Dynamics of Two-Strain Influenza with Isolation and Partial Cross-Immunity

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Abstract

The evolution of influenza A virus is linked to a non-fixed evolutionary landscape driven by tight co-evolutionary interactions between hosts and influenza strains. Herd-immunity, cross-immunity and age-structure are among the factors shown to support the coexistence of multiple strain oscillations. In this study, we incorporate two influenza strains and allow for levels of cross-immunity supported by previous studies. Three specific pairs of strain interactions are considered. Some of the strain definitions can be extended to \(n\) interacting strains if strains are properly defined. This framework allows for a biologically interpretable approach since appropriate levels of cross-immunity as suggested by each strain definition can be applied. We show that strong cross-immunity along with reasonable periods of host isolation lead to periodic epidemic outbreaks (sustained oscillations). We establish the system’s stability in the absence of infection via the basic reproductive number (\(R_0\)). The presence of two boundary endemic equilibria is found analytically. For isolation periods and cross-immunity levels pertaining to the influenza virus, our system supports the existence of sustained oscillations. These predictions are established via Hopf-bifurcation theory, and results are illustrated with numerical simulations.

Key words: Isolation periods; Cross-immunity; Multiple strains; Oscillations; Bifurcation; Stability;

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1 Introduction

About two-three decades ago several epidemiological studies were carried out to measure the ability (at the population level) of the immune's system history of prior exposure to influenza type A in the fight against invasions by new, possibly, related strains [1, 2]. The results of these studies support the view that partial cross-immunity is an important mechanism in the study of influenza dynamics and evolution [3, 4].

1.1 Epidemiology and immunology of cross-immunity in influenza

A

Recent documentation of the dynamics of coexistence of multiple strains also seems to be affected by partial cross-immunity effects [5]. The phenomenon of 'original antigenic sin' [6], that is, the virus capacity to evade the immune response, is supported by strain evolution. Moreover, asymmetric patterns of protective antibody cross reactivity determined by exposure to previously existing strains make full cross-immunity impossible. Original antigenic sin by antibodies or CTL leads to impaired clearance of variant viruses infecting the same individual and so may enhance the immune escape of mutant viruses evolving in an individual host [4].

On epidemiological level the antigenic variability of influenza type A viruses has caused major outbreaks in the past. It is believed that pandemics result from the appearance of new subtypes or distinctly new strains. The generation of new subtypes is assumed to be the result of major genetic changes. New subtypes are connected to the process of antigenic shift, new proteins hemagglutinin and/or neuraminidase are born immunologically different from that of previous circulating subtypes. The generation of highly distinct strains may be connected to key point mutations. Regardless of the mechanism, a population is seriously impacted by a new strain or subtype only when its previous immunological history is "useless" in the prevention of new invasions.

Three different influenza A subtypes have been isolated in the past century each of them generating a major pandemic. In 1918, the most severe pandemic (Spanish flu) took place. It is estimated that approximately 20 million individuals worldwide died from the H1N1 subtype [3, 4]. In 1957, the Asian viruses of the H2N2 subtype were responsible for the second pandemic. The H3N2 subtype is referred to as the Hong Kong subtype and is responsible for the most recent pandemic in 1968.

Antigenic drift involves relatively minor, but frequent changes (variants) that take place yearly [5]. They result from the accumulation of protein altering nucleotide substitutions in the genes encoding the HA and NA proteins [8]. Only the surface antigens, hemagglutinin and neuraminidase, are responsible for the virus variability. HA is the major surface glycoprotein of the influenza virus that interacts with infectivity-neutralizing antibodies. Alterations in the HA and/or NA molecule enable the virus to escape immune surveillance and cause epidemics of the disease. Although antigenic neuraminidase (NA) antibodies are not as effective as HA antibodies, they neutralize viral infectivity at high levels.
of concentrations [8, 4]. Furthermore, they modify the disease in favor of the host by reducing both the levels of the virus in lungs and the extent of lung lesions [4].

Type A influenza virus has been isolated and classified according to HA and NA composition into three subtypes: H1N1, H2N2, and H3N2 and a number of strains (see Table 1, [9]). Although we ignore factors that give origin to the complexity of influenza A viruses, studies indicate that influenza strains crossbreed (reassortment) more strongly than other viruses.

1.2 Prior relevant modeling frameworks

Due to the long-lasting cross-immunity between related strains, serious considerations have been made to study partial cross-immunity [11, 9, 10, 14, 15]. Interaction of multiple strains for influenza virus have been analyzed under various frameworks [16, 8]. Infection with a specific influenza strain provides permanent immunity to that strain. Typically an epidemic of influenza in a 'virgin' population, that is, a population with no previous exposure to any strain of the associated subtype, may result in about 30% levels of permanent immunity [2]. This level of herd-immunity makes it difficult for the same strain to re-invade. However, the population dynamics guarantees the introduction of new susceptibles, a reduction of the levels of herd-immunity, and the likelihood of a new invasion by the same strain. Cross-immunity enhances the concept of herd-immunity. In other words, high cross-immunity reduces the likelihood of invasion also by related strains while enhancing the capacity of 'highly' different strains to invade. Partial cross-immunity enhances the likelihood of coexistence of diverse strains. In this paper, we explore the relevance and impact of this evolutionary paradigm.

