

Cross-Immunity-Induced Backward Bifurcation for a Model of Transmission Dynamics of Two Strains of Influenza

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Abstract

A new deterministic model for the transmission dynamics of two strains of influenza is designed and used to qualitatively assess the role of cross-immunity on the transmission process. It is shown that incomplete cross-immunity could induce the phenomenon of backward bifurcation when the associated reproduction number is less than unity. The model undergoes competitive exclusion (where Strain i drives out Strain j to extinction whenever $\mathcal{R}_{0i} > 1 > \mathcal{R}_{0j}$; $i, j = 1, 2, i \neq j$). For the case where infection with one strain confers complete immunity against infection with the other strain, it is shown that the disease-free equilibrium of the model is globally-asymptotically stable whenever the reproduction number is less than unity. In the absence of cross-immunity, the model can have a continuum of co-existence endemic equilibria (which is shown to be globally-asymptotically stable for a special case). When infection with one strain confers incomplete immunity against the other. Numerical simulations of the model show that the two strains co-exist, with Strain i dominating (but not driving out Strain j), whenever $\mathcal{R}_{0i} > \mathcal{R}_{0j} > 1$.

Keywords: cross-immunity; multiple strains; equilibria; co-existence; stability.

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1 Introduction

One of the important problems in mathematical epidemiology is the study of the transmission dynamics of diseases with multiple strains in the presence of partial or complete immunity. Consequently, the mathematical modeling of diseases with multiple pathogen strains, such as dengue fever, HIV/AIDS, influenza, malaria and West Nile virus, has received considerable attention (see, for instance, [1, 2, 12, 15, 19, 27, 29, 23, 26, 34, 39] and some of the references therein). These studies have, in general, focussed on the determination of threshold condition(s) for the co-existence of the strains, as well as the evaluation of the role of cross-immunity (defined as a scenario where infection with one strain confers partial or complete protection against infection with another strain) in the transmission dynamics of the disease strains.

In a multi-strain dynamics situation, infection by one or more of the strains may modify the sensitivity to infection by the other strains [15, 23, 26, 29, 38]. Some of the main questions of epidemiological interest, in studies of modeling multi-strain dynamics, are:

- (i) which strain(s) will dominate in the long run (i.e., does competitive exclusion phenomenon occurs)?
- (ii) under what conditions will the strains co-exist?
- (iii) what is the effect of cross-immunity (partial or complete) on the multi-strain dynamics?

These questions could be addressed using the threshold quantity known as the *basic reproduction number* of the disease [3, 4, 27], which represents the average number of secondary cases generated by a typical infected individual in a completely susceptible population. Past research has estimated that the reproduction number of the 1918-1919 influenza pandemic and other seasonal strains of influenza ranged between 1.5 and 5.4 [15, 16, 17, 18, 21, 26, 35, 36].

Using an SIQR deterministic model for the dynamics of two strains of influenza in the presence of isolation of symptomatic cases, Nuno et al. [29] showed that cross-immunity and host isolation could induce sustained periodic oscillations. Bremmerman and Thieme [8] shows the phenomenon of competitive exclusion (where the strain with the largest reproduction number persists and eliminates the remaining strains) in a simple model with multiple strains (similar results were obtained in [11, 20, 23]). Gumel [26] shows co-existence of two strains (avian and mutant) of influenza when their reproduction numbers exceed unity using avian-human model in the presence of isolation (system does not undergo competitive exclusion).

The aim of this study is to rigorously assess the role of cross-immunity on the transmission dynamics of two strains of influenza in a population. To achieve this objective, a new deterministic model (which extends the model in [29]) will be designed.

The paper is organized as follows. The extended model is formulated in Section 2 and analysed in Section 3.

2 Formulation of Mathematical Model

The model is based on the transmission dynamics of two strains of influenza. The total population at time t , denoted by $N(t)$, is subdivided into susceptible ($S(t)$); exposed to strain i ($i = 1, 2$) (E_i); infectious with strain i (I_i); recovered from strain i (R_i); recovered from strain i and exposed to strain j ($i, j = 1, 2$ $i \neq j$) (E_{ij}); recovered from strain i and infectious with strain j (I_{ij}); and individuals recovered from infection with both strains (M), so that

$$N(t) = S(t) + E_1(t) + I_1(t) + R_1(t) + E_2(t) + I_2(t) + R_2(t) + E_{12}(t) + I_{12}(t) + E_{21}(t) + I_{21}(t) + M(t).$$

The model to be considered is given by the following deterministic system of non-linear differential equations (where a dot represents differentiation with respect to t ; and all associated parameters are non-negative for all $t \geq 0$):

$$\begin{aligned}
\dot{S} &= \Pi + \xi M - \frac{\beta_1 S(\eta_1 E_1 + I_1)}{N} - \frac{\beta_2 S(\eta_2 E_2 + I_2)}{N} - \frac{\beta_{12} S(\eta_{12} E_{12} + I_{12})}{N} \\
&\quad - \frac{\beta_{21} S(\eta_{21} E_{21} + I_{21})}{N} - \mu S, \\
\dot{E}_1 &= \frac{\beta_1(\eta_1 E_1 + I_1)}{N} S + \frac{\beta_{21}(\eta_{21} E_{21} + I_{21})}{N} S - \sigma_1 E_1 - \mu E_1, \\
\dot{I}_1 &= \sigma_1 E_1 - \gamma_1 I_1 - \mu I_1 - \delta_1 I_1, \\
\dot{R}_1 &= \gamma_1 I_1 - \theta_2 \frac{\beta_2 R_1(\eta_2 E_2 + I_2)}{N} - \theta_2 \frac{\beta_{12} R_1(\eta_{12} E_{12} + I_{12})}{N} - \mu R_1, \\
\dot{E}_2 &= \frac{\beta_2(\eta_2 E_2 + I_2)}{N} S + \frac{\beta_{12}(\eta_{12} E_{12} + I_{12})}{N} S - \sigma_2 E_2 - \mu E_2, \\
\dot{I}_2 &= \sigma_2 E_2 - \gamma_2 I_2 - \mu I_2 - \delta_2 I_2, \\
\dot{R}_2 &= \gamma_2 I_2 - \theta_1 \frac{\beta_1 R_2(\eta_1 E_1 + I_1)}{N} - \theta_1 \frac{\beta_{21} R_2(\eta_{21} E_{21} + I_{21})}{N} - \mu R_2, \\
\dot{E}_{12} &= \theta_2 \frac{\beta_2 R_1(\eta_2 E_2 + I_2)}{N} + \theta_2 \frac{\beta_{12} R_1(\eta_{12} E_{12} + I_{12})}{N} - \sigma_{12} E_{12} - \mu E_{12}, \\
\dot{I}_{12} &= \sigma_{12} E_{12} - \gamma_{12} I_{12} - \mu I_{12} - \delta_{12} I_{12}, \\
\dot{E}_{21} &= \theta_1 \frac{\beta_1 R_2(\eta_1 E_1 + I_1)}{N} + \theta_1 \frac{\beta_{21} R_2(\eta_{21} E_{21} + I_{21})}{N} - \sigma_{21} E_{21} - \mu E_{21}, \\
\dot{I}_{21} &= \sigma_{21} E_{21} - \gamma_{21} I_{21} - \mu I_{21} - \delta_{21} I_{21}, \\
\dot{M} &= \gamma_{12} I_{12} + \gamma_{21} I_{21} - \xi M - \mu M,
\end{aligned} \tag{1}$$

where Π is the recruitment rate into the community, ξ is the rate of loss of natural immunity by recovered individuals, β_i (where $i = 1, 2$ here and elsewhere below) is the infection rate with strain i , β_{ij} ($i, j = 1, 2$; $i \neq j$) represents the transmission rate for

individuals who recovered from strain i but exposed to strain j and μ is the natural death rate. The modification parameters $\eta_i < 1$ accounts for the assumed reduction of exposed individuals (those in the E_i classes) in relation to infectious individuals (in the I_i classes); the parameters η_{ij} are similarly defined.

Furthermore, σ_i is the transition rate of individuals exposed with strain i (i.e., those in the E_i class) to the corresponding infectious (I_i) class (the parameters σ_{ij} are similarly defined). The parameters γ_i and δ_i represent, respectively, the recovery rates and disease-induced death rate of individuals infected with strain i (the parameters γ_{ij} and δ_{ij} are defined similarly). The modification parameters $0 \leq \theta_i \leq 1$ account for the assumed reduction of susceptibility to strain j of individuals who recovered from strain i (i.e., $0 \leq \theta_i \leq 1$) captures the cross-immunity of individuals who recovered from one strain against acquiring infection with the other). These parameters are described in Table 1, and a flow diagram of the model is depicted in Figure 1.

The model (1) is an extension of the two-strain influenza model developed by Nuno et al. [29], by

- (i) adding epidemiological compartments for exposed individuals (E_1 , E_2 , E_{12} and E_{21}). The incubation period of influenza is 1-4 days (average is about 2 days) [14];
- (ii) allowing for disease transmission by exposed individuals (at reduced rates $\beta_i \eta_i$ for those with primary infection; and $\beta_{ij} \eta_{ij}$ for those with secondary infection). Clinical evidence suggests that individuals infected with an influenza virus can transmit infection even before the onset of symptoms (typically a day before symptoms develop) [14];
- (iii) allowing heterogeneity in transmission due to recovery from infection with one strain (i.e., individuals in the E_{ij} and I_{ij} classes transmit infection at different rates in comparison to those in the corresponding E_i and I_i classes). Same rate (β_i) is used in Nuno et al. [29], for disease transmission by individuals infected with strain i (regardless of whether or not the infected individuals recover from strain j). Clinical studies show differential heterogeneity in disease transmission by individuals previously infected with different disease strain [9, 17, 25];
- (iv) allow for the loss of natural immunity in individuals who recovered from both strains (at the rate ξ) [6].

It should be noted that, unlike in [29], the model (1) does not incorporate the isolation of symptomatic cases (i.e., while isolation-adjusted incidence is used to model the infection rate in [29], standard incidence function is used in (1); the reader may refer to [15] for the disadvantages associated with implementing isolation strategy, including the difficulty of detecting infected individuals and the cost of isolation in the context

of influenza). Furthermore, the model (1) can also be used for any influenza-like illness (where exposed individuals can transmit infection) with two strains. In addition to the above extensions, rigorous qualitative analysis will be provided for the resulting model.

2.1 Basic Properties of the Model

For the model (1) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time (t). In other words, the solutions of the model (1) with positive initial data will remain positive for all $t \geq 0$. The following result can be proven (see, for instance, [8, 22, 24, 37, 40])

Theorem 1 *Let the initial data $S(0) > 0$, $E_1(0) > 0$, $I_1(0) > 0$, $R_1(0) > 0$, $E_2(0) > 0$, $I_2(0) > 0$, $R_2(0) > 0$, $E_{12}(0) > 0$, $I_{12}(0) > 0$, $E_{21}(0) > 0$, $I_{21}(0) > 0$, $M(0) > 0$, then the solutions $S, E_1, I_1, R_1, E_2, I_2, R_2, E_{12}, I_{12}, E_{21}, I_{21}, M$ of the model (1) are positive for all $t \geq 0$. Furthermore,*

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{\Pi}{\mu}.$$

2.1.1 Invariant region

Lemma 1 *The region*

$$\Omega = \left\{ (S, E_1, I_1, R_1, E_2, I_2, R_2, E_{12}, I_{12}, E_{21}, I_{21}, M) \in \mathbb{R}_+^{12} : \right. \\ \left. S + E_1 + I_1 + R_1 + E_2 + I_2 + R_2 + E_{12} + I_{12} + E_{21} + I_{21} + M \leq \frac{\Pi}{\mu} \right\}$$

is positively-invariant for the model (1).

