \beta s(x_1 + y_1) \end{aligned}$$

$$
\begin{aligned}
x_2'(t) &= -(d+\gamma)x_2 + \beta s(x_2+y_2)\\
c_1'(t) &= -(d+\omega)c_1 + \gamma x_1\\
c_2'(t) &= -(d+\omega)c_2 + \gamma x_2\\
r_1'(t) &= -\alpha\phi r_1(x_2+y_2) + \omega c_1 - d r_1\\
r_2'(t) &= -\alpha\phi r_2(x_1+y_2) + \omega c_2 - d r_2\\
y_1'(t) &= -(d+\gamma)y_1 + \alpha\phi r_2(x_1+y_1)\\
y_2'(t) &= -(d+\gamma)y_2 + \alpha\phi r_1(x_2+y_2).
\end{aligned}
\tag{48}
$$

We re-scale the parameters in relation to $\mu$, letting $\beta = \frac{\beta_0}{\mu}$, $\alpha = \frac{\alpha_0}{\mu}$, $\omega = \frac{\omega_0}{\mu}$, $\gamma = \frac{\gamma_0}{\mu}$, and in the sequence, we set the birth rate $\mu$ and, the mortality rate $d$. The constraint $d = 0$ (because $d$ is of $\mathcal{O}(\mu)$) simplifies the model near the equilibrium. Then, the resulting local dynamics can be described by the following system

$$
\begin{aligned}
s'(t) &= \mu - \beta s(x_1+x_2+y_1+y_2)\\
x_1'(t) &= -\gamma x_1 + \beta s(x_1+y_1)\\
x_2'(t) &= -\gamma x_2 + \beta s(x_2+y_2)\\
c_1'(t) &= -\omega c_1 + \gamma x_1\\
c_2'(t) &= -\omega c_2 + \gamma x_2\\
r_1'(t) &= -\alpha\phi r_1(x_2+y_2) + \omega c_1\\
r_2'(t) &= -\alpha\phi r_2(x_1+y_2) + \omega c_2\\
y_1'(t) &= -\gamma y_1 + \alpha\phi r_2(x_1+y_1)\\
y_2'(t) &= -\gamma y_2 + \alpha\phi r_1(x_2+y_2).
\end{aligned}
\tag{49}
$$

The endemic equilibrium of the system (49), considering, $x_i \neq 0$ and $y_i \neq 0$, is given by

$$
E_A = \left(\frac{\gamma_0}{2\beta_0}, \frac{\mu^2}{2\gamma_0}, \frac{\mu^2}{2\gamma_0}, \frac{\mu^2}{2\omega_0}, \frac{\mu^2}{2\omega_0}, \frac{\gamma_0}{2\alpha_0\phi}, \frac{\gamma_0}{2\alpha_0\phi}, \frac{\mu^2}{2\gamma_0}, \frac{\mu^2}{2\gamma_0}\right). \tag{50}
$$

And, the Jacobian matrix of the reduced associated system (49) at the steady state $E_A$ is given by

$$
J(E_A) = \begin{bmatrix}
-\frac{2\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & -\frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & -\frac{\gamma_0}{2\mu} & -\frac{\gamma_0}{2\mu}\\
\frac{\beta_0\mu}{\gamma_0} & -\frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\gamma_0}{2\mu}\\
\frac{\beta_0\mu}{\gamma_0} & 0 & -\frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & \frac{\gamma_0}{2\mu} & 0\\
0 & \frac{\gamma_0}{\mu} & 0 & -\frac{\omega_0}{\mu} & 0 & 0 & 0 & 0 & 0\\
0 & 0 & \frac{\gamma_0}{\mu} & 0 & -\frac{\omega_0}{\mu} & 0 & 0 & 0 & 0\\
0 & 0 & -\frac{\gamma_0}{2\mu} & \frac{\omega_0}{\mu} & 0 & -\frac{\alpha_0\phi\mu}{\gamma_0} & 0 & -\frac{\gamma_0}{2\mu} & 0\\
0 & -\frac{\gamma_0}{2\mu} & 0 & 0 & \frac{\omega_0}{\mu} & 0 & -\frac{\alpha_0\phi\mu}{\gamma_0} & 0 & -\frac{\gamma_0}{2\mu}\\
0 & 0 & \frac{\gamma_0}{2\mu} & 0 & 0 & \frac{\alpha_0\phi\mu}{\gamma_0} & 0 & -\frac{\gamma_0}{2\mu} & 0\\
0 & \frac{\gamma_0}{2\mu} & 0 & 0 & 0 & 0 & \frac{\alpha_0\phi\mu}{\gamma_0} & 0 & -\frac{\gamma_0}{2\mu}
\end{bmatrix},
\tag{51}
$$