There have been several studies that focus on the identification of mechanisms capable of supporting the coexistence of multiple strains for diseases that provide permanent or temporary immunity [17, 20]. Earlier work [11, 9, 10, 14] focuses on the identification of coexistence mechanisms that are capable of generating sustained oscillations. It was found that cross-immunity in SIR models was only capable of generating damped oscillations in non-structured populations facing two competing strains. Age-structure alone seemed incapable of generating sustained oscillations on SIR populations in one-strain influenza models [11, 9] albeit they can support sustained oscillations in a general SIR model [18]. Although, damped oscillations have been observed for one-strain influenza models, this has not been established rigorously. Our believe is that if this is so, then it is due to the difference of time scales between the life of an influenza infection (3-7 days), and the life of a host (25550 days) [19]. In [11, 9] it was suggested that the interactions between the natural demographic age-structured dynamics of a population facing two strains of influenza and cross-immunity was enough to generate sustained oscillations. Recently Feng and Thieme [13, 12] showed that the addition of a quarantine class was sufficient to support sustained oscillations albeit not necessarily in the appropriate parameter regime for influenza. Hethcote et al. [21] showed that a variant of Feng and Thieme’s model was also capable of generating sustained oscillations. Although, there have been additional frameworks that are capable of generating sustained oscillations [10, 14], here we focus on the expansion of the results.
of Feng and Thieme [13] and Hethcote et al. [21] to the two-strain framework as developed in [11, 9].

1.3 Overview of our modeling framework

The main focus of this paper is the study of competitive outcomes that result from the interactions between two related strains of influenza, capable of generating sustained oscillations independently. Single-strain SIQR models have shown that the addition of a quarantine class which directly impacts the force of infection, coupled with the natural addition of new susceptibles via the demographic process, are enough to generate sustained oscillations (periodic dynamics) [21]. The introduction of a second competing strain in this framework implies that competition for susceptibles (a process mediated by cross-immunity) may be such that the possibility of sustained oscillations is no longer feasible. We show that this is not the case, that is, there is a significant region of parameter space that supports the coexistence of both strains in the oscillatory regime. Using the data available [2, 5] we illustrate that oscillatory dynamics are indeed possible for reasonable influenza parameters (Figure 4).

In this paper we introduce a two-strain model. We assume the strains are chosen according to 3 distinct possibilities classified with regard to the cross-immunity between them. First, we consider type A virus as strain 1 and type B virus as strain 2. Since surface proteins hemagglutinin (HA) and neuraminidase (NA) for type A and B are genetically distinct, no cross-immunity is shared and the strains are strongly coupled \( (\sigma \approx 1) \). According to this definition, the strains can also be two of the influenza A subtypes H1, H2, and H3 (e.g. A/Puerto Rico/8/34 (H1N1), A/Japan/305/57 (H2N2)). Studies suggest no cross-immunity between H2 and H3 [3]. In addition, subtypes H1 and H3 are shown to have no cross-reactive protection [3]. Again, no cross-immunity is shared and \( \sigma \approx 1 \). The second definition of the two strains refers to subtype variants (genetic drifts) of HA proteins of either H1, H2 or H3 subtypes (e.g. A/Hong Kong/9/68, A/England/42/72 strains of the H3N2 subtype). In this case the cross-immunity is non-trivial and depends on the specific strains chosen. In most of this paper we will assume that the strains are chosen according to this strain definition. Nonetheless, we introduce and consider briefly a third definition, namely when the two strains are both of type B virus. That is, we take strain 1 to be the Yamagata and strain 2 to be the Victoria strain. As suggested in [24], cross-immunity to a Victoria strain exists only if previously exposed to a Yamagata strain, but not vice-versa. Consequently, the cross-immunity parameters will differ for each strain \( (\sigma_1 \neq \sigma_2) \). We consider this case only numerically. Despite the numerous attempts to elucidate the dynamics of co-circulating strains [10, 11, 13, 14, 25], precise strain definitions have been neglected. In particular, models in [10, 11, 14] concern influenza multiple-strain interactions without specifics on how the strains are chosen. However, host-strain interactions and corresponding levels of cross-immunity depend strongly on the definition of the strains.

Our aim is to combine strain definitions via cross-immunity and isolation to address whether coexistence of sustained oscillations can be expected. Since isolation of children from school in the
1968 pandemic appeared to play a role in decreasing the attack rate, we suspect that pertinent periods of isolation may assist in the control of disease progression. On the other hand, it is highly likely that host isolation and untimely release (during outbreak peak) may lead to further propagation of infection.

In this paper we explore the role of isolation in a system of two co-circulating influenza strains that share host immunity depending on the proposed definitions of the strains. Using Hopf-bifurcation theory, we characterize the stability of the disease-free and endemic state equilibria. Via numerical simulations, we demonstrate that sustained oscillations may persist under strong cross-immunity for reasonable periods of isolation. That is, as protection between strains decreases, the probability of a secondary infection increases. We begin our analysis of stability with a simplified version of our model for which the parameter values for the two strains are equal (symmetric case). The strains are coupled by a single parameter of cross-immunity, $\sigma$. This version of the model is similar to a one strain model with $\sigma \approx 0$ [13]. In contrast to [13], we consider two co-circulating strains and include the quarantine period as an additional state to recovery. That is, instead of assuming that all infected are quarantined as in [13], we allow recovery as well as quarantine.

Our results for the symmetric model are consistent with the single strain case under complete cross-immunity ($\sigma = 0$). That is, with complete cross-immunity strains become uncoupled. Moreover, periodic oscillations can be observed by the persisting strain [13]. Considering strong cross-immunity ($0 \neq \sigma << 1$), interacting strains compete for susceptibles. If the quarantine state is not included, cross-immunity alone is not sufficient to drive sustained oscillations [11]. In this work we demonstrate that strong cross-immunity along with pertinent isolation periods may be a driving source for periodic behavior.

Our paper is structured as follows. Section 2 introduces the general two-strain model that is used throughout; Section 3 carries out the stability analysis of the model in Section 2; Section 4 uses Hopf-bifurcation to establish the necessary conditions for the existence of periodic solutions while computing useful formulae; Section 5 illustrates the results of the prior analysis using a variety of values for the cross-immunity including those derived from the literature [2, 5]. In Section 6 we summarize our findings and give our conclusions.
2 Two-strain model

The population is divided into ten different classes: susceptibles ($S$), infected with strain $i$ ($I_i$, primary infection), quarantined with strain $i$ ($Q_i$), recovered from strain $i$ ($R_i$, as result of primary infection), infected with strain $i$ ($I_i^*$, secondary infection), and recovered from both strains ($W$).