Proof. Adding the equations in the model system (1) gives

$$\frac{dN(t)}{dt} = \Pi - \mu N(t) - (\delta_1 I_1 + \delta_2 I_2 + \delta_{12} I_{12} + \delta_{21} I_{21}). \quad (2)$$

It follows from (2) that

$$\frac{dN(t)}{dt} \leq \Pi - \mu N(t). \quad (3)$$

Thus (using standard comparison theorem [32]), $N(t) \leq N(0)e^{-\mu t} + \frac{\Pi}{\mu}[1 - e^{-\mu t}]$. In particular, $N(t) \leq \Pi/\mu$. Thus, Ω is positively-invariant. Hence, it is sufficient to consider the dynamics of the model (1) in Ω . In this region, the model can be considered as been epidemiologically and mathematically well-posed [27]. \square

2.2 Stability of Disease-Free Equilibria (DFE)

2.2.1 Local stability

The DFE of the model (1) is given by

$$\begin{aligned} \mathcal{E}_0 &= (S^*, E_1^*, I_1^*, R_1^*, E_2^*, I_2^*, R_2^*, E_{12}^*, I_{12}^*, E_{21}^*, I_{21}^*, M^*), \\ &= \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0 \right). \end{aligned} \quad (4)$$

The linear stability of \mathcal{E}_0 can be established using the next generation operator method on system (1). Using the notation in [41], the matrices F (for the new infection terms) and V (of the transition terms) are given, respectively, by

$$F = \begin{bmatrix} \beta_1 \eta_1 & \beta_1 & 0 & 0 & 0 & 0 & \beta_{21} \eta_{21} & \beta_{21} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 \eta_2 & \beta_2 & \beta_{12} \eta_{12} & \beta_{12} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} K_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_1 & K_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & K_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\sigma_2 & K_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & K_5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -\sigma_{12} & K_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & K_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\sigma_{21} & K_8 \end{bmatrix},$$

where, $K_1 = \mu + \sigma_1$, $K_2 = \mu + \gamma_1 + \delta_1$, $K_3 = \mu + \sigma_2$, $K_4 = \mu + \gamma_2 + \delta_2$, $K_5 = \mu + \sigma_{12}$, $K_6 = \mu + \gamma_{12} + \delta_{12}$, $K_7 = \mu + \sigma_{21}$ and $K_8 = \mu + \gamma_{21} + \delta_{21}$.

It follows that the *basic reproduction number* of the model (1), denoted by \mathcal{R}_0 , is given by (where ρ is the spectral radius)

$$\mathcal{R}_0 = \rho(FV^{-1}) = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\},$$

where \mathcal{R}_{01} and \mathcal{R}_{02} are the associated *reproduction numbers* for strain 1 and strain 2, respectively, given by

$$\mathcal{R}_{01} = \frac{\beta_1(\eta_1 K_2 + \sigma_1)}{K_1 K_2} \quad \text{and} \quad \mathcal{R}_{02} = \frac{\beta_2(\eta_2 K_4 + \sigma_2)}{K_3 K_4}. \quad (5)$$

Lemma 2 *The DFE, \mathcal{E}_0 , of the model (1) is locally-asymptotically stable (LAS) if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The threshold quantity, $\mathcal{R}_0 = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\}$, is the *basic reproduction number* of the disease [3, 4, 27]. It represents the average number of secondary cases generated by a typical infected individual in a completely susceptible population. The epidemiological implication of Lemma 2 is that when \mathcal{R}_0 is less than unity, a small influx of infected individuals into the community would not generate large outbreaks, and the disease dies out in time.

2.2.2 Backward bifurcation analysis

It is instructive to characterize the types of bifurcation the model (1) may undergo. We claim the following result (the proof is given in Appendix A):

Theorem 2 *The model (1) exhibits backward bifurcation at $\mathcal{R}_0 = 1$ whenever a bifurcation coefficient, denoted by a (and given by (32)), is positive.*

The public health implication of the backward bifurcation phenomenon of the model (1) is that the classical epidemiological requirement of having the reproduction number (\mathcal{R}_0) to be less than unity, while necessary, is no longer sufficient for the effective control of the disease. In other words, the backward bifurcation property of the model (1) makes effective diseases control difficult. It is worth stating that, setting $\theta_1 = \theta_2 = 0$ in the inequality (32) gives (noting that all parameters of the model are positive and $\beta_1^* > 0$ is given in Appendix A):

$$a = -\frac{4\mu}{\Pi} \left[\frac{\beta_1^*(\eta_1 K_2 + \sigma_1)}{\sigma_1} + \frac{\beta_2(\eta_2 K_4 + \sigma_2)}{\sigma_2} \right] \left(2 + \frac{K_2}{\sigma_1} + \frac{K_4}{\sigma_2} + \frac{\gamma_1 + \gamma_2}{\mu} \right) < 0. \quad (6)$$

Thus, it follows from Theorem 4.5 in [13] that the model (1) does not undergo backward bifurcation in this setting. Hence, this study shows that the backward bifurcation phenomenon of the model (1) is caused by the incomplete cross-immunity property of the model ($0 < \theta_1, \theta_2 < 1$). A global asymptotic stability result is established below for the DFE of the model (to completely rule out backward bifurcation for the case when infection with one strain confers complete cross-immunity against the other strain). It is worth stating that the phenomenon of backward bifurcation is not rigorously established in the study by Nuno et al. [29] (the phenomenon was shown using numerical simulations). This, to the authors' knowledge, is the first time it is rigorously shown that incomplete cross-immunity could induce backward bifurcation in the transmission dynamics of two strains of influenza. Garba and Gumel [23] also established similar result in the dynamics of two strains of dengue fever.

2.3 Global Stability of DFE: Special Case $\theta_1 = \theta_2 = 0$

Consider the model (1), for the case when infection with one strain confers complete immunity against infection with the other strain (i.e., $\theta_1 = \theta_2 = 0$). It follows, by setting $\theta_1 = \theta_2 = 0$ in (1), that $E_{12} \rightarrow 0$, $I_{12} \rightarrow 0$, $E_{21} \rightarrow 0$, $I_{21} \rightarrow 0$ and $M \rightarrow 0$ as $t \rightarrow \infty$. Thus, the last five equations of the model decouple, so that the model (1) reduces to:

$$\begin{aligned}
 \dot{S} &= \Pi - \lambda_1 S - \lambda_2 S - \mu S, \\
 \dot{E}_1 &= \lambda_1 S - K_1 E_1, \\
 \dot{I}_1 &= \sigma_1 E_1 - K_2 I_1, \\
 \dot{R}_1 &= \gamma_1 I_1 - \mu R_1, \\
 \dot{E}_2 &= \lambda_2 S - K_3 E_2, \\
 \dot{I}_2 &= \sigma_2 E_2 - K_4 I_2, \\
 \dot{R}_2 &= \gamma_2 I_2 - \mu R_2.
 \end{aligned} \tag{7}$$

where, now, $\lambda_1 = \frac{\beta_1(\eta_1 E_1 + I_1)}{N}$ and $\lambda_2 = \frac{\beta_2(\eta_2 E_2 + I_2)}{N}$.

The dynamics of the reduced model (7) will be considered in the following invariant region

$$\Gamma = \left\{ (S, E_1, I_1, R_1, E_2, I_2, R_2) \in \mathbb{R}_+^7 : N \leq \frac{\Pi}{\mu} \right\}. \tag{8}$$

The DFE of the reduced model is given by $\mathcal{E}_0^r = (S, E_1, I_1, R_1, E_2, I_2, R_2) = \left(\frac{\Pi}{\mu}, 0, 0, 0, 0, 0, 0 \right)$.

The model (7) has the same reproduction number, $\mathcal{R}_0 = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\}$, as model (1).

Theorem 3 *The DFE, \mathcal{E}_0^r , of the reduced model (7) is GAS in Γ whenever $\mathcal{R}_0 \leq 1$.*

Proof. Consider the Lyapunov function for the model (7):

$$\mathcal{F} = \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) E_1 + I_1 + \left(\frac{\eta_2 K_4 + \sigma_2}{K_3} \right) E_2 + I_2, \tag{9}$$

with Lyapunov derivative given by

$$\begin{aligned}
\dot{\mathcal{F}} &= \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) \dot{E}_1 + \dot{I}_1 + \left(\frac{\eta_2 K_4 + \sigma_2}{K_3} \right) \dot{E}_2 + \dot{I}_2, \\
&= \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) \left[\frac{\beta_1 (\eta_1 E_1 + I_1)}{N} S - K_1 E_1 \right] + \sigma_1 E_1 - K_2 I_1 \\
&\quad + \left(\frac{\eta_2 K_4 + \sigma_2}{K_3} \right) \left[\frac{\beta_2 (\eta_2 E_2 + I_2)}{N} S - K_3 E_2 \right] + \sigma_2 E_2 - K_4 I_2, \\
&\leq \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) \left[\beta_1 (\eta_1 E_1 + I_1) - K_1 E_1 \right] + \sigma_1 E_1 - K_2 I_1 \\
&\quad + \left(\frac{\eta_2 K_4 + \sigma_2}{K_3} \right) \left[\beta_2 (\eta_2 E_2 + I_2) - K_3 E_2 \right] + \sigma_2 E_2 - K_4 I_2 \text{ since } S \leq N \text{ in } \Gamma, \\
&= \beta_1 \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) (\eta_1 E_1 + I_1) - (\eta_1 K_2 + \sigma_1) E_1 + \sigma_1 E_1 - K_2 I_1 \\
&\quad + \beta_2 \left(\frac{\eta_2 K_4 + \sigma_2}{K_3} \right) (\eta_2 E_2 + I_2) - (\eta_2 K_4 + \sigma_2) E_2 + \sigma_2 E_2 - K_4 I_2, \\
&= K_2 \mathcal{R}_{01} (\eta_1 E_1 + I_1) - \eta_1 K_2 E_1 - K_2 I_1 + K_4 \mathcal{R}_{02} (\eta_2 E_2 + I_2) - \eta_2 K_4 E_2 - K_4 I_2, \\
&= K_2 \mathcal{R}_{01} (\eta_1 E_1 + I_1) - (\eta_1 E_1 + I_1) K_2 + K_4 \mathcal{R}_{02} (\eta_2 E_2 + I_2) - (\eta_2 E_2 + I_2) K_4, \\
&= K_2 (\eta_1 E_1 + I_1) (\mathcal{R}_{01} - 1) + K_4 (\eta_2 E_2 + I_2) (\mathcal{R}_{02} - 1).
\end{aligned}$$

Thus $\dot{\mathcal{F}} \leq 0$ if $\mathcal{R}_0 = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\} \leq 1$ with $\dot{\mathcal{F}} = 0$ if $E_1 = I_1 = E_2 = I_2 = 0$. Substituting $E_1 = I_1 = E_2 = I_2 = 0$ in the first equation in (7) shows that $S(t) \rightarrow \Pi/\mu$ as $t \rightarrow \infty$. Similarly, substituting $E_1 = I_1 = E_2 = I_2 = 0$ in the equations for R_1 and R_2 show that $(R_1, R_2) \rightarrow (0, 0)$ as $t \rightarrow \infty$. Further, the largest compact invariant set in $\{(S, E_1, I_1, R_1, E_2, I_2, R_2) \in \Gamma : d\mathcal{F}/dt = 0\}$ is the singleton $\{\mathcal{E}_0^r\}$. It follows, from the LaSalle's Invariance Principle [33], that every solution to the equations in (7) with initial conditions in Γ converges to the DFE \mathcal{E}_0^r as $t \rightarrow \infty$. \square

This result shows that, for the case when infection with one strain confers complete immunity against the other strain, the DFE of the model (1) is GAS (hence, the disease (i.e., both strains) will be eliminated from the community if $\mathcal{R}_0 < 1$ in this case). It should be mentioned that such global-asymptotic result was not established for the

DFE of the model presented by Nuno et al. [29].