with the characteristic polynomial $n(\lambda) = n_0 + n_1\lambda + n_2\lambda^2 + n_3\lambda^3 + n_4\lambda^4 + n_5\lambda^5 + n_6\lambda^6 + n_7\lambda^7 + n_8\lambda^8 + n_9\lambda^9$ and coefficients given by

$$
n_0 = -\frac{2\alpha_0^2\phi^2\beta_0\omega_0^2}{\mu^3}
$$

$$
\begin{aligned}
n_1 &= -\frac{\alpha_0\phi\beta_0\omega_0[\gamma_0^2\omega_0+\alpha_0\phi(3\gamma_0+7\omega_0)\mu^2]}{\mu^4}\\
n_2 &= -\frac{\alpha_0\phi\beta_0\gamma_0^2\omega_0(3\gamma_0+13\omega_0)}{2\gamma_0\mu^3} - \frac{\alpha_0^2\phi^2(\gamma_0^2\omega_0(\gamma_0+3\omega_0))}{2\gamma_0\mu^3} - \frac{\alpha_0^2\phi^2 2\beta_0(\gamma_0^2+12\gamma_0\omega_0+10\omega_0^2)\mu^2}{2\gamma_0\mu^3}\\
n_3 &= -\frac{4\beta_0\gamma_0^4\omega_0^2+4\alpha_0\phi\gamma_0^4\omega_0^2}{4\gamma_0^2\mu^4)} - \frac{20\alpha_0^2\phi^2\beta_0\gamma_0^2+76\alpha_0^2\phi^2\beta_0\gamma_0\omega_0+28\alpha_0^2\phi^2\beta_0\omega_0^2}{4\gamma_0^2}\\
&\quad - \frac{\alpha_0^2\gamma_0^4\phi^2+12\alpha_0^2\gamma_0^3\phi^2\omega_0+13\alpha_0^2\gamma_0^2\phi^2\omega_0^2+2\alpha_0\phi\beta_0\gamma_0^2(\gamma_0^2+23\gamma_0\omega_0+27\omega_0^2)}{4\gamma_0^2\mu^2}\\
n_4 &= -\frac{\mu(18\alpha_0^2\phi^2\beta_0\gamma_0^2+28\alpha_0^2\beta_0\gamma_0\phi^2\omega_0+4\alpha_0^2\beta_0\phi^2\omega_0^2)}{2\gamma^3}\\
&\quad - \frac{4\beta_0\gamma_0^4\omega_0(\gamma_0+2\omega_0)+4\alpha_0\gamma_0^4\phi\omega_0(\gamma_0+2\omega_0)}{2\gamma^3\mu^3}\\
&\quad - \frac{3\alpha_0^2\gamma_0^4\phi^2+13\alpha_0^2\gamma_0^3\phi^2\omega_0+6\alpha_0^2\gamma_0^2\phi^2\omega_0^2+2\alpha_0\beta_0\gamma_0^2\phi(5\gamma_0^2+26\gamma_0\omega_0+12\omega_0^2)}{2\gamma_0^3\mu}\\
n_5 &= -\frac{\gamma_0^2\omega_0^2}{\mu^4} - \frac{\mu^2(7\alpha_0^2\beta_0\gamma_0\phi^2+4\alpha_0^2\beta_0\phi^2\omega_0)}{\gamma_0^3}\\
&\quad - \frac{\beta_0\gamma^5+8\beta_0\gamma_0^4\omega_0+6\beta_0\gamma_0^3\omega_0^2+\alpha_0\gamma_0^3\phi(\gamma_0^2+8\gamma_0\omega_0+5\omega_0^2)}{\gamma_0^3\mu^2}\\
&\quad - \frac{50\alpha_0\beta_0\gamma_0^3\phi+96\alpha_0\beta\gamma_0^2\phi\omega_0+16\alpha_0\beta_0\gamma_0\phi\omega_0^2+\alpha_0^2\gamma_0\phi^2(13\gamma_0^2+24\gamma_0\omega_0+4\omega_0^2)}{4\gamma_0^3}\\
n_6 &= -\frac{2\alpha_0^2\phi^2\beta_0\mu^3}{\gamma_0^3} - \frac{2\gamma_0\omega_0(\gamma_0+\omega_0)}{\mu^3} - \frac{\mu(12\alpha_0\gamma_0^2\phi+8\alpha_0\phi\beta_0\gamma_0\omega_0+\alpha_0^2\phi^2\gamma_0(3\gamma_0+2\omega_0))}{\gamma_0^3}\\
&\quad - \frac{4\beta_0\gamma_0^4+10\beta_0\gamma_0^3\omega_0+2\beta_0\gamma_0^2\omega^2+2\alpha_0\gamma_0^2\phi(2\gamma_0^2+5\gamma_0\omega_0+\omega_0^2)}{\gamma_0^3\mu}\\
n_7 &= -\frac{\gamma_0^4+\alpha_0\phi(4\beta_0+\alpha_0\phi)\mu^4+4\gamma_0^3\omega_0+4\gamma_0\omega_0(\beta_0+\alpha_0\phi)\mu^2+5\gamma_0^2(\beta_0+\alpha_0\phi)\mu^2+\gamma_0^2\omega_0^2}{\gamma^2\mu^2}\\
n_8 &= -\frac{2(\gamma_0^2+\gamma_0\omega_0+(\beta_0+\alpha_0\phi)\mu^2)}{\gamma_0\mu}\\
n_9 &= -1.
\end{aligned}
$$