Figure 1. Schematic diagram of the dynamics in host exposed to two co-circulating influenza strains. $\Lambda$ is the rate at which individuals are born into the population, $\beta_i$ denotes the transmission coefficient for strain $i$, $\mu$ is the per-capita mortality rate, $\delta_i$ is the per-capita quarantine rate for strain $i$, $\gamma_i$ denotes the per-capita recovery rate from strain $i$, $\alpha_i$ is the per-capita rate at which individuals leave the isolated class as a result of infection with strain $i$, and $\sigma$ is the relative susceptibility to strain $j$ for an individual that has been infected with and recovered from strain $i$ ($i \neq j$). Strains share total cross-immunity if $\sigma = 0$. Conversely, $\sigma = 1$ indicates no cross-immunity between strains. We assume strong protection if $0 \leq \sigma << 1$, and weak for $0 << \sigma \leq 1$.

Using Figure 1 we formulate the following model

\[
\begin{align*}
\frac{dS}{dt} &= \Lambda - \sum_{i=1}^{2} \frac{\beta_i S (I_i + I_i^*)}{A} - \mu S, \\
\frac{dI_i}{dt} &= \beta_i S \left( \frac{I_i + I_i^*}{A} \right) - (\mu + \gamma_i + \delta_i) I_i, \\
\frac{dQ_i}{dt} &= \gamma_i I_i - (\mu + \alpha_i) Q_i, \\
\frac{dI_i^*}{dt} &= \delta_i I_i - (\mu + \alpha_i) Q_i, \\
\frac{dR_i}{dt} &= \gamma_i I_i + \alpha_i Q_i - \beta_i \sigma R_j \left( \frac{I_i + I_i^*}{A} \right) - \mu R_i, \quad j \neq i \\
\frac{dI_i^*}{dt} &= \beta_i \sigma R_j \left( \frac{I_i + I_i^*}{A} \right) - (\mu + \gamma_i) I_i^*, \quad j \neq i \\
\frac{dW}{dt} &= \sum_{i=1}^{2} \gamma_i I_i^* - \mu W, \\
A &= S + W + \sum_{i=1}^{2} (I_i + I_i^* + R_i).
\end{align*}
\]
where $A$ is the active (non-isolated) individuals and $\frac{\beta_i S(I_i^* + I_i^+)}{A}$ gives the rate at which the susceptibles get infected with strain $i$. Note that this incidence rate is proportional to the number of susceptibles as well as the probability $\frac{(I_i^* + I_i^+)}{A}$ that a contact will be with a non-isolated host infected with strain $i$. It is easy to show that the model is well-posed in the sense that there exists a unique nonnegative solution to (1) for all $t \geq 0$ when non-negative initial data are specified.

3 Disease free equilibrium and stability

System (1) has several equilibria. The two kinds of equilibria of interest are those in which the disease is absent (a disease-free equilibrium), and those in which the disease is present (endemic). Analysis of equilibria in the absence of disease typically gives conditions under which an epidemic will be established or eradicated in the population. In addition, exploring stability conditions for endemic equilibria allows us to determine when a new strain will evade the population in which disease is already endemic. As in the age-independent model in [11], we suspect that strong partial cross-immunity may lead to the exclusion of one of the strains. That is, prevalence of either strain is reduced by the presence of the other strain. As we introduce isolation, we observe sustained oscillations as in the age-structured model studied in [11].

Adding the differential equations in (1), we find for the population size $N = S + W + \sum_{i=1}^{2}(I_i + I_i^* + Q_i + R_i)$ that

$$\frac{d}{dt}N = \Lambda - \mu N.$$

Hence $N(t) \to \frac{\Lambda}{\mu}$ as $t \to \infty$. We assume that the total size of the population has reached its limit value, that is,

$$N \equiv \frac{\Lambda}{\mu} \equiv S + W + \sum_{i=1}^{2}(I_i + I_i^* + Q_i + R_i) = A + Q,$$

where $Q = Q_1 + Q_2$. Note that $A = N - Q$.

The basic reproductive number associated with strain $i$ is

$$R_i = \frac{\beta_i}{\mu + \gamma_i + \delta_i}.$$

$R_i$ gives the number of secondary infective cases of strain $i$ produced by an individual infected with strain $i$ during his or her effective infective period when introduced in a population of susceptibles. Let

$$R_0 = \max\{R_1, R_2\}.$$

The disease (both strains) will die out if $R_0 < 1$ while the disease (at least one stain) may become endemic if $R_0 > 1$. The disease-free equilibrium is $E_0 = (S_0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$, $S_0 = \Lambda/\mu$.

**Theorem 1.** The disease-free equilibrium is locally asymptotically stable (l.a.s.) if $R_i < 1$ for $i = 1, 2$ and unstable if either $R_1 > 1$ or $R_2 > 1$. 

7
Proof. By (1) at disease-free state we partition the $10 \times 10$ Jacobian matrix into the following block form:

$$J = \begin{pmatrix}
-\mu & * & * & 0 \\
0 & G_1 & 0 & 0 \\
0 & 0 & G_2 & 0 \\
0 & * & * & -\mu
\end{pmatrix}$$

where

$$G_1 = \begin{pmatrix}
\beta_1 - (\mu + \gamma_1 + \delta_1) & 0 & 0 & \beta_1 \\
\delta_1 & -(\mu + \alpha_1) & 0 & 0 \\
\gamma_1 & \alpha_1 & -\mu & 0 \\
0 & 0 & 0 & -(\mu + \gamma_1)
\end{pmatrix},$$

and

$$G_2 = \begin{pmatrix}
\beta_2 - (\mu + \gamma_2 + \delta_2) & 0 & 0 & \beta_2 \\
\delta_2 & -(\mu + \alpha_2) & 0 & 0 \\
\gamma_2 & \alpha_2 & -\mu & 0 \\
0 & 0 & 0 & -(\mu + \gamma_2)
\end{pmatrix}.$$ 

"**" represents a nonzero block matrix.