3 Existence and Stability of Boundary Equilibria

The approach in [23, 31] will be used to explore the possibility of the existence and stability of the positive equilibria (i.e., equilibria where at least one of the infected variables of the model (1) is non-zero). Let

$$\mathcal{E}_{12} = (S^{**}, E_1^{**}, I_1^{**}, R_1^{**}, E_2^{**}, I_2^{**}, R_2^{**}, E_{12}^{**}, I_{12}^{**}, R_{12}^{**}, E_{21}^{**}, I_{21}^{**}, M^{**})$$

represents any arbitrary equilibrium of the model (1). Further, let

$$\lambda_1^{**} = \frac{\beta_1(\eta_1 E_1^{**} + I_1^{**}) + \beta_{21}(\eta_{21} E_{21}^{**} + I_{21}^{**})}{N^{**}} \quad \text{and} \quad \lambda_2^{**} = \frac{\beta_2(\eta_2 E_2^{**} + I_2^{**}) + \beta_{12}(\eta_{12} E_{12}^{**} + I_{12}^{**})}{N^{**}} \quad (10)$$

be the *forces of infection* of strains 1 and 2, respectively, at endemic steady-state (where N^{**} is the total population size at the endemic steady-state). Solving the equations in (1) at endemic steady-state gives

$$\begin{aligned} S^{**} &= \frac{\Pi}{A_1}, \quad E_1^{**} = \frac{\Pi \lambda_1^{**}}{K_1 A_1}, \quad I_1^{**} = \frac{\Pi \lambda_1^{**} \sigma_1}{K_1 K_2 A_1}, \quad R_1^{**} = \frac{\Pi \lambda_1^{**} \sigma_1 \gamma_1}{K_1 K_2 A_1 A_3}, \\ E_2^{**} &= \frac{\Pi \lambda_2^{**}}{K_3 A_1}, \quad I_2^{**} = \frac{\Pi \lambda_2^{**} \sigma_2}{K_3 K_4 A_1}, \quad R_2^{**} = \frac{\Pi \lambda_2^{**} \sigma_2 \gamma_2}{K_3 K_4 A_1 A_2}, \quad E_{12}^{**} = \frac{\Pi \lambda_1^{**} \lambda_2^{**} \sigma_1 \gamma_1 \theta_2}{K_1 K_2 K_5 A_1 A_3}, \\ I_{12}^{**} &= \frac{\Pi \lambda_1^{**} \lambda_2^{**} \sigma_1 \sigma_3 \gamma_1 \theta_2}{K_1 K_2 K_5 K_6 A_1 A_3}, \quad E_{21}^{**} = \frac{\Pi \lambda_1^{**} \lambda_2^{**} \sigma_2 \gamma_2 \theta_1}{K_3 K_4 K_7 A_1 A_2}, \quad I_{21}^{**} = \frac{\Pi \lambda_1^{**} \lambda_2^{**} \sigma_2 \sigma_4 \gamma_2 \theta_1}{K_3 K_4 K_7 K_8 A_1 A_2}, \\ M^{**} &= \frac{\Pi \lambda_1^{**} \lambda_2^{**} \sigma_2 \theta_1 (\gamma_3 K_8 + \gamma_4 \sigma_4)}{K_3 K_4 K_7 K_8 K_9 A_1 A_2}, \end{aligned} \quad (11)$$

with $A_1 = \lambda_1^{**} + \lambda_2^{**} + \mu$, $A_2 = \lambda_1^{**} \theta_1 + \mu$ and $A_3 = \lambda_2^{**} \theta_2 + \mu$.

The equilibria of the model (1) can then be obtained by finding the fixed-points of the equation

$$x = \Phi(x) = \begin{pmatrix} \phi_1(\lambda_1^{**}, \lambda_2^{**}) \\ \phi_2(\lambda_1^{**}, \lambda_2^{**}) \end{pmatrix}, \quad \text{where} \quad x = \begin{pmatrix} \lambda_1^{**} \\ \lambda_2^{**} \end{pmatrix}. \quad (12)$$

3.1 Strain 1-only Boundary Equilibrium (\mathcal{E}_1)

Setting $\lambda_2^{**} = 0$ in (11) gives the following general form of the strain 1-only boundary equilibrium (denoted by \mathcal{E}_1)

$$\mathcal{E}_1 = \left(S_1^*, E_1^*, I_1^*, R_1^*, 0, 0, 0, 0, 0, 0, 0 \right)$$

where,

$$S_1^* = \frac{\Pi}{\lambda_1^{**} + \mu}, \quad E_1^* = \frac{\lambda_1^{**}\Pi}{K_1(\lambda_1^{**} + \mu)}, \quad I_1^* = \frac{\lambda_1^{**}\Pi\sigma_1}{K_1K_2(\lambda_1^{**} + \mu)}, \quad R_1^* = \frac{\lambda_1^{**}\Pi\sigma_1\gamma_1}{K_1K_2\mu(\lambda_1^{**} + \mu)}.$$

We claim the following.

Theorem 4 *The model (1) has a unique and LAS strain 1-only boundary equilibrium, \mathcal{E}_1 , whenever $\mathcal{R}_{02} < 1 < \mathcal{R}_{01}$.*

Proof. Consider, first of all, the model (1) with strain 2-only (i.e., the case where all components of Strain 1 are removed from the model). The following result can be proven (see Appendix B for the proof):

Lemma 3 *In the absence of Strain 1, the DFE of the model (1) with strain 2-only is GAS in Ω whenever $\mathcal{R}_{02} \leq 1$.*

It is clear from the fixed-point system, (12) with (11), that $\phi_2(\lambda_1^{**}, 0) = 0$. Thus, a fixed-point of $\phi_1(\lambda_1^{**}, \lambda_2^{**})$ is obtained by solving the equation $\phi_1(\lambda_1^{**}, 0) = \lambda_1^{**}$. It follows, after some algebraic manipulations, that λ_1^{**} is the root of the equation

$$x_1\lambda_1^{**} + y_1 = 0, \tag{13}$$

where, $x_1 = \sigma_1(\mu + \gamma_1) + \mu K_2$ and $y_1 = \mu K_1 K_2 (1 - \mathcal{R}_{01})$. Clearly, the coefficient x_1 is always positive, and y_1 is positive (negative) if \mathcal{R}_{01} is less than (greater than) unity, respectively. Further, it should be stated that for \mathcal{E}_1 to exist, it is necessary that strain 2 does not (i.e., $\mathcal{R}_{02} < 1$). Thus, a unique strain 1-only boundary equilibrium exists whenever $\mathcal{R}_{02} < 1 < \mathcal{R}_{01}$.

Let $\mathcal{R}_{02} < 1$ (so that strain 2 dies out, in line with Lemma 3). The local stability property of \mathcal{E}_1 is established by evaluating Jacobian of the system (11) at $(\lambda_1^{**}, \lambda_2^{**})$. This gives.

$$J(\lambda_1^{**}, \lambda_2^{**}) = \begin{bmatrix} \frac{\partial\phi_1(\lambda_1^{**}, \lambda_2^{**})}{\partial\lambda_1^{**}} & \frac{\partial\phi_1(\lambda_1^{**}, \lambda_2^{**})}{\partial\lambda_2^{**}} \\ \frac{\partial\phi_2(\lambda_1^{**}, \lambda_2^{**})}{\partial\lambda_1^{**}} & \frac{\partial\phi_2(\lambda_1^{**}, \lambda_2^{**})}{\partial\lambda_2^{**}} \end{bmatrix},$$

so that,

$$J(\lambda_1^{**}, 0) = \begin{bmatrix} \frac{1}{\mathcal{R}_{01}} & \left. \frac{\partial \phi_1(\lambda_1^{**}, \lambda_2^{**})}{\partial \lambda_2^{**}} \right|_{(\lambda_1^{**}, 0)} \\ 0 & \frac{\mathcal{R}_{02}}{\mathcal{R}_{01}} \end{bmatrix}.$$

For stability, we require $\frac{1}{\mathcal{R}_{01}} < 1$ (i.e., $\mathcal{R}_{01} > 1$) and $\frac{\mathcal{R}_{02}}{\mathcal{R}_{01}} < 1$ (i.e., $\mathcal{R}_{02} < \mathcal{R}_{01}$). Combining all these, and noting that $\mathcal{R}_{02} \leq 1$, shows that the boundary equilibrium, \mathcal{E}_1 , is LAS provided $\mathcal{R}_{02} < 1 < \mathcal{R}_{01}$. \square

The boundary equilibrium \mathcal{E}_1 can be shown to be GAS for a special case as below. Consider the model (1) with the associated disease-induced mortality rates ($\delta_1, \delta_2, \delta_{12}, \delta_{21}$) set to zero. Setting $\delta_1 = \delta_2 = \delta_{12} = \delta_{21} = 0$ in (1) gives $N(t) \rightarrow \frac{\Pi}{\mu}$ as $t \rightarrow \infty$. Let $\tilde{\beta}_i = \frac{\mu\beta_i}{\Pi}$ and $\tilde{\beta}_{ij} = \frac{\mu\beta_{ij}}{\Pi}$, so that

$$\lambda_1 = \tilde{\beta}_1(\eta_1 E_1 + I_1) + \tilde{\beta}_{21}(\eta_{21} E_{21} + I_{21}) \quad \text{and} \quad \lambda_2 = \tilde{\beta}_2(\eta_2 E_2 + I_2) + \tilde{\beta}_{12}(\eta_{12} E_{12} + I_{12}). \quad (14)$$

Furthermore, let

$$\Omega_0 = \left\{ (S, E_1, I_1, R_1, E_2, I_2, R_2, E_{12}, I_{12}, E_{21}, I_{21}, M) \in \Omega : \right. \\ \left. E_1 = I_1 = E_2 = I_2 = E_{12} = I_{12} = E_{21} = I_{21} = 0 \right\}.$$

We claim the following result.

Theorem 5 *Let $\mathcal{R}_{02} < 1$, so that $\lambda_2^{**} = 0$ and strain 2 dies out. The unique strain 1-only boundary equilibrium, \mathcal{E}_1 of the model (1) with (14), is GAS in $\Omega \setminus \Omega_0$, whenever $\mathcal{R}_{02} < 1 < \mathcal{R}_{01}$.*

Proof. Consider the model (1) with (14). Further, let $\mathcal{R}_{02} < 1 < \mathcal{R}_{01}$, so that the boundary equilibrium \mathcal{E}_1 exists (Theorem 4) and strain-2 dies out (Lemma 3). Consider the following non-linear Lyapunov function, of Goh-Volterra type (functions of this type have been used in the mathematical ecology/epidemiology literature, such as those in [7, 22, 26, 28]):

$$\mathcal{F} = S - S^{**} - S^{**} \ln \left(\frac{S}{S^{**}} \right) + E_1 - E_1^{**} - E_1^{**} \ln \left(\frac{E_1}{E_1^{**}} \right) \\ + \left(\frac{K_1 - \tilde{\beta}_1 \eta_1 S^{**}}{\sigma_1} \right) \left[I_1 - I_1^{**} - I_1^{**} \ln \left(\frac{I_1}{I_1^{**}} \right) \right],$$

with Lyapunov derivative,

$$\dot{\mathcal{F}} = \dot{S} - \frac{S^{**}}{S} \dot{S} + \dot{E}_1 - \frac{E_1^{**}}{E_1} \dot{E}_1 + \left(\frac{K_1 - \tilde{\beta}_1 \eta_1 S^{**}}{\sigma_1} \right) \left(\dot{I}_1 - \frac{I_1^{**}}{I_1} \dot{I}_1 \right),$$

so that,

$$\begin{aligned} \dot{\mathcal{J}} &= \Pi - \lambda_1 S - \mu S - \frac{S^{**}}{S} (\Pi - \lambda_1 S - \mu S) + \lambda_1 S - K_1 E_1 - \frac{E_1^{**}}{E_1} (\lambda_1 S - K_1 E_1) \\ &+ \left(\frac{K_1 - \tilde{\beta}_1 \eta_1 S^{**}}{\sigma_1} \right) \left[\sigma_1 E_1 - K_2 I_1 - \frac{I_1^{**}}{I_1} (\sigma_1 E_1 - K_2 I_1) \right]. \end{aligned}$$

Hence,

$$\begin{aligned} \dot{\mathcal{J}} &= \Pi \left(1 - \frac{S^{**}}{S} \right) + \mu S^{**} \left(1 - \frac{S}{S^{**}} \right) + \tilde{\beta}_1 S^{**} I_1 + \tilde{\beta}_2 S^{**} I_2 \\ &- \tilde{\beta}_1 \eta_1 S E_1^{**} - \tilde{\beta}_1 S I_1 \frac{E_1^{**}}{E_1} + K_1 E_1^{**} - \frac{K_1 K_2 I_1}{\sigma_1} + \frac{\tilde{\beta}_1 \eta_1 S^{**} K_2 I_1}{\sigma_1} \\ &- K_1 E_1 \frac{I_1^{**}}{I_1} + \frac{K_1 K_2 I_1^{**}}{\sigma_1} + \tilde{\beta}_1 \eta_1 S^{**} E_1 \frac{I_1^{**}}{I_1} - \frac{\tilde{\beta}_1 \eta_1 S^{**} K_2 I_1^{**}}{\sigma_1}. \end{aligned} \quad (15)$$