The characteristic polynomial of the reduced model obtained through the symmetry in the variables among the serotypes are a particular case of the model (49). Since there is no bifurcation structure in the reduced model, we consider only the quotient polynomial $\frac{m(\lambda)}{n(\lambda)} = r(\lambda)$.

If a bifurcation structure exists, that can be only found in the quotient polynomial $r(\lambda) = r_0+r_1\lambda+r_2\lambda^2+r_3\lambda^3+r_4\lambda^4$, where

$$
\begin{aligned}
r_0 &= \frac{\alpha_0\phi\gamma_0\omega_0}{\mu^2}\\
r_1 &= \frac{\alpha_0\phi(\gamma_0+3\omega_0)}{2\mu}\\
r_2 &= \frac{\alpha_0\phi(3\gamma_0+2\omega_0)}{2\gamma_0} + \frac{\gamma_0\omega_0}{\mu^2}\\
r_3 &= \frac{\gamma_0+\omega_0}{\mu} + \frac{\alpha_0\mu}{\gamma_0}\\
r_4 &= 1
\end{aligned}
\tag{52}
$$

The coefficients of the polynomial are of order $\mathcal{O}(1/\mu^2)$. We redefine the polynomial $R(\lambda) = \mu^2 r(\lambda)$ and apply the regular perturbation theory, assuming that the solutions of the polynomial $R(\lambda)$ are of the form $\lambda = z_0 + z_1\mu + z_2\mu^2 + \mathcal{O}(\mu^3)$. By substituting the solutions $\lambda$ in the polynomial $R(\lambda) = \mu^2 r(\lambda)$ and equalise the terms of the same order, we have

$$
\begin{aligned}
z_0^2 &= -\alpha_0\phi\\
z_1 &= \frac{\alpha_0\phi}{4\gamma_0\omega_0}[\gamma_0-\omega_0]
\end{aligned}
\tag{53}
$$

$$z_2 = \pm v_1 \sqrt{\alpha_0 \phi} i.$$

where $v_1 = \frac{1}{2\gamma_0\omega_0\alpha_0\phi}\left[\alpha_0^2\phi^2 - \alpha_0^2\phi^2(\frac{3\gamma_0+2\omega_0}{2\gamma_0}) - \frac{\alpha_0^2\phi^2}{4\gamma_0\omega_0}(\gamma_0-\omega_0)(\frac{5\gamma_0+3\omega_0}{2})\right]$, thus, the approximation of the $\mathcal{O}(\mu^3)$ of the eigenvalues are given by

$$\lambda_{1,2} = \left(\frac{\alpha_0\phi}{4\gamma_0\omega_0}[\gamma_0-\omega_0]\right)\mu \pm (1+v_1\mu^2)\sqrt{\alpha_0\phi}i, \tag{54}$$

with the positive real part, since $\omega \leq \gamma$.