If $R_i < 1$ for $i = 1, 2$ the eigenvalues of the Jacobian $\lambda_i < 0 \ \forall \ i = 1, 2, ..., 10$. Therefore, solutions decay exponentially and disease dies-out.

Hence, $E_0$ is locally asymptotically stable.

If $R_i > 1$ for $i = 1$ or $i = 2$ at least one $\lambda_i > 0$ for some $i$.

Hence, $E_0$ is an unstable saddle. \qed

4 Nontrivial equilibria and sustained oscillations

In this section we establish the existence of two boundary equilibria and examine their stability. We find explicit conditions for stability and show via Hopf-bifurcation that boundary equilibria can lose stability which leads to the presence of oscillatory solutions.

When the disease is endemic, there is a possibility that it is represented by strain 1 only, by strain 2 only or both strains. Since the two strains are mathematically symmetric ($\sigma_1 = \sigma_2$), we consider the case when only strain 1 is present and strain 2 dies out. The other case when strain 2 is present and strain 1 dies out is similar. For convenience we arrange the variables in the order $U = (S, I_1, Q_1, R_1, I_1^*, I_2, Q_2, R_2, I_2^*, W)$ and rewrite system (1) as $dU/dt = F(U)$. To find the boundary equilibrium for strain 1

$$E_1 = (\bar{S}, \bar{I}_1, \bar{Q}_1, \bar{R}_1, 0, 0, 0, 0, 0, 0),$$

8
we set \( F(U) = 0 \) and let \( I_1^* = I_2 = Q_2 = R_2 = I_2^* = W = 0 \).

We obtain

\[
\begin{align*}
\frac{\dot{S}}{A} &= \frac{1}{R_1}, \\
\frac{\dot{Q}}{A} &= \mu \delta_1 \phi, \\
\frac{\dot{I}}{A} &= \mu (\mu + \alpha_1) \phi, \\
\frac{\dot{R}}{A} &= (\gamma_1 (\mu + \alpha_1) + \alpha_1 \delta_1) \phi,
\end{align*}
\]

where

\[
\phi = \frac{(1 - \frac{1}{R_1})}{(\mu + \gamma_1 (\mu + \alpha_1) + \alpha_1 \delta_1)}.
\]

We can see that \( E_1 \) exists and it is unique if and only if \( R_1 > 1 \). For simplicity using \( A = N - Q \) and \( S = A - \sum_{i=1}^{2} (I_i + I_i^* + R_i) - W \) we eliminate the \( S \) equation and rewrite the \( I_i \) equation as

\[
\frac{dI_i}{dt} = \beta_i \left( 1 - \frac{W + \sum_{i=1}^{2} (I_i + R_i + I_i^*)}{A} \right) (I_i + I_i^*) - (\mu + \gamma_i) I_i.
\]

The Jacobian at \( E_1, J \), is then a \( 9 \times 9 \) (without \( S \)) matrix and it can be partitioned into the following block form:

\[
J = \begin{pmatrix}
G_1 & * & 0 & * \\
0 & -(\mu + \gamma_1) & * & 0 \\
0 & 0 & G_2 & 0 \\
0 & * & * & -\mu
\end{pmatrix}
\]

where

\[
G_1 = \begin{pmatrix}
-\frac{\beta_1 \delta}{R_1} & 0 & -\frac{\beta_1 \gamma}{R_1} \\
\delta_1 & -(\mu + \alpha_1) & 0 \\
\gamma_1 & \alpha_1 & -\mu
\end{pmatrix},
\]

and

\[
G_2 = \begin{pmatrix}
\beta_2 \frac{\dot{S}}{A} - (\mu + \gamma_2 + \alpha_2) & 0 & 0 & \beta_2 \frac{\dot{S}}{A} \\
\delta_2 & -(\mu + \alpha_2) & 0 & 0 \\
\gamma_2 & \alpha_2 & -\beta_1 \gamma_2 & 0 \\
\beta_2 \sigma \frac{\dot{R}}{A} & 0 & 0 & \beta_2 \sigma \frac{\dot{R}}{A} - (\mu + \gamma_2)
\end{pmatrix}.
\]

“*" represents a nonzero block matrix.

We establish stability conditions for endemic steady state by first analyzing matrix \( G_2 \). Note that \( G_2 \) has two negative eigenvalues \(-(\mu + \alpha_2)\) and \(-(\mu + \frac{\dot{I}}{A})\), and two other eigenvalues given by the equation

\[
\lambda^2 - c_1 \lambda + c_2 = 0,
\]

(4)
where

\[ c_1 = (\mu + \gamma_2 + \delta_2) \left( \frac{R_2 - R_1}{R_1} \right) + \beta_2 \sigma \frac{\bar{\beta}_1}{A} - (\mu + \gamma_2), \]

\[ c_2 = - (\mu + \gamma_2 + \delta_2) \left[ \beta_2 \sigma \frac{\bar{\beta}_1}{A} + (\mu + \gamma_2) \left( \frac{R_2 - R_1}{R_1} \right) \right]. \tag{5} \]