It can be shown from the model (1) with (14) and $\lambda_2^{**} = 0$, at endemic steady-state, that

$$\begin{aligned} \Pi &= \tilde{\beta}_1 (\eta_1 E_1^{**} + I_1^{**}) S^{**} + \mu S^{**}, \\ K_1 E_1^{**} &= \tilde{\beta}_1 (\eta_1 E_1^{**} + I_1^{**}) S^{**}, \quad \sigma_1 E_1^{**} = K_2 I_1^{**}, \quad \gamma_1 I_1^{**} = \mu R_1^{**}. \end{aligned} \quad (16)$$

Substituting the relations in (16) into (15) gives

$$\begin{aligned} \dot{\mathcal{J}} &= [\tilde{\beta}_1 \eta_1 S^{**} E_1^{**} + \tilde{\beta}_1 S^{**} I_1^{**} + \mu S^{**}] \left(1 - \frac{S^{**}}{S} \right) + \mu S^{**} \left(1 - \frac{S}{S^{**}} \right) \\ &- \tilde{\beta}_1 \eta_1 S E_1^{**} - \tilde{\beta}_1 S I_1 \frac{E_1^{**}}{E_1} \tilde{\beta}_1 \eta_1 S^{**} E_1^{**} + \tilde{\beta}_1 S^{**} I_1^{**} - \tilde{\beta}_1 \eta_1 S^{**} E_1 \frac{I_1^{**}}{I_1} \\ &- \tilde{\beta}_1 S^{**} I_1 \frac{E_1 I_1^{**}}{E_1^{**} I_1} + \tilde{\beta}_1 S^{**} I_1^{**}, \end{aligned}$$

which can be simplified to,

$$\begin{aligned} &= \mu S^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \right) + \tilde{\beta}_1 \eta_1 S^{**} E_1^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \right) \\ &+ \tilde{\beta}_1 S^{**} I_1^{**} \left(3 - \frac{S^{**}}{S} - \frac{E_1 I_1^{**}}{E_1^{**} I_1} - \frac{I_1 E_1^{**} S}{I_1^{**} E_1 S^{**}} \right). \end{aligned} \quad (17)$$

Finally, since the arithmetic mean exceeds the geometric mean, the following inequalities from (17) hold:

$$2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \leq 0, \quad 3 - \frac{S^{**}}{S} - \frac{E_1 I_1^{**}}{E_1^{**} I_1} - \frac{I_1 E_1^{**} S}{I_1^{**} E_1 S^{**}} \leq 0.$$

Thus, $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_{01} > 1$. Hence, \mathcal{F} is a Lyapunov function on Ω . The proof is completed as in the proof of Theorem 3. \square

Figures 2A-B depict simulations for the case where $\mathcal{R}_{02} < 1 < \mathcal{R}_{01}$, showing the persistence of strain 1, while strain 2 dies out.

3.2 Strain 2-only Boundary Equilibrium (\mathcal{E}_2)

Setting $\lambda_1^{**} = 0$ in (11) gives the following general form of the strain 2-only boundary equilibrium (denoted by \mathcal{E}_2)

$$\mathcal{E}_2 = \left(S_2^*, 0, 0, 0, E_2^*, I_2^*, R_2^*, 0, 0, 0, 0, 0 \right),$$

where,

$$S_2^* = \frac{\Pi}{\lambda_2^{**} + \mu}, \quad E_2^* = \frac{\lambda_2^{**}\Pi}{K_3(\lambda_2^{**} + \mu)}, \quad I_2^* = \frac{\lambda_2^{**}\Pi\sigma_2}{K_3K_4(\lambda_2^{**} + \mu)}, \quad R_2^* = \frac{\lambda_2^{**}\Pi\sigma_2\gamma_2}{K_3K_4\mu(\lambda_2^{**} + \mu)}.$$

The following result can be shown using the approach in Section 3.1.

Theorem 6 *The model (1) has a unique and LAS strain 2-only boundary equilibrium, \mathcal{E}_2 , whenever $\mathcal{R}_{01} < 1 < \mathcal{R}_{02}$.*

Furthermore, the result below holds (see Appendix C for the proof):

Theorem 7 *The unique strain 2-only boundary equilibrium \mathcal{E}_2 , of the model (1) with (14), is GAS in $\Omega \setminus \Omega_0$, whenever $\mathcal{R}_{01} < 1 < \mathcal{R}_{02}$.*

Numerical simulations for the case when $\mathcal{R}_{01} < 1 < \mathcal{R}_{02}$, depicted in Figure 3, show that strain 1 dies out while strain 2 establishes itself at steady-state. Thus, the model undergoes competitive exclusion, with Strain i driving out Strain j if $\mathcal{R}_{0i} > 1 > \mathcal{R}_{0j}$ ($i, j = 1, 2; i \neq j$). It should be mentioned that the results for the boundary equilibria of the model (1) are consistent with those reported in [19, 20, 23], associated with the modeling of the spread of dengue fever. The numerical simulations carried out in this study are based on using the parameter values tabulated in Table 2, which are consistent with the transmission dynamics of influenza (in particular, $1.5 < \mathcal{R}_{01}, \mathcal{R}_{02} < 5.4$ [15, 16, 17, 18, 21, 26, 35, 36]).

Exploring the possible existence of co-existence equilibria of the model (1) theoretically proved to be quite challenging (due to its large size and nonlinearity). However, numerical simulations suggest that the model (1) has a co-existence (endemic) equilibrium (where both strains co-exist) whenever $\mathcal{R}_{0i} > \mathcal{R}_{0j} > 1; i, j = 1, 2; i \neq j$.

Furthermore, although the strain with the higher reproduction number dominates the other, the two strains always co-exist (i.e., the strain with the higher reproduction number does not drive out the other strain to extinction) as depicted in Figures 4A and B. The two strains co-exist for the case when $\mathcal{R}_{0i} = \mathcal{R}_{0j} > 1$ ($i \neq j$) (Figure 4C). This suggests the following conjecture.

Conjecture 1 *The model (1) has a unique co-existence equilibrium whenever $\mathcal{R}_{0i} > \mathcal{R}_{0j} > 1$.*

It is worth mentioning, unlike in Theorems 5 and 7, that the global-asymptotic stability of the associated boundary equilibria of the model considered in [29] was not established.

3.3 Existence and Stability of Co-existence (Endemic) Equilibria: Special Case $\theta_1 = \theta_2 = 0$

The existence of co-existence (endemic) equilibrium of the model (1) is explored for the special case where infection with one strain confers complete immunity against infection with the other strain (i.e. $\theta_1 = \theta_2 = 0$). Consider the model (1) with $\theta_1 = \theta_2 = 0$ (or, equivalently, the reduced model (7)). Let $\mathcal{E}_2 = (S^{**}, E_1^{**}, I_1^{**}, R_1^{**}, E_2^{**}, I_2^{**}, R_2^{**})$ represent any arbitrary equilibrium of the reduced model (7). It should be recalled that, in this setting,

$$\lambda_1^{**} = \frac{\beta_1(\eta_2 E_1^{**} + I_1^{**})}{N^{**}} \quad \text{and} \quad \lambda_2^{**} = \frac{\beta_2(\eta_2 E_2^{**} + I_2^{**})}{N^{**}}. \quad (18)$$

Substituting the expressions in (11) into (18) gives,

$$\lambda_1^{**} = \frac{\mu K_3 K_4 \lambda_1^{**} \beta_1 (\eta_1 K_2 + \sigma_1)}{\mu K_1 K_2 K_3 K_4 + \lambda_1^{**} Q_1 + \lambda_2^{**} Q_2} \quad \text{and} \quad \lambda_2^{**} = \frac{\mu K_1 K_2 \lambda_2^{**} \beta_2 (\eta_2 K_4 + \sigma_2)}{\mu K_1 K_2 K_3 K_4 + \lambda_1^{**} Q_1 + \lambda_2^{**} Q_2}, \quad (19)$$

where, $Q_1 = K_3 K_4 [\sigma_1 (\mu + \gamma_1) + K_2 \mu]$ and $Q_2 = K_1 K_2 [\sigma_2 (\mu + \gamma_2) + K_4 \mu]$.

The expressions in (19) can be re-written as:

$$\lambda_1^{**} = \frac{\mu K_3 K_4 \lambda_1^{**} \beta_1 (\eta_1 K_2 + \sigma_1)}{\mu K_1 K_2 K_3 K_4 + \lambda_1^{**} Q_1 + \lambda_2^{**} Q_2} \equiv \frac{\lambda_1^{**} \mu K_1 K_2 K_3 K_4 \mathcal{R}_{01}}{\mu K_1 K_2 K_3 K_4 + \lambda_1^{**} Q_1 + \lambda_2^{**} Q_2}, \quad (20)$$

$$\lambda_2^{**} = \frac{\mu K_1 K_2 \lambda_2^{**} \beta_2 (\eta_2 K_4 + \sigma_2)}{\mu K_1 K_2 K_3 K_4 + \lambda_1^{**} Q_1 + \lambda_2^{**} Q_2} \equiv \frac{\lambda_2^{**} \mu K_1 K_2 K_3 K_4 \mathcal{R}_{02}}{\mu K_1 K_2 K_3 K_4 + \lambda_1^{**} Q_1 + \lambda_2^{**} Q_2}.$$

It follows from (20) that

$$\lambda_1^{**} Q_1 + \lambda_2^{**} Q_2 = \mu K_1 K_2 K_3 K_4 (\mathcal{R}_{01} - 1), \quad (21)$$

$$\lambda_1^{**} Q_1 + \lambda_2^{**} Q_2 = \mu K_1 K_2 K_3 K_4 (\mathcal{R}_{02} - 1).$$

Since the left-hand sides of the equations in (21) are always positive, it is necessary that $\mathcal{R}_{01} > 1$ and $\mathcal{R}_{02} > 1$. If $\mathcal{R}_{01} \neq \mathcal{R}_{02}$, then the system (21) is inconsistent (and there is no positive co-existence equilibrium in this case). Hence, for the two equations in (21) to be consistent, it is necessary that $\mathcal{R}_{01} = \mathcal{R}_{02} > 1$. It follows then that a continuum (family) of endemic equilibria will arise in this case. That is, setting $\mathcal{R}_{01} = \mathcal{R}_{02} = \mathcal{R}_{0i} > 1$ implies that

$$\lambda_1^{**} Q_1 + \lambda_2^{**} Q_2 = \mu K_1 K_2 K_3 K_4 (\mathcal{R}_{0i} - 1), \quad (22)$$

so that $0 < \lambda_1^{**} < \frac{\mu K_1 K_2 K_3 K_4 (\mathcal{R}_{01} - 1)}{Q_1}$ and $0 < \lambda_2^{**} < \frac{\mu K_1 K_2 K_3 K_4 (\mathcal{R}_{02} - 1)}{Q_2}$. This result is summarized below.

Theorem 8 *The model (1) with $\theta_1 = \theta_2 = 0$ (or, equivalently, (7)) has a continuum of positive co-existence equilibria, denoted by E_c^n ($n \in \mathbb{Z}_+$), whenever the following conditions hold*

(i) $\mathcal{R}_{01} = \mathcal{R}_{02} = \mathcal{R}_{0i} > 1$,

(ii) $0 < \lambda_1^{**} < \frac{\mu K_1 K_2 K_3 K_4 (\mathcal{R}_{01} - 1)}{Q_1}$,

(iii) $0 < \lambda_2^{**} < \frac{\mu K_1 K_2 K_3 K_4 (\mathcal{R}_{02} - 1)}{Q_2}$,

and no co-existence equilibria otherwise.

We claim the following result.

Theorem 9 *Let $\mathcal{R}_c^n = \frac{L_0 + \sqrt{L_0^2 - 4L_1}}{2}$, ($n \in \mathbb{Z}_+$), with*

$$L_0 = \left(\frac{\partial \phi_1}{\partial \lambda_1^{**}} + \frac{\partial \phi_2}{\partial \lambda_2^{**}} \right) \Big|_{(\lambda_1^{**}, \lambda_2^{**})} \quad \text{and} \quad L_1 = \left(\frac{\partial \phi_1}{\partial \lambda_1^{**}} \frac{\partial \phi_2}{\partial \lambda_2^{**}} - \frac{\partial \phi_1}{\partial \lambda_2^{**}} \frac{\partial \phi_2}{\partial \lambda_1^{**}} \right) \Big|_{(\lambda_1^{**}, \lambda_2^{**})}.$$

Then, the family of co-existence equilibria, E_c^n , of (7) is LAS whenever $\mathcal{R}_c^n < 1$, for each $n \in \mathbb{Z}_+$.