The other eigenvalues can be determined by their magnitude, via the analysis of the coefficients of the characteristic polynomial, showing that the other solutions of the polynomial $r(\lambda)$ are of the order $\mathcal{O}(\frac{1}{\mu})$. Dividing $r(\lambda)$ by the roots found $\lambda_{1,2}$ (see equation 54 ), shows that the roots are real and of the form

$$\lambda_{3,4} = -2\frac{(\gamma_0+\omega_0)}{\mu} - \alpha_0\phi\mu(\frac{1}{\gamma_0}+\frac{1}{\omega_0}) \pm (\frac{2}{\mu}\sqrt{(\gamma_0+\omega_0)^2 - \mathcal{O}(\mu^4)}). \tag{55}$$

Moreover, the roots are negative (with the positive term being smaller than the negative term of the eigenvalue), hence the endemic equilibrium is always unstable. This can be easily confirmed numerically. On the other hand, the eigenvalues of the whole system are always negative, except for a pair of complex eigenvalues that have positive real part, showing a unstable dynamic near the endemic equilibrium. While it was not possible to show analytically the bifurcation structure, we could prove analytically the instability of the endemic equilibrium, leading to complicated dynamic.

**Remark 3.** Note that, Case (ii) is the classical ODE system, assuming the immunity period being exponentially distributed, i.e. with a constant temporary immunity cross-protection $\omega$, and the classical addition of the temporary immunity class as described in [32], with different assumption on the disease enhancement process.

**Remark 4.** Billings at al. [41] used the same method for a similar ODE model, assuming symmetry among variables and parameters. The authors have used regular perturbation to show analytically the value of the parameter $\phi$ where the Hopf bifurcation occurs. In that case, bifurcation occurs in the symmetric manifold having the assumption for the ADE parameter $\phi$ as increasing transmissibility in secondary infections and no temporary cross-immunity.

**Remark 5.** In this work, the enhancement parameter is assumed to act on the susceptibility of secondary infections, with additional class for cross-protection which clearly showed a different and more complex dynamics with Hopf bifurcation and thus, the instability of endemic equilibria occurring only out of symmetric manifold.

## 6. Discussion and Conclusions

In this paper we have investigated the symmetric case of the mathematical model proposed by Steindorf et al. [37], an integro-differential equation system motivated by dengue fever epidemiology. The model includes two important biological features, the temporary cross-immunity period (incorporated as a general form) and susceptibility enhancement, both occurring after a primary infection.

In the previous work of Steindorf et al. [37], the analysis of the asymmetric model was carried out showing four equilibria, the disease-free equilibrium, two boundary equilibria and the coexistence equilibrium, with the stability of each one of them being analysed in detail, showing an important threshold value for invasion scenario of one strain and extinction of the other. In the asymmetric case, the boundary equilibria can be stable, and thus, the most pathogenic strain, i.e. with higher transmission rate, will be predominant, protecting the population from the another strain, while in the symmetric case studied here, that can not occur.

For symmetric case, the disease either dies out or become prevalent with both strains coexisting, i.e, the boundary equilibria can never be stable. The parameter representing susceptibility enhancement ($\phi$) is an important parameter to described the dynamics of disease, whether the coexistence of strains will persist or periodic outbreaks with coexistence of strains will occur. In detail, if $\phi$ is small, disease will persist with coexistence of strains. A supercritical Hopf bifurcation occurs at the threshold value, $\phi_c$, leading to periodic solutions. Finally, for larger $\phi$, the endemic equilibrium

is unstable, with complex attractors up to chaotic behaviour occurring. These findings are very important in dengue fever epidemiology, since the available incidence data resemble chaotic dynamics as revealed by Aguiar et al. [51]. The complex dynamics of the system stabilizes for $\phi > 1.2$, with only periodic solutions observed.

It is important to mention that, close to the endemic equilibrium, the results for the symmetric case show a very similar dynamical behaviour found in the asymmetric case, justifying the evaluation of the reduced system obtained by considering symmetry among serotypes and allowing further analytical computations and results, such as the analytical proof of the instability of the endemic equilibrium and the changes in the dynamics. Therefore, in the scenario that represents an endemic region, the study of the behavior of the disease could be accessed by both models. The limitation of the symmetric model, though, remains in the study of the invasion and persistence of a new strain.