The roots of (4) will have negative real part if and only if the trace is negative and the determinant is positive. That is, \((c_1 < 0 \text{ and } c_2 > 0)\). We remark that \(R_i\) varies with the transmission parameter \(\beta_i\). Rewriting expression for \(R_i\) and plugging in for \(\beta_i\) in system (5), it can be shown that

\[ c_1 < 0 \iff F_1(R_1, R_2) := (\mu + \gamma_2 + \delta_2) \left( \frac{R_2}{R_1} - 1 + \sigma R_2 \frac{\bar{\beta}_1}{A} \right) - (\mu + \gamma_2) < 0, \]

\[ c_2 > 0 \iff F_2(R_1, R_2) := \sigma (\mu + \gamma_2 + \delta_2) R_2 \frac{\bar{\beta}_1}{A} + (\mu + \gamma_2) \left( \frac{R_2}{R_1} - 1 \right) < 0. \tag{6} \]

where \(\bar{\beta}_1/A\) is given in (2). It is obvious that in the case of full immunity \((\sigma = 0)\), conditions in (6) hold if and only if \(R_2 < R_1\). As immunity diminishes between strains \((\sigma > 0)\), additional conditions need to be considered to ensure that (6) holds. To ensure condition \(F_2 < 0\), it is sufficient that \(R_2 < R_1\) holds. To find necessary conditions pertaining to \(F_1\), we rewrite \(F_1\) in terms of \(F_2\) and obtain the following.

\[ F_1(R_1, R_2) = (\mu + \gamma_2) F_2(R_1, R_2) + \delta_2 \left( \frac{R_2}{R_1} - 1 \right) - (\mu + \gamma_2), \]

We have that \(F_1 \leq (\mu + \gamma_2) F_2\) when \(R_2 < R_1\). Since we previously concluded that \(R_2 < R_1\) implies that \(F_2 < 0\), then conditions (c1) and (c2) for \(\sigma > 0\) hold if and only if \(R_2 < R_1\) and \(F_2 < 0\). Note that \(\bar{\beta}_1/A\) and \(\phi\) are given in 2. Let

\[ f(R_1) = \frac{R_1}{1 + \sigma (R_1 - 1) \left( 1 + \frac{\delta_2}{\mu + \gamma_2} \right) \left( 1 - \frac{\mu (\mu + \alpha_1)}{(\mu + \gamma_1)(\mu + \alpha_1) + \alpha_1 \delta_1} \right)}. \tag{7} \]

Then \(F_2 < 0\) if and only if \(R_2 < f(R_1)\). It is easy to see that \(0 < f(R_1) < R_1\). Hence, if \(R_2 < f(R_1)\), then \(F_1 \leq (\mu + \gamma_2) F_2 < 0\). It follows that all eigenvalues of \(G_2\) have negative real part if and only if

\[ R_2 < f(R_1). \tag{8} \]

For \(G_1\) we have used the equality

\[ \beta_1 \frac{\bar{\beta}}{A} \left( 1 - \frac{\bar{I}}{A} \right) - (\mu + \gamma_1 + \alpha_1) = \frac{\beta_1 \bar{I}}{R_1 A}. \]
Remark. As $R_1$ does not depend on $\alpha_1$, the dependence of $f$ on $\alpha_1$ is in the order of $\mu$. We continue our analysis of endemic state by finding conditions of stability pertaining to matrix $G_1$. The characteristic equation of $G_1$ is given by

$$\omega^3 + a_1\omega^2 + a_2\omega + a_3 = 0 \quad (9)$$

where

$$
\begin{align*}
    a_1 &= 2\mu + \alpha_1 + \mu(\mu + \alpha_1)(\mu + \gamma_1 + \delta_1), \\
    a_2 &= \mu(\mu + \alpha_1)(1 + (\mu + \gamma_1 + \delta_1)(2\mu + \gamma_1 + \alpha_1)), \\
    a_3 &= \mu(\mu + \alpha_1)(\mu + \gamma_1 + \delta_1)((\gamma_1 + \mu)(\mu + \alpha_1) + \alpha_1\delta_1) \phi.
\end{align*} \quad (10)$$

Clearly $a_1$, $a_2$, and $a_3$ are all positive. Hence (8) has either three negative roots or one negative root and two complex conjugate roots. Note that the mean life expectation $1/\mu$ is in the order of decades, whereas the infective period $1/\delta_i$ or $1/\gamma_i$ and the isolation period $1/\alpha_i$ are in terms of days. Hence $\mu$ is much smaller than $\delta_i$, $\gamma_i$, and $\alpha_i$.

From (9) we know that $a_i$ are analytic functions of $\mu > -\epsilon$ for some $\epsilon > 0$ and

$$
\begin{align*}
    a_1 &= \alpha_1 + \left(3 - \frac{1}{R_1^*}\right)\mu + O(\mu^2), \\
    a_2 &= \left(\alpha_1 + (1 - \frac{1}{R_1^*})(\gamma_1 + \alpha_1)\right)\mu + O(\mu^2), \\
    a_3 &= \alpha_1(\gamma_1 + \delta_1)(1 - \frac{1}{R_1^*})\mu + O(\mu^2),
\end{align*} \quad (11, 12, 13)$$

where $R_1^*$ denotes $R_1$ evaluated at $\mu = 0$. Let $\omega_i = \omega_i(\mu)$, $i = 1, 2, 3$, be the roots of (8). These are analytic functions of $\mu > -\epsilon$. In the limiting case, $\mu = 0$, (8) is

$$\omega^3 + \alpha_1\omega^2 = 0.$$

It has a double root $0$ and the simple root $\omega = -\alpha_1$. From the continuity we have $\omega_1(0) = -\alpha_1$, $\omega_2(0) = \omega_3(0) = 0$. Thus, $\omega_1(\mu) = -\alpha_1 + O(\mu)$ is a negative real root of (9) for small $\mu > 0$. Using a similar argument as in [23, 12, 13] and Kato [23, II, §1, Section 2] the roots $\omega_2(\mu)$ and $\omega_3(\mu)$ have an expression

$$\omega(\mu) = \sum_{j=1}^{\infty} \xi_j \nu^j, \quad \nu = \mu^{\frac{1}{3}}. \quad (14)$$