Proof. Evaluating the Jacobian of Φ at each $(\lambda_1^{**}, \lambda_2^{**})$ in the regions (i) to (iii), gives

$$J(\lambda_1^{**}, \lambda_2^{**}) = \begin{bmatrix} \frac{\partial \phi_1(\lambda_1^{**}, \lambda_2^{**})}{\partial \lambda_1^{**}} & \frac{\partial \phi_1(\lambda_1^{**}, \lambda_2^{**})}{\partial \lambda_2^{**}} \\ \frac{\partial \phi_2(\lambda_1^{**}, \lambda_2^{**})}{\partial \lambda_1^{**}} & \frac{\partial \phi_2(\lambda_1^{**}, \lambda_2^{**})}{\partial \lambda_2^{**}} \end{bmatrix},$$

with eigenvalues given by the roots of the characteristic polynomials

$$\Lambda^2 - \Lambda L_0 + L_1 = 0.$$

It can be shown that the dominant eigenvalue of $J(\lambda_1^{**}, \lambda_2^{**})$ is $\Lambda = |\mathcal{R}_c^n|$. Thus, the family of co-existence endemic equilibria, E_c^n , is LAS whenever $|\mathcal{R}_c^n| < 1$ for each n . \square

Figures 5A and B illustrate the existence of the continuum of co-existence equilibria when the two reproduction numbers are equal and greater than unity ($\mathcal{R}_{01} = \mathcal{R}_{02} > 1$). It is worth stating that the phenomenon of having infinitely many co-existence equilibria has been observed in other epidemiological settings, such as in the study of the dynamics of multiple strains of TB [11], dengue fever [23] and HIV [39].

3.3.1 Global stability of continuum of co-existence equilibria: special case $\delta_1 = \delta_2 = 0$

Here, the global stability of the continuum of co-existence equilibria of the model (7) is given for the special case where the disease-induced mortality rates (δ_1 and δ_2) are set to zero. Setting $\delta_1 = \delta_2 = 0$ in (7) shows that $N \rightarrow \frac{\Pi}{\mu}$ as $t \rightarrow \infty$. Furthermore, let $\tilde{\beta}_1 = \frac{\beta_1 \mu}{\Pi}$ and $\tilde{\beta}_2 = \frac{\beta_2 \mu}{\Pi}$. It follows from (7), with $N = \Pi/\mu$, that

$$\lambda_1 = \tilde{\beta}_1(\eta_1 E_1 + I_1) \quad \text{and} \quad \lambda_2 = \tilde{\beta}_2(\eta_2 E_2 + I_2). \quad (23)$$

Define

$$\Gamma_0 = \left\{ (S, E_1, I_1, R_1, E_2, I_2, R_2) \in \Gamma : E_1 = I_1 = E_2 = I_2 = 0 \right\},$$

the stable manifold of the DFE (\mathcal{E}_0^r). We claim the following.

Theorem 10 *Consider the model (7) with (23). The continuum of co-existence equilibria of the model is GAS in $\Gamma \setminus \Gamma_0$ if $\mathcal{R}_{01} = \mathcal{R}_{02} > 1$.*

Proof. Consider the model (7) with (23) and $\mathcal{R}_{01} = \mathcal{R}_{02} = \mathcal{R}_0 > 1$, so that the continuum of equilibria of the model exists. Further, consider the following Lyapunov function:

$$\begin{aligned} \mathcal{F} = & S - S^{**} - S^{**} \ln \left(\frac{S}{S^{**}} \right) + E_1 - E_1^{**} - E_1^{**} \ln \left(\frac{E_1}{E_1^{**}} \right) + E_2 - E_2^{**} - E_2^{**} \ln \left(\frac{E_2}{E_2^{**}} \right) \\ & + \left(\frac{K_1 - \tilde{\beta}_1 \eta_1 S^{**}}{\sigma_1} \right) \left[I_1 - I_1^{**} - I_1^{**} \ln \left(\frac{I_1}{I_1^{**}} \right) \right] + \left(\frac{K_3 - \tilde{\beta}_2 \eta_2 S^{**}}{\sigma_2} \right) \left[I_2 - I_2^{**} - I_2^{**} \ln \left(\frac{I_2}{I_2^{**}} \right) \right], \end{aligned}$$

with Lyapunov derivative,

$$\begin{aligned}\dot{\mathcal{F}} &= \dot{S} - \frac{S^{**}}{S}\dot{S} + \dot{E}_1 - \frac{E_1^{**}}{E_1}\dot{E}_1 + \dot{E}_2 - \frac{E_2^{**}}{E_2}\dot{E}_2 + \left(\frac{K_1 - \tilde{\beta}_1\eta_1 S^{**}}{\sigma_1}\right) \left(\dot{I}_1 - \frac{I_1^{**}}{I_1}\dot{I}_1\right) \\ &+ \left(\frac{K_3 - \tilde{\beta}_2\eta_2 S^{**}}{\sigma_2}\right) \left(\dot{I}_2 - \frac{I_2^{**}}{I_2}\dot{I}_2\right),\end{aligned}$$

so that,

$$\begin{aligned}\dot{\mathcal{F}} &= \Pi - \lambda_1 S + \lambda_2 S - \mu S - \frac{S^{**}}{S}(\Pi - \lambda_1 S + \lambda_2 S - \mu S) \\ &+ \lambda_1 S - K_1 E_1 - \frac{E_1^{**}}{E_1}(\lambda_1 S - K_1 E_1) + \lambda_2 S - K_3 E_2 - \frac{E_2^{**}}{E_2}(\lambda_2 S - K_3 E_2) \\ &+ \left(\frac{K_1 - \tilde{\beta}_1\eta_1 S^{**}}{\sigma_1}\right) \left[\sigma_1 E_1 - K_2 I_1 - \frac{I_1^{**}}{I_1}(\sigma_1 E_1 - K_2 I_1)\right] \\ &+ \left(\frac{K_3 - \tilde{\beta}_2\eta_2 S^{**}}{\sigma_2}\right) \left[\sigma_2 E_2 - K_4 I_2 - \frac{I_2^{**}}{I_2}(\sigma_2 E_2 - K_4 I_2)\right].\end{aligned}$$

Hence,

$$\begin{aligned}\dot{\mathcal{F}} &= \Pi \left(1 - \frac{S^{**}}{S}\right) + \mu S^{**} \left(1 - \frac{S}{S^{**}}\right) + \tilde{\beta}_1 S^{**} I_1 + \tilde{\beta}_2 S^{**} I_2 \\ &- \tilde{\beta}_1 \eta_1 S E_1^{**} - \tilde{\beta}_1 S I_1 \frac{E_1^{**}}{E_1} + K_1 E_1^{**} - \tilde{\beta}_2 \eta_2 S E_2^{**} - \tilde{\beta}_2 S I_2 \frac{E_2^{**}}{E_2} + K_3 E_2^{**} \\ &- \frac{K_1 K_2 I_1}{\sigma_1} + \frac{\tilde{\beta}_1 \eta_1 S^{**} K_2 I_1}{\sigma_1} - K_1 E_1 \frac{I_1^{**}}{I_1} + \frac{K_1 K_2 I_1^{**}}{\sigma_1} + \tilde{\beta}_1 \eta_1 S^{**} E_1 \frac{I_1^{**}}{I_1} - \frac{\tilde{\beta}_1 \eta_1 S^{**} K_2 I_1^{**}}{\sigma_1} \\ &- \frac{K_3 K_4 I_2}{\sigma_2} + \frac{\tilde{\beta}_2 \eta_2 S^{**} K_4 I_2}{\sigma_2} - K_3 E_2 \frac{I_2^{**}}{I_2} + \frac{K_3 K_4 I_2^{**}}{\sigma_2} + \tilde{\beta}_2 \eta_2 S^{**} E_2 \frac{I_2^{**}}{I_2} - \frac{\tilde{\beta}_2 \eta_2 S^{**} K_4 I_2^{**}}{\sigma_2}.\end{aligned}\quad (24)$$

It can be shown from the model (7) with (23), at endemic steady-state, that

$$\begin{aligned}\Pi &= \tilde{\beta}_1(\eta_1 E_1^{**} + I_1^{**})S^{**} + \tilde{\beta}_2(\eta_2 E_2^{**} + I_2^{**})S^{**} + \mu S^{**}, \\ K_1 E_1^{**} &= \tilde{\beta}_1(\eta_1 E_1^{**} + I_1^{**})S^{**}, \quad \sigma_1 E_1^{**} = K_2 I_1^{**}, \quad \gamma_1 I_1^{**} = \mu R_1^{**} \\ K_3 E_2^{**} &= \tilde{\beta}_2(\eta_2 E_2^{**} + I_2^{**})S^{**}, \quad \sigma_2 E_2^{**} = K_4 I_2^{**}, \quad \gamma_2 I_2^{**} = \mu R_2^{**}.\end{aligned}\quad (25)$$

Substituting the relations in (25) into (24) gives

$$\begin{aligned}\dot{\mathcal{F}} &= [\tilde{\beta}_1 \eta_1 S^{**} E_1^{**} + \tilde{\beta}_1 S^{**} I_1^{**} + \tilde{\beta}_2 \eta_2 S^{**} E_2^{**} + \tilde{\beta}_2 S^{**} I_2^{**} + \mu S^{**}] \left(1 - \frac{S^{**}}{S}\right) + \\ &\mu S^{**} \left(1 - \frac{S}{S^{**}}\right) - \tilde{\beta}_1 \eta_1 S E_1^{**} - \tilde{\beta}_1 S I_1 \frac{E_1^{**}}{E_1} \tilde{\beta}_1 \eta_1 S^{**} E_1^{**} + \tilde{\beta}_1 S^{**} I_1^{**} - \tilde{\beta}_2 \eta_2 S E_2^{**} - \\ &\tilde{\beta}_2 S I_2 \frac{E_2^{**}}{E_2} + \tilde{\beta}_2 S^{**} \eta_2 E_2^{**} + \tilde{\beta}_2 S^{**} I_2^{**} - \tilde{\beta}_1 \eta_1 S^{**} E_1^{**} \frac{I_1}{I_1^{**}} - \tilde{\beta}_1 S^{**} I_1^{**} \frac{E_1 I_1^{**}}{E_1^{**} I_1} + \\ &\tilde{\beta}_1 S^{**} I_1^{**} - \tilde{\beta}_2 S^{**} I_2^{**} \frac{E_2 I_2^{**}}{E_2^{**} I_2} + \tilde{\beta}_2 S^{**} I_2^{**},\end{aligned}\quad (26)$$

which can be simplified to,

$$\begin{aligned}
&= \mu S^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \right) + \tilde{\beta}_1 \eta_1 S^{**} E_1^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \right) + \tilde{\beta}_2 \eta_2 S^{**} E_2^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \right) \\
&+ \tilde{\beta}_1 S^{**} I_1^{**} \left(3 - \frac{S^{**}}{S} - \frac{E_1 I_1^{**}}{E_1^{**} I_1} - \frac{I_1 E_1^{**} S}{I_1^{**} E_1 S^{**}} \right) + \tilde{\beta}_2 S^{**} I_2^{**} \left(3 - \frac{S^{**}}{S} - \frac{E_2 I_2^{**}}{E_2^{**} I_2} - \frac{I_2 E_2^{**} S}{I_2^{**} E_2 S^{**}} \right).
\end{aligned} \tag{27}$$

Finally, since the arithmetic mean exceeds the geometric mean, the following inequalities from (27) hold:

$$\begin{aligned}
2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} &\leq 0, \quad 3 - \frac{S^{**}}{S} - \frac{E_1 I_1^{**}}{E_1^{**} I_1} - \frac{I_1 E_1^{**} S}{I_1^{**} E_1 S^{**}} \leq 0, \\
3 - \frac{S^{**}}{S} - \frac{E_2 I_2^{**}}{E_2^{**} I_2} - \frac{I_2 E_2^{**} S}{I_2^{**} E_2 S^{**}} &\leq 0.
\end{aligned}$$

Furthermore, since I_1^{**} and I_2^{**} approaches their endemic state as $t \rightarrow \infty$, it follows that, $R_1(t) \rightarrow \frac{\gamma_1 I_1^{**}}{\mu}$ and $R_2(t) \rightarrow \frac{\gamma_2 I_2^{**}}{\mu}$. Thus, $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_{01} = \mathcal{R}_{02} = \mathcal{R}_0 > 1$. Hence, \mathcal{F} is a Lyapunov function on Γ . The proof is completed as in the proof of Theorem 3. \square

It should be emphasized that the global asymptotic stability results in Section 3 were not shown in some of the earlier related studies such as those in [23, 29].