In this work, we have used a specific function for the kernel of the integral to first transform IDE into an ODE system. Then, using perturbation theory, we have shown that the bifurcation and the instability occur outside of the symmetric manifold. That is, under the assumption of symmetries in the variables, the dimension of the model could be reduced and represent the symmetric part of the entire model, showing only stable dynamics. Using the perturbation theory in the whole model, the analytic form of the endemic equilibrium is obtained when the mortality term is neglected. And by separating the symmetric manifold, it allows to show the eigenvalues and the instability of the coexistence equilibrium out of the symmetric manifold. Although the Hopf bifurcation could not be obtained due to the small perturbation in the mortality term.

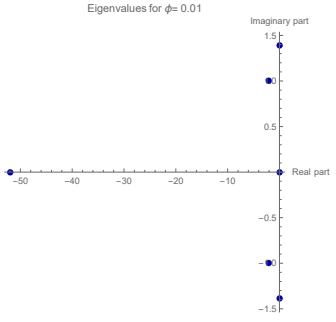
Finally, using a method to transform IDEs into ODEs, as proposed by Domoshnitsky et al. [50], we observed that the choice of the function ( which satisfies the epidemiological conditions and the specific kernel features) had no effect on the qualitative behavior of the system, when comparing the particular case (ODE case), by using the exponential distributed function for the immunity period, with the more general case (IDE case) by using a general function. Nevertheless, future study can be developed with generalizations for the function selection that explain the immunity phase.

While a rigorous analysis of such systems is required for true predictive power and more accurate disease control decision making, the findings presented here should be taken into account when mathematical models applied to dengue fever epidemiology continue to be developed in order to give insights on epidemic scenarios, in collaboration with public health authorities for disease control measures.

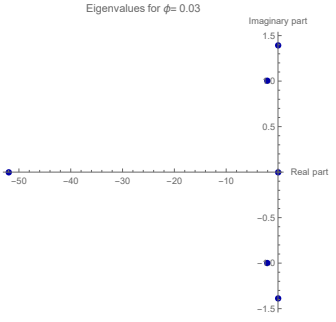
# A. Complementary numerical simulations

## A.1. Case (i): $P(s) = cos(As)e^{-\omega s}$, $A > 0$

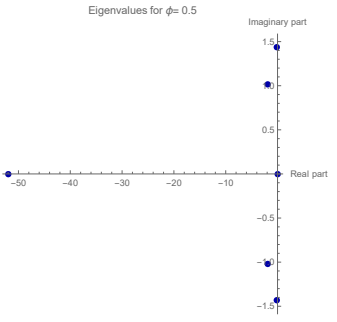
Figures show the eigenvalues of Jacobian matrix at the endemic equilibrium of the system (19), with symmetry in the variables and without the perturbation in the mortality term. The eigenvalues have always negative real part, independent of the size of the parameter $\phi$.