Fitting this expression into (10) yields

$$
\begin{align*}
    \left[\alpha_1\xi_1^2 + \alpha_1(\gamma_1 + \delta_1)(1 - \frac{1}{R_1^*})\right]\nu^2 \\
    + \left[\xi_1^3 + 2\xi_1\xi_2\alpha_1 + \left(\alpha_1 + (\gamma_1 + \alpha_1)(1 - \frac{1}{R_1^*})\right)\xi_1\right]\nu^3 = O(\nu^4).
\end{align*} \quad (15)$$

11
Hence,

\[ \xi_1^2 = -\left(\gamma_1 + \delta_1\right)\left(1 - \frac{1}{\mathcal{R}_1^*}\right), \quad \xi_2 = -\frac{1}{2\alpha_1} \left(\xi_1^2 + \alpha_1 + \left(\gamma_1 + \alpha_1\right)\left(1 - \frac{1}{\mathcal{R}_1^*}\right)\right). \]

Note that as \( \mathcal{R}_1^* > 1 \), we have

\[ \xi_{1,2} = \pm i \sqrt{\left(\gamma_1 + \delta_1\right)\left(1 - \frac{1}{\mathcal{R}_1^*}\right)}, \quad \xi_3 = -\frac{1}{2\alpha_1} \left(\alpha_1 + \left(\gamma_1 - \delta_1\right)\left(1 - \frac{1}{\mathcal{R}_1^*}\right)\right). \]  

(15)

Hence the three roots are

\[ \omega_1(\nu) = -\alpha_1 + O(\mu), \]  

(16)

and

\[ \omega_{2,3}(\nu) = \pm i \left(\left(\gamma_1 + \delta_1\right)\left(1 - \frac{1}{\mathcal{R}_1^*}\right)\right)^{\frac{1}{2}} \nu \quad \left[-\frac{1}{2\alpha_1} \left(\alpha_1 + \left(\gamma_1 - \delta_1\right)\left(1 - \frac{1}{\mathcal{R}_1^*}\right)\right)\nu^2 + O(\nu^3). \right. \] 

(17)

Choose \( \alpha_1 \) to be a bifurcation parameter (\( 1/\alpha_1 \) is the isolation period for strain 1) and consider \( \alpha_1 = \alpha_1(\nu) \) to be a function of \( \nu \) satisfying \( \xi_2(\alpha_1(0)) = 0 \), i.e.,

\[ \alpha_1(0) = \frac{\delta_1(\mathcal{R}_1^* - 1)}{2\mathcal{R}_1^* - 1}. \]

Let \( \omega_{2,3} = \omega_{2,3}(\alpha_1, \nu) \) and let

\[ H(\alpha_1, \nu) = \frac{1}{\nu^2} \Re \omega_{2,3}(\alpha_1, \nu). \]

Then \( H(\alpha_1(0), 0) = \xi_2(\alpha_1(0)) = 0 \). Using the implicit function theorem we know that for small \( \nu > 0 \), there exits a critical value

\[ \alpha_{1c}(\nu) = \frac{\delta_1(\mathcal{R}_1^* - 1)}{2\mathcal{R}_1^* - 1} + O(\nu) \]

such that \( H(\alpha_{1c}(\nu), \nu) = 0 \). Clearly \( \alpha_{1c} > 0 \) as \( \mathcal{R}_1^* > 1 \). As

\[ H_{\alpha_1}(\alpha_{1c}, 0) = -\frac{(2\mathcal{R}_1^* - 1)^2}{2\delta_1\mathcal{R}_1^*(\mathcal{R}_1^* - 1)} < 0, \]

we know that non resonance holds. That is, as the frequency of strain 1 approaches that of strain 2, or vice-versa, corresponding amplitude is finite. It follows that there is a Hopf bifurcation at \( \alpha_1 = \alpha_{1c} \). Moreover, \( \omega_{2,3} \) cross the imaginary axis from left to right when \( \alpha_1 \) crosses \( \alpha_{1c} \) from left to right. We have established the following result:
Theorem 2. There are two functions, \( f(R_1) \), defined in 7, and \( \alpha_{1c}(\mu) \) defined for small \( \mu > 0 \) as
\[
\alpha_{1c}(\mu) = \frac{\delta_1(R_1^* - 1)}{2R_1^* - 1} + O(\mu^{1/2}),
\]
with the following properties:

(i) The boundary endemic equilibrium \( E_1 \) is locally asymptotically stable if \( R_2 < f(R_1) \) and \( \alpha_1 < \alpha_{1c}(\mu) \), and unstable if \( R_2 > f(R_1) \) or \( \alpha_1 > \alpha_{1c}(\mu) \).

(ii) When \( R_2 < f(R_1) \), there is a Hopf bifurcation of periodic solutions at \( \alpha_1 = \alpha_{1c}(\mu) \) for small enough \( \mu > 0 \). The periods are approximately
\[
T = \frac{2\pi}{|3\omega_{2,3}|} \approx \frac{2\pi}{(\gamma_1 + \delta_1)(1 - \frac{1}{R_1^*})^{1/2} \mu^{1/2}}.
\]

Remarks. (i) From (2) the period \( T \) can also be written as
\[
T \approx \frac{2\pi}{(\gamma_1 + \delta_1) \left( \frac{1}{A} \right)^{1/2} \mu^{1/2}},
\]
where \( \tilde{I}/\tilde{A} \) denotes \( \frac{1}{\mu} \tilde{I}/\tilde{A} \) evaluated at \( \mu = 0 \). This expression for \( T \) allows one to compare the formula of the period from this model with the formula of the quasi-period from other models which do not include a quarantine class and produce no periodic solutions.