Conclusions

A new deterministic model for the transmission dynamics of two strains of influenza is designed and rigorously analyzed. Some of the theoretical and epidemiological findings of the study are:

- (i) The model (1) has a locally-asymptotically stable disease-free equilibrium whenever the *associated reproduction number* (\mathcal{R}_0) is less than unity. This model undergoes the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium. This phenomenon is caused by the incomplete cross-immunity property of the model. For the case when infection with one strain confers complete immunity against the other, the DFE of the model is shown to be globally-asymptotically stable when $\mathcal{R}_0 < 1$.
- (ii) For the case when infection with one strain confers incomplete immunity against the other, the model (1) exhibits the phenomenon of competitive exclusion, where strain i drives out strain j whenever the *associated reproduction number* $\mathcal{R}_{0i} > 1 > \mathcal{R}_{0j}$, where $(i, j = 1, 2; i \neq j)$. Global asymptotic stability properties of

the two boundary equilibria are established for the case where disease-induced mortality is zero.

- (iii) Numerical simulations of the model (with partial cross-immunity) show that the two strains coexist with strain i dominating, but not driving out strain j , if $\mathcal{R}_{0i} > \mathcal{R}_{0j} > 1$.
- (iv) The model can have a continuum of co-existence equilibria when $\mathcal{R}_0 > 1$ for the case when infection with one strain confers complete immunity against the other strain. The continuum of equilibria is shown to be globally-asymptotically stable for a special case.

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Appendix A: Proof of Theorem 2

Proof. Suppose

$$\mathcal{E}_e = (S^{**}, E_1^{**}, I_1^{**}, R_1^{**}, E_2^{**}, I_2^{**}, R_2^{**}, E_{12}^{**}, I_{12}^{**}, E_{21}^{**}, I_{21}^{**}, M^{**}) \quad (28)$$

represents any arbitrary endemic equilibrium of the model (1) (that is, an equilibrium in which at least one of the infected components is non-zero). The existence of backward bifurcation will be explored using the Centre Manifold theory [10, 13, 41]. To apply this theory, it is convenient to carry out the following change of variables. Let $S = x_1$, $E_1 = x_2$, $I_1 = x_3$, $R_1 = x_4$, $E_2 = x_5$, $I_2 = x_6$, $R_2 = x_7$, $E_{12} = x_8$, $I_{12} = x_9$, $E_{21} = x_{10}$, $I_{21} = x_{11}$, and $M = x_{12}$, so that $N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8 + x_9 + x_{10} + x_{11} + x_{12}$. Further, by using the vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12})^T$, the model (1) can be written in the form $\frac{dX}{dt} = F(X)$, with $(f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10}, f_{11}, f_{12})^T$, as follows:

$$\begin{aligned} \frac{dx_1}{dt} &\equiv f_1 = \Pi + \xi x_{12} - \lambda_1 x_1 - \lambda_2 x_1 - \mu x_1, \\ \frac{dx_2}{dt} &\equiv f_2 = \lambda_1 x_1 - K_1 x_2, \\ \frac{dx_3}{dt} &\equiv f_3 = \sigma_1 x_2 - K_2 x_3, \\ \frac{dx_4}{dt} &\equiv f_4 = \gamma_1 x_3 - \theta_2 \lambda_2 x_4 - \mu x_4, \\ \frac{dx_5}{dt} &\equiv f_5 = \lambda_2 x_1 - K_3 x_5, \\ \frac{dx_6}{dt} &\equiv f_6 = \sigma_2 x_5 - K_4 x_6, \\ \frac{dx_7}{dt} &\equiv f_7 = \gamma_2 x_6 - \theta_1 \lambda_1 x_7 - \mu x_7, \\ \frac{dx_8}{dt} &\equiv f_8 = \theta_2 \lambda_2 x_4 - K_5 x_8, \\ \frac{dx_9}{dt} &\equiv f_9 = \sigma_{12} x_8 - K_6 x_9, \\ \frac{dx_{10}}{dt} &\equiv f_{10} = \theta_1 \lambda_1 x_7 - K_7 x_{10}, \\ \frac{dx_{11}}{dt} &\equiv f_{11} = \sigma_{21} x_{10} - K_8 x_{11}, \\ \frac{dx_{12}}{dt} &\equiv f_{12} = \gamma_{12} x_9 + \gamma_{21} x_{11} - K_9 x_{12}, \end{aligned} \quad (29)$$

with the forces of infection given by

$$\lambda_1 = \frac{\beta_1(\eta_1 x_2 + x_3) + \beta_{21}(\eta_{21} x_{10} + x_{11})}{\sum_{i=1}^{12} x_i}, \quad \lambda_2 = \frac{\beta_2(\eta_2 x_5 + x_6) + \beta_{12}(\eta_{12} x_8 + x_9)}{\sum_{i=1}^{12} x_i}.$$

Consider the case when $\mathcal{R}_0 = 1$. Suppose, further, that $\beta_1 = \beta_1^*$ is chosen as a bifurcation parameter. Solving for $\beta_1 = \beta_1^*$ from $\mathcal{R}_0 = 1$ in (5) gives

$$\beta_1 = \beta_1^* = \frac{K_1 K_2}{\eta_1 K_2 + \sigma_1}.$$

The Jacobian of the transformed system (1) at the DFE, \mathcal{E}_0 with $\beta_1 = \beta_1^*$, is given by

$$J^* = \begin{bmatrix} -\mu & -\beta_1^* \eta_1 & -\beta_1^* & 0 & -\beta_2 \eta_2 & -\beta_2 & 0 & -\beta_3 \eta_3 & -\beta_3 & \beta_4 \eta_4 & -\beta_4 & \xi \\ 0 & \beta_1^* \eta_1 - K_1 & \beta_1^* & 0 & 0 & 0 & 0 & 0 & 0 & \beta_4 \eta_4 & \beta_2 & 0 \\ 0 & \sigma_1 & -K_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_1 & -\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_2 \eta_2 - K_3 & \beta_2 & 0 & \beta_3 \eta_3 & \beta_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma_2 & -K_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_2 & -\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -K_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_3 & -K_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & K_7 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_4 & -K_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_3 & \gamma_4 & -K_9 \end{bmatrix},$$

where $K_9 = \mu + \xi$. The Jacobian (J^*) of the linearized system has a simple zero eigenvalue (with all other eigenvalues having negative real part). Hence, the Centre Manifold Theory [10, 13, 41] can be used to analyse the dynamics of the system (29). In particular, Theorem 4.5 in [13] will be used.

In order to apply Theorem 4.5 in [13], the following computation are necessary. The right eigenvector of $J(\mathcal{E}_0)|_{\beta_1=\beta_1^*}$ is given by $\mathbf{w} = (\omega_1, \omega_2, \dots, \omega_{12})^T$,

where,

$$\begin{aligned} \omega_1 &= - \left[(\eta_1 K_2 + \sigma_1) \frac{\beta_1^*}{\sigma_1} + (\eta_2 K_4 + \sigma_2) \frac{\beta_2 \omega_6}{\sigma_2} \right] \frac{1}{\mu}, \\ \omega_2 &= \frac{K_2}{\sigma_1}, \omega_3 = 1, \omega_4 = \frac{\gamma_1}{\mu}, \omega_5 = \frac{K_4 \omega_6}{\sigma_2}, \omega_6 = \omega_6, \omega_7 = \frac{\gamma_2 \omega_6}{\mu}, \\ \omega_8 &= \omega_9 = \omega_{10} = \omega_{11} = \omega_{12} = 0. \end{aligned} \tag{30}$$

Similarly, the components of the left eigenvector of J^* (corresponding to the zero eigenvalue), denoted by $\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12}]$, satisfying $\mathbf{v} \cdot \mathbf{w} = 1$, are given by,

$$\begin{aligned} v_1 &= 0, v_2 = \frac{\sigma_1 K_1}{K_1 K_2 + \sigma_1 \beta_1^*}, v_3 = \frac{\beta_1^* v_2}{K_1}, v_4 = 0, v_5 = 0, v_6 = 0, \\ v_7 &= 0, v_8 = 0, v_9 = 0, v_{10} = \frac{(K_8 \beta_4 \eta_4 + \sigma_4) v_2}{K_7 K_8}, v_{11} = \frac{\beta_4 v_2}{K_8}, v_{12} = 0. \end{aligned} \tag{31}$$

Computation of bifurcation coefficient a

It can be shown, by computing the associated non-zero partial derivatives of $F(x)$ (evaluated at the DFE \mathcal{E}_0) that

$$a = \frac{2\mu}{\Pi} \left[\frac{\beta_1^*(\eta_1 K_2 + \sigma_1)}{\sigma_1} + \frac{\beta_2(\eta_2 K_4 + \sigma_2)}{\sigma_2} \right] \times \left\{ \left[\frac{\theta_2 \beta_{21}(\eta_{21} K_8 + \sigma_{21})}{\sigma_{21}} + \frac{\theta_1 \beta_{12}(\eta_{12} K_6 + \sigma_{12})}{\sigma_{12}} \right] - 2 \left(2 + \frac{K_2}{\sigma_1} + \frac{K_4}{\sigma_2} + \frac{\gamma_1 + \gamma_2}{\mu} \right) \right\}. \quad (32)$$

Computation of bifurcation coefficient b

Substituting the eigenvectors \mathbf{v} and \mathbf{w} and the respective partial derivatives (evaluated at the DFE \mathcal{E}_0) into the expression

$$b = \sum_{k,i=1}^{12} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_1^*}(0,0) = \frac{\eta_1 K_2 + \sigma_1}{\sigma_1} > 0.$$

Since the coefficient b is automatically positive, it follows that the model (1) (or its transformed equivalent (29)) will undergo backward bifurcation if the coefficient a , given by (32), is positive. \square

Appendix B: Proof of Lemma 3

Proof. Consider the the model (1) with strain 1-only (i.e., let $R_{02} < 1$, so that strain 2 dies out as in Theorem 4). Further, let $\mathcal{R}_{01} > 1$ Lyapunov function:

$$\mathcal{F} = \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) E_1 + I_1, \quad (33)$$

with Lyapunov derivative given by

$$\begin{aligned}
\dot{\mathcal{F}} &= \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) \dot{E}_1 + \dot{I}_1, \\
&= \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) \left[\frac{\beta_1 (\eta_1 E_1 + I_1)}{N} S - K_1 E_1 \right] + \sigma_1 E_1 - K_2 I_1 \\
&\leq \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) \left[\beta_1 (\eta_1 E_1 + I_1) - K_1 E_1 \right] + \sigma_1 E_1 - K_2 I_1, \text{ since } S \leq N \text{ in } \Omega, \\
&= \beta_1 \left(\frac{\eta_1 K_2 + \sigma_1}{K_1} \right) (\eta_1 E_1 + I_1) - (\eta_1 K_2 + \sigma_1) E_1 + \sigma_1 E_1 - K_2 I_1, \\
&= K_2 \mathcal{R}_{01} (\eta_1 E_1 + I_1) - \eta_1 K_2 E_1 - K_2 I_1 = K_2 \mathcal{R}_{01} (\eta_1 E_1 + I_1) - (\eta_1 E_1 + I_1) K_2, \\
&= K_2 (\eta_1 E_1 + I_1) (\mathcal{R}_{01} - 1) \leq 0. \text{ if } \mathcal{R}_{01} > 1
\end{aligned}$$

The proof is completed using the same approach as in the proof of Theorem 3. \square