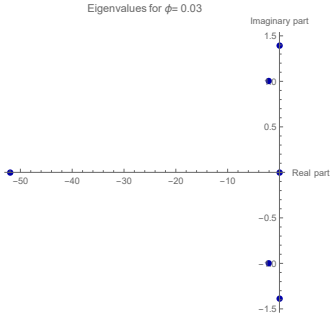

(a) $\phi = 0.01$



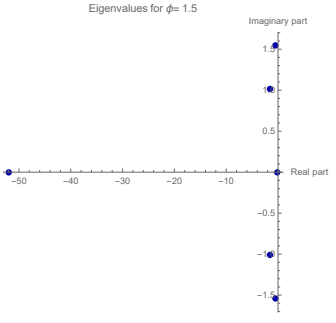

(b) $\phi = 0.03$



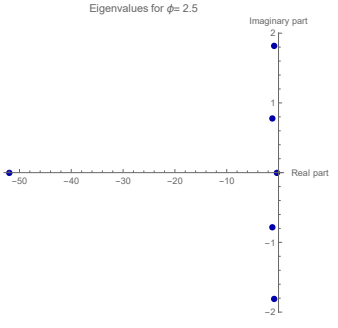

(c) $\phi = 0.5$




(d) $\phi = 1$




(e) $\phi = 1.5$



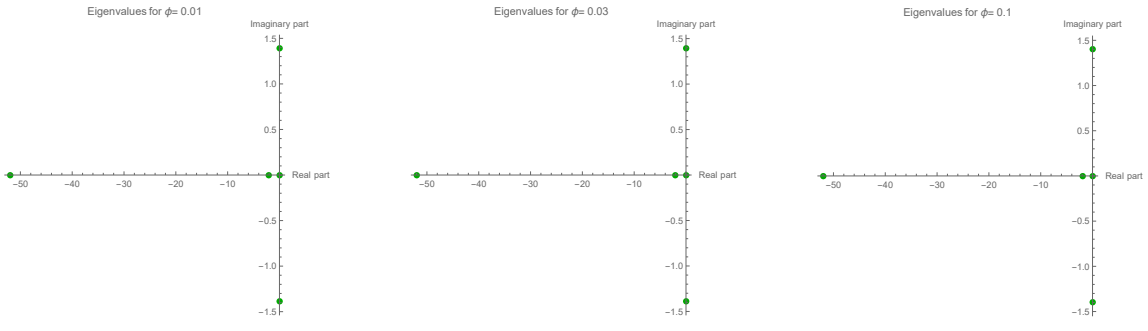

(f) $\phi = 2.5$

**Figure 4:** The figures show the eigenvalues of the endemic equilibrium in the complex plane, for each value of $\phi$, for (19) system (with symmetry in the variables and without the perturbation in the mortality term). The values used in the simulations are found on Table (1) with $\beta = 180$.

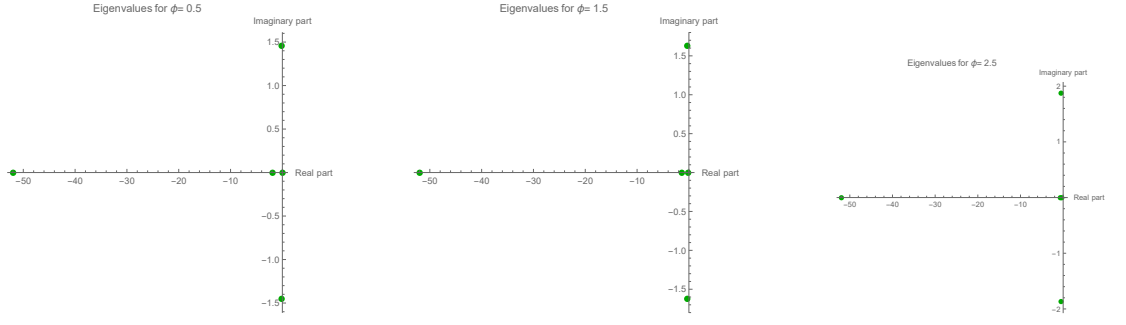
## A.2. Case (ii): $P(t) = e^{-\omega t}$

Figures show the eigenvalues of Jacobian matrix at the endemic equilibrium of the system (38), with symmetry in the variables and without the perturbation in the mortality term. The eigenvalues have always negative real part, independent of the size of the parameter $\phi$.

# B. Table for numerical simulations




(a) $\phi = 0.01$ (b) $\phi = 0.03$ (c) $\phi = 0.5$




(d) $\phi = 1$ (e) $\phi = 1.5$ (f) $\phi = 2.5$

**Figure 5:** Figures show the eigenvalues of the endemic equilibrium in the complex plane, for each value of $\phi$, at symmetric case, for symmetric system (38) (with symmetry in the variables and without the perturbation in the mortality term). The values used in the simulations are found on Table (1) with $\beta = 180$.

**Table 1**
Parameter values used in the simulations. Source [37, 40].

| Parameter | Meaning | Value | Unity | Reference |
|---|---|---|---|---|
| $d$ | Mortality rate | 0.015 | $y^{-1}$ | [49] |
| $\gamma$ | Recovery rate | 52 | $y^{-1}$ | [47, 48] |
| $\omega$ | Cross immunity protection rate | 2 | $y^{-1}$ | [47] |
| $\beta$ | Infection rate (susceptible individuals) | $40-200$ | - | [37] |
| $\alpha$ | Reinfection rate (recovered individuals from a primary infection) | $40-200$ | - | [37] |
| $\phi$ | ADE factor | $0-5$ | - | [28] |

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