(ii) Since the two strains are mathematically symmetric, we can state a result for the boundary endemic equilibrium \( E_2 \) at which only strain 2 is present. The result will read the same as Theorem 2 with indices 1 and 2 switched.

The expression of \( f(R_1) \) also allows us to explore the effect of the cross immunity, \( \sigma \), on the behavior of the model. For example, from (7) we can find a critical value
\[
\sigma^* = \left( 1 + \frac{\delta_2}{\mu + \gamma_2} \right) \left( 1 - \frac{\mu(\mu + \alpha_1)}{(\mu + \gamma_1)(\mu + \alpha_1 + \alpha_1\delta_1)} \right),
\]
such that for \( R_1 > 1 \)
\[
f'(R_1) > 0, \quad f(R_1) > 1 \quad \text{if} \ \sigma < \sigma^*,
\]
\[
f'(R_1) < 0, \quad f(R_1) < 1 \quad \text{if} \ \sigma > \sigma^*,
\]
\[
f'(R_1) = 0, \quad f(R_1) = 1 \quad \text{if} \ \sigma = \sigma^*.
\]

Here we have used the fact that \( f(1) = 1 \). Note that \( R_2 < f(R_1) \) is a necessary condition for the stability of strain 1 (either a stable boundary endemic equilibrium \( E_1 \) or a sustained oscillation of strain 1 only). Also note that the boundary equilibrium for strain 2, \( E_2 \), is unstable when \( R_2 < f(R_1) \) (recall that \( f(R_1) < R_1 \)). Noticing that \( f(1) = 1 \), we can draw a diagram showing the stability region for strain 1 in the \((R_1, R_2)\) plane (see Fig.2, region I). Using the symmetry we can find another curve given by a function \( g(R_1) \) which determines the stability region for strain 2 (see Fig 2, Region II). We
see from Fig 2 that the stability region for a single strain increase when \( \sigma \) decreases. Consequently, it follows that stronger cross-immunity promotes competitive exclusion.

When \((R_1, R_2)\) is in the region \(III\), there is no stability of a single strain, i.e., neither one of the two strains will die out while the other strain remains endemic. In this case we expect the coexistence of both strains, either in the form of a stable interior equilibrium or in the form of sustained oscillations of both strains. We do not have an analytic proof for this due to the complexity of the model. Some numerical results will be presented in the next section.
Figure 2. Describes the stability and coexistence regions as we vary cross-immunity. Note that for $\sigma < \sigma^*$ the region of interaction among both strains is relative smaller than for $\sigma > \sigma^*$. This suggests that for larger values of $\sigma$ (no cross-immunity) strains are antigenically distinct and therefore both will coexist.

5 Simulations

In this section we explore the model equations numerically for parameter values that pertain to the strain definitions proposed (see Section 1). We assume that individuals infected with strain $i$, go to isolation at a rate $\delta_i$ as a result of ineffective recovery and have a life expectation of 70 years.

We calculate the eigenvalues for different isolation periods and transmission coefficients. In all cases eigenvalues have zero real part and the corresponding imaginary parts are of order $10^{-3}$. Calculations presented in Table 1 indicate that as the transmission coefficient $\beta_i$ increases, $R_0$ increases and the period of the oscillations decreases. That is, as the number of secondary infections generated by a single infected individual increase from one, population epidemic outbreaks persist and peak more often. The higher the $R_0$, the more frequent and endemic are the epidemics.

Table 1. Parameters chosen for the calculations below pertain to symmetric contacts. The first column gives transmission coefficient, the second gives the isolation periods; the third and fourth columns give the imaginary eigenvalues $\xi_1$ and $\xi_2$ (see (15)); and the remaining columns give the bifurcating parameter and corresponding periods of oscillation ($\gamma = 0.33$, $\delta = 0.7$, $\mu = 0.00004$, 

15
\( \sigma = 0.01 \).

<table>
<thead>
<tr>
<th>( \beta )</th>
<th>( \frac{1}{\sigma}(\text{days}) )</th>
<th>( \text{Im}(\xi_1) )</th>
<th>( \text{Im}(\xi_2) )</th>
<th>( \frac{1}{\alpha_{14}}(\text{days}) )</th>
<th>( T ) (days)</th>
<th>( \mathcal{R}_0 )</th>
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The simulations in Figure 3 illustrate that for the symmetric contact case ($\beta = \beta_1 = \beta_2, \sigma = \sigma_1 = \sigma_2$) the system goes through cycles where the period and amplitude are determined by the quarantine and cross-immunity correspondingly. For very strong cross-immunity ($\sigma = 0.01$) as in the second strain definition (see Section 1), strains are strongly coupled and the amplitudes of the oscillations increase with the quarantine periods (see Figure 3). Although the strong coupling between the strains suggests that strain with the highest infectivity remains in the population, reappearance of previously circulating strains may cause the future epidemics as shown in Figure 3.
Figure 3. Numerical integration of the model equations according to Matlab. Proportion $\frac{I}{N}$, of the population infected (non-isolated) with strain 1 with $\sigma = 0.01$ and transmission rate $\beta = 1.7$ is plotted against time. Cross-immunity chosen according to strain definition 2.
We further decrease cross-immunity corresponding to the second strain definition. Simulations indicate similar yearly oscillations as supported by the antigenic drifts (see Figure 4). For the intermediate cross-immunity ($0.3 \leq \sigma \leq 0.7$), the system exhibits complicated dynamics with multiple outbreaks during some years as we increase the periods of quarantine (see Figure 4). In contrast to the simulations for strong cross-immunity ($\sigma = 0.01$), sustained oscillations dampen only in the presence of extremely large periods of quarantine ($\frac{1}{\sigma} = 3000$ days). We notice that the form of the persistence of the epidemic in the case of strong cross-immunity ($\sigma = 0.01$) and the case of intermediate cross-immunity ($\sigma = 0.5$) is very different. While in the case of intermediate cross-immunity the proportion of infected exhibits sustained oscillations of close peaks (approximately 5 in a 10 year period) in the case of strong cross-immunity the epidemic seemingly disappears from the population for long intervals of time (up to 20 years) and is present for intervals of time of about 10 years when it exhibits one or multiple peaks. We believe that at strong cross-immunity levels the two strains "work together" for depleting the susceptible pool since infection with one of the strains protects against infection with the other and the disease. When no more susceptibles are available to be infected, this leads to a temporary fading out (vanishing) of the epidemic. Simulations pertaining to cases of weak to non cross-immunity ($0.7 \leq \sigma \leq 1$) are not included, nevertheless it can be observe that strains continue to become uncoupled.
Figure 4. Proportion $\frac{I}{N}$, of the population infected (non-isolated) with strain 1 with $\sigma = 0.5$ and transmission rate $\beta = 1.7$ is plotted against time.
Finally, we explore the effects of strain coexistence and competition for susceptible population as in the asymmetric cross-immunity case ($\sigma_1 \neq \sigma_2$). In Figure 5 parameters are chosen according to influenza B strains (strain definition 3). In this asymmetric case, cross-immunity against strain 2 (Victoria) exists only after a previous exposure to strain 1 (Yamagata), but not vice-versa. We assume that strain 1 has strong cross-immunity ($0.1 \leq \sigma_1 \leq 0.3$) and strain 2 has weak cross-immunity ($0.7 \leq \sigma_2 \leq 0.9$).

Figure 5. Proportion $I/N$, of the population infected (non-isolated) with strain 1 and strain 2 is plotted against time. Transmission rates $\beta_1 = 4.6$, $\beta_2 = 4.7$, $\sigma_1 = 0.1$, $\sigma_2 = 0.7$ are chosen according to influenza B strains (strain definition 3). To understand the mechanisms behind the observed sustained oscillations we have explored simulations that pertain to the symmetric as well as the non-symmetric case. It can be observed that isolation drives sustained oscillations independently of the assumptions made on cross-immunity and the given strain definitions. In agreement with the results
by Feng and Thieme [13], for the symmetric case oscillations dampened for large periods of isolation (600 days). Furthermore, the system’s steady state is sensitive to initial conditions. In the case \( R_1 = R_2 \), the number of initial infecteds with either strain determines the steady state reached by the corresponding strain. This fact suggests the presence of multiple stable equilibria.

In contrast to Feng and Thieme’s results, our model supports sustained oscillations for realistic transmission rates and isolation periods that agree with influenza A virus dynamics, \( R_0 \in (1.3, 2) \). In particular, sustained oscillations are observed for strong to intermediate cross-immunity (\( \sigma = 0.01, 0.5 \)), transmission coefficient (\( \beta = 1.7 \)), and quarantine periods (\( \frac{1}{\alpha} \in (3, 30) \) days), (see Figures 3 and 4. For the simulations of asymmetric cross-immunity, we observe that transmission rates \( \beta_1, \beta_2 \) for strain 1 and 2 must be higher to ensure strain coexistence (see Figure 5). Cross-immunity levels are pertinent to influenza B strains (\( \sigma_1 \neq \sigma_2 \)). When the two strains have equal transmission rates (\( \beta_1 = \beta_2 \)) and different cross-immunity coefficients (\( \sigma_1 = 0.1, \sigma_2 = 0.7 \)), simulations show that the amplitude and period of the oscillations increases with the period of isolation. Similarly, for equal cross-immunity but different transmission rates the changes in cycles and amplitude are less pronounced for short periods of isolation. Although simulations of asymmetric cases included here are not extensive, it is clear that for \( \sigma_1 \) different than \( \sigma_2 \), as \( |\sigma_1 - \sigma_2| \) increases strains become coupled and persistence depends heavily on their transmission rate. That is, as the levels of cross-immunity between the strains is simultaneously shared (bigger \( |\sigma_1 - \sigma_2| \)), a single strain prevails. In all simulations explored it is clear that isolation has a destabilizing effect (see Table 1). The magnitude of the periodic outbreaks and frequency is characteristic of cross-immunity and quarantine period.

6 Discussion

Mechanisms responsible for influenza outbreaks have been explored in the last decades. Models incorporating factors such as age-structure, seasonal effects, cross-immunity and interactions among viral strains have been analyzed [10, 11, 9, 14]. In this study we incorporate two influenza strains and emphasize the importance of a precise strain definition. In most studies that reveal the existence of cross-immunity, \( \sigma \) is approximated by considering relative frequencies of infection or the levels of antibody-positive sera present in a population once a new subtype or strain has been established [3].

The impact of cross-immunity on the dynamics of models with co-circulating strains depends strongly in the modeling approach. In the two-strain model proposed by the authors in [11], it is assumed that cross-immunity reduces the pool of susceptibles for co-circulating strains and influences the survival of the strains. It is shown that age-structure leads to sustained oscillations with periods of 10 to 20 years for the case of strong cross-immunity (\( \sigma = 0.01 \)) and periods of 3 to 4 years for intermediate cross-immunity (\( \sigma = 0.50 \)). Although our model does not consider age-structure, sustained oscillations are also observed as we include quarantine periods. Our results are similar to those in [11] in the fact that variation of transmission coefficients \( \beta_1, \beta_2 \) has a significant effect on the
amplitude of the observed oscillations. Moreover, the periods of oscillations pertaining to the strong and intermediate cross-immunity obtained in our model are similar to those obtained in [11, 3].

In later models, cross-immunity acts by reducing the probability of future infections when the immune system is challenged with a related strain as specified by our strain definition 2 [10]. In fact, it has been shown that for a fixed host life span, cross-immunity destabilizes the system by introducing a