Appendix C: Proof of Theorem 7

Proof. Consider the model (1) with (14), $\lambda_1^{**} = 0$ and $\mathcal{R}_{01} < 1 < \mathcal{R}_{02}$ (so that the associated unique strain 2-only boundary equilibrium of the model exists). Further, consider the following Lyapunov function:

$$\begin{aligned}
\mathcal{F} &= S - S^{**} - S^{**} \ln \left(\frac{S}{S^{**}} \right) + E_2 - E_2^{**} - E_2^{**} \ln \left(\frac{E_2}{E_2^{**}} \right) \\
&\quad + \left(\frac{K_3 - \tilde{\beta}_2 \eta_2 S^{**}}{\sigma_2} \right) \left[I_2 - I_2^{**} - I_2^{**} \ln \left(\frac{I_2}{I_2^{**}} \right) \right],
\end{aligned}$$

with Lyapunov derivative,

$$\dot{\mathcal{F}} = \dot{S} - \frac{S^{**}}{S} \dot{S} + \dot{E}_2 - \left(\frac{E_2^{**}}{E_2} \dot{E}_2 + \frac{K_3 - \tilde{\beta}_2 \eta_2 S^{**}}{\sigma_2} \right) \left(\dot{I}_2 - \frac{I_2^{**}}{I_2} \dot{I}_2 \right),$$

so that,

$$\begin{aligned}
\dot{\mathcal{F}} &= \Pi - \lambda_2 S - \mu S - \frac{S^{**}}{S} (\Pi - \lambda_2 S - \mu S) + \lambda_2 S - K_3 E_2 - \frac{E_2^{**}}{E_2} (\lambda_2 S - K_3 E_2) \\
&\quad + \left(\frac{K_3 - \tilde{\beta}_2 \eta_2 S^{**}}{\sigma_2} \right) \left[\sigma_2 E_2 - K_4 I_2 - \frac{I_2^{**}}{I_2} (\sigma_2 E_2 - K_4 I_2) \right].
\end{aligned}$$

Hence,

$$\begin{aligned}
\dot{\mathcal{F}} &= \Pi \left(1 - \frac{S^{**}}{S}\right) + \mu S^{**} \left(1 - \frac{S}{S^{**}}\right) + \tilde{\beta}_2 S^{**} I_2 \\
&\quad - \tilde{\beta}_2 \eta_2 S E_2^{**} - \tilde{\beta}_2 S I_2 \frac{E_2^{**}}{E_2} + K_3 E_2^{**} - \frac{K_3 K_4 I_2}{\sigma_2} + \frac{\tilde{\beta}_2 \eta_2 S^{**} K_4 I_2}{\sigma_2} - K_3 E_2 \frac{I_2^{**}}{I_2} \\
&\quad + \frac{K_3 K_4 I_2^{**}}{\sigma_2} + \tilde{\beta}_2 \eta_2 S^{**} E_2 \frac{I_2^{**}}{I_2} - \frac{\tilde{\beta}_2 \eta_2 S^{**} K_4 I_2^{**}}{\sigma_2}.
\end{aligned} \tag{34}$$

It can be shown from the model (1) with (14) and $\lambda_2^{**} = 0$, at endemic steady-state, that

$$\begin{aligned}
\Pi &= \tilde{\beta}_2 (\eta_2 E_2^{**} + I_2^{**}) S^{**} + \mu S^{**}, \\
K_3 E_2^{**} &= \tilde{\beta}_2 (\eta_2 E_2^{**} + I_2^{**}) S^{**}, \quad \sigma_2 E_2^{**} = K_4 I_2^{**}, \quad \gamma_2 I_2^{**} = \mu R_2^{**}.
\end{aligned} \tag{35}$$

Substituting the relations in (35) into (34) gives

$$\begin{aligned}
\dot{\mathcal{F}} &= [\tilde{\beta}_2 \eta_2 S^{**} E_2^{**} + \tilde{\beta}_2 S^{**} I_2^{**} + \mu S^{**}] \left(1 - \frac{S^{**}}{S}\right) + \mu S^{**} \left(1 - \frac{S}{S^{**}}\right) \\
&\quad - \tilde{\beta}_2 \eta_2 S E_2^{**} - \tilde{\beta}_2 S I_2 \frac{E_2^{**}}{E_2} \tilde{\beta}_2 \eta_2 S^{**} E_2^{**} + \tilde{\beta}_2 S^{**} I_2^{**} - \tilde{\beta}_2 \eta_2 S^{**} E_2^{**} \frac{I_2}{I_2^{**}} \\
&\quad - \tilde{\beta}_2 S^{**} I_2^{**} \frac{E_2 I_2^{**}}{E_2^{**} I_2} + \tilde{\beta}_2 S^{**} I_2^{**},
\end{aligned}$$

which can be simplified to,

$$\begin{aligned}
&= \mu S^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) + \tilde{\beta}_2 \eta_2 S^{**} E_2^{**} \left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) \\
&\quad + \tilde{\beta}_2 S^{**} I_2^{**} \left(3 - \frac{S^{**}}{S} - \frac{E_2 I_2^{**}}{E_2^{**} I_2} - \frac{I_2 E_2^{**} S}{I_2^{**} E_2 S^{**}}\right).
\end{aligned} \tag{36}$$

Finally, since the arithmetic mean exceeds the geometric mean, the following inequalities from (17) hold:

$$2 - \frac{S^{**}}{S} - \frac{S}{S^{**}} \leq 0, \quad 3 - \frac{S^{**}}{S} - \frac{E_2 I_2^{**}}{E_2^{**} I_2} - \frac{I_2 E_2^{**} S}{I_2^{**} E_2 S^{**}} \leq 0.$$

The proof is completed using the same approach as in the proof of Theorem 3. \square

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Table 1: Description of variables and parameters of the model (1)

Variable	Interpretation
S	Population of susceptible individuals
E_i ($i = 1, 2$)	Population of individuals exposed to (latently-infected with) strain i
I_i	Population of infectious (symptomatically-infected) individuals with strain i
R_i	Population of individuals who recovered from strain i
E_{ij} ($i = 1, 2; i \neq j$)	Population of individuals who recovered from strain i but exposed to strain j
I_{ij} ($i = 1, 2; i \neq j$)	Population of infectious (with symptoms) individuals who recovered from strain i and infectious with strain j
M	Population of individuals who recovered from infection with both strains
Parameter	Interpretation
Π	Recruitment rate
$\frac{1}{\mu}$	Average lifespan
β_i, β_{ij}	Transmission rates
η_i, η_{ij}	Modification parameters
γ_i, γ_{ij}	Recovery rates
σ_i	Progression rate from E_i to I_i classes
θ_i	Modification parameter of reduced infectivity due to cross-immunity
δ_i, δ_{ij}	Disease-induced death rates
ξ	Rate of loss of natural immunity

Table 2: Parameter Values

Parameter	kazaure1 Value	Reference
Π	100 days ⁻¹	Assumed
ξ	0.4 day ⁻¹	Assumed
μ	0.00004 day ⁻¹ ($1/\mu = 68$ years)	[26, 29, 30]
$\beta_1, \beta_2, \beta_{12}, \beta_{21}$	[0.3,1] day ⁻¹	[29]
$\eta_1, \eta_2, \eta_{12}, \eta_{21}$	0.5	[30]
$\gamma_1, \gamma_2, \gamma_{12}, \gamma_{21}$	0.1428 day ⁻¹	[30]
$\delta_1, \delta_2, \delta_{12}, \delta_{21}$	0.04227 day ⁻¹	[37]
$\sigma_1, \sigma_2, \sigma_{12}, \sigma_{21}$	0.5 day ⁻¹	[30]
θ_1, θ_2	0.5	[29]

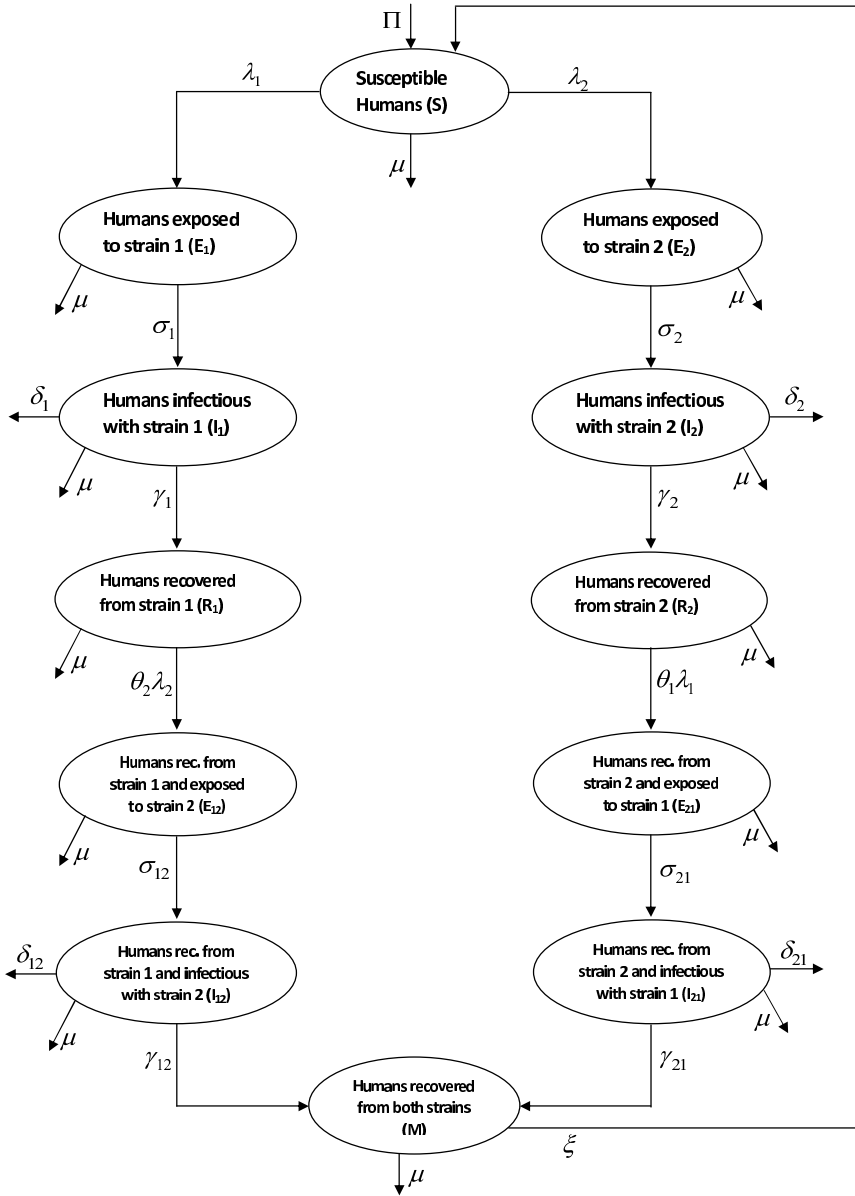


Figure 1: Schematic diagram of the model (1).

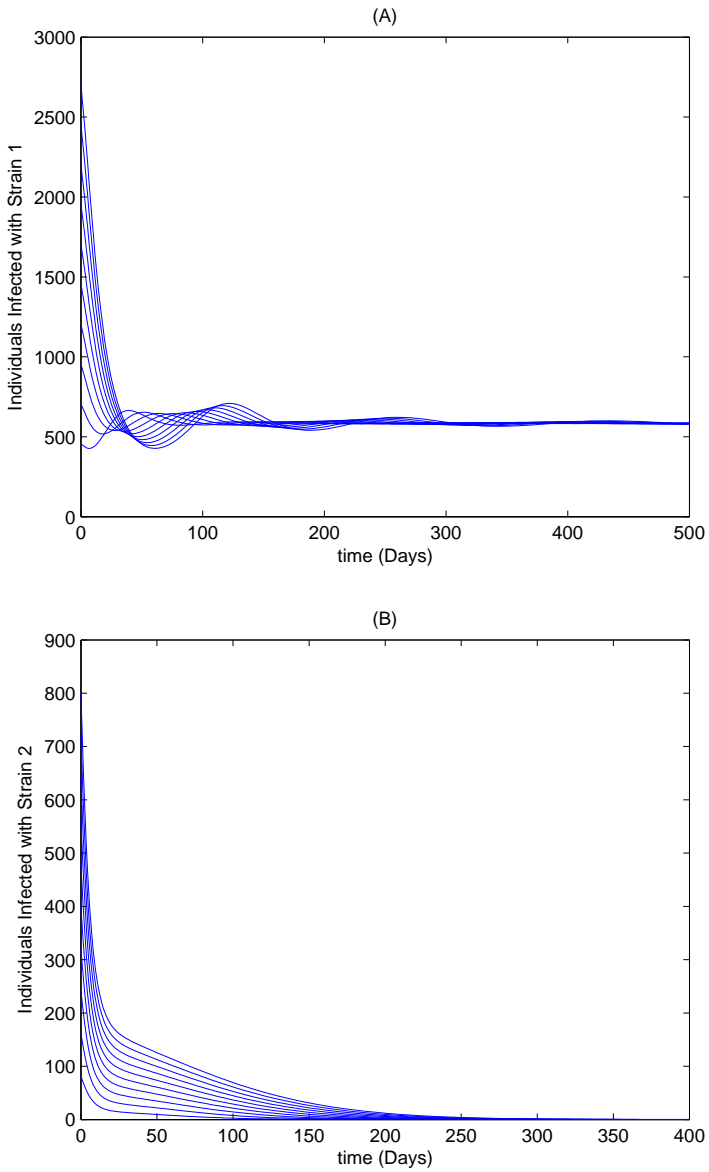


Figure 2: Simulations of the model (1). (A) Population of individuals infected with strain 1 ($E_1 + I_1 + E_{21} + I_{21}$); (B) Population of individuals infected with strain 2 ($E_2 + I_2 + E_{12} + I_{12}$). Parameter values used are: $\beta_1 = 0.6$, $\beta_2 = 0.1$, $\beta_{12} = 0.3$, $\beta_{21} = 0.5$ (so that, $\mathcal{R}_{02} = 0.6402 < 1 < \mathcal{R}_{01} = 3.8410$). Other parameter values used are as given in Table 2.

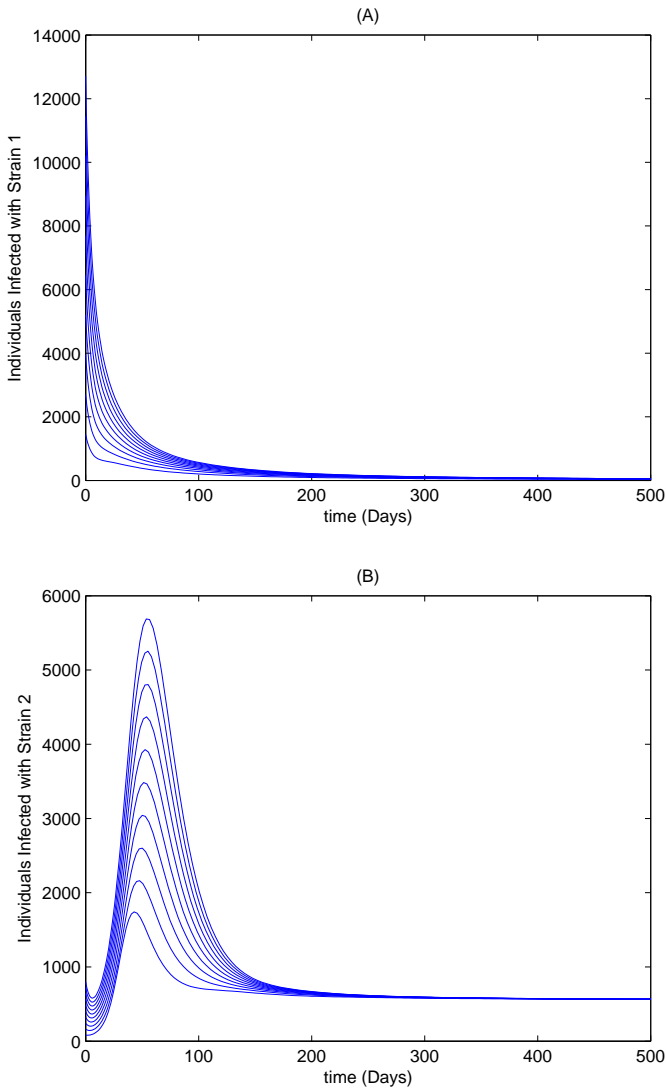


Figure 3: Simulations of the model (1). (A) Population of individuals infected with strain 1 ($E_1 + I_1 + E_{21} + I_{21}$); (B) Population of individuals infected with strain 2 ($E_2 + I_2 + E_{12} + I_{12}$). Parameter values used are: $\beta_1 = 0.1$, $\beta_2 = 0.6$, $\beta_{12} = 0.5$, $\beta_{21} = 0.5$ (so that, $\mathcal{R}_{01} = 0.6402 < 1 < \mathcal{R}_{02} = 3.2008$). Other parameter values used are as given in Table 2.

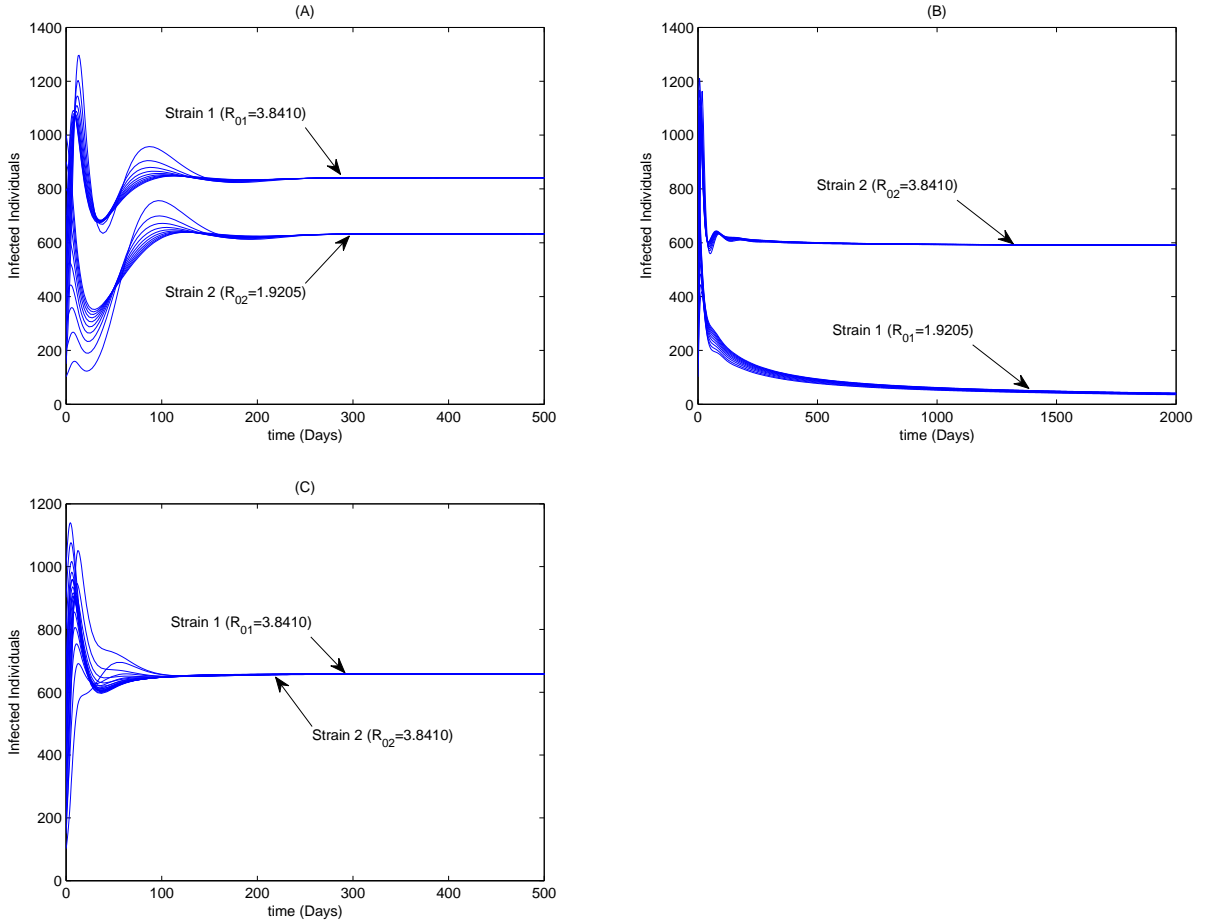


Figure 4: Simulations of model (1) showing co-existence equilibria for: (A) $\mathcal{R}_{01} > \mathcal{R}_{02} > 1, \beta_1 = 0.6, \beta_2 = 0.3$ (so that, $\mathcal{R}_{01} = 3.8410, \mathcal{R}_{02} = 1.9205$) (B) $\mathcal{R}_{02} > \mathcal{R}_{01} > 1, \beta_1 = 0.3, \beta_2 = 0.6, \beta_{12} = 0.5, \beta_{21} = 0.5$, (so that, $\mathcal{R}_{02} = 3.8410, \mathcal{R}_{01} = 1.9205$) (C) $\mathcal{R}_{01} = \mathcal{R}_{02} > 1, \beta_1 = 0.6, \beta_2 = 0.6$ (so that, $\mathcal{R}_{01} = 3.8410, \mathcal{R}_{02} = 3.8410$). Other parameter values used are as given in Table 2.

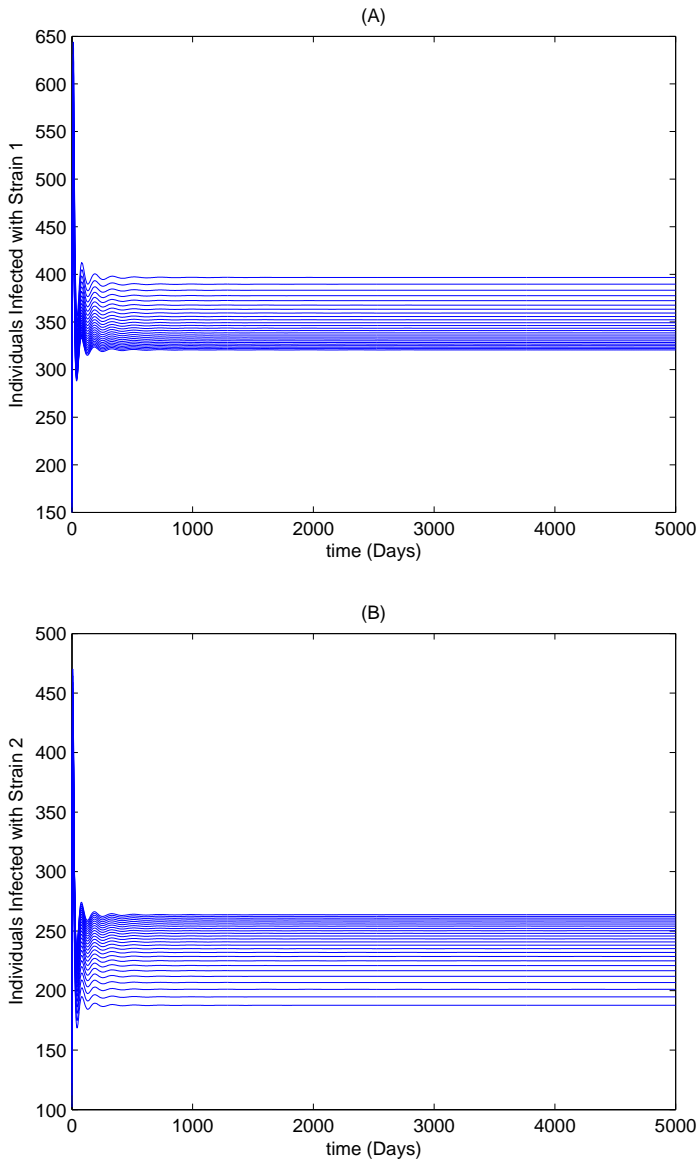


Figure 5: Simulations of the reduced model (7), showing continuum of positive coexistence equilibria for: (A) strain 1 ($E_1 + I_1 + E_{21} + I_{21}$); and (B) strain 2 ($E_2 + I_2 + E_{12} + I_{12}$). Parameter values used are: $\beta_1 = 0.6$, $\beta_2 = 0.6$, $\beta_{12} = 0.5$, $\beta_{21} = 0.5$, $\theta_1 = 0$, $\theta_2 = 0$ (so that, $\mathcal{R}_{01} = \mathcal{R}_{02} = 3.8410$). Other parameter values used are as given in Table 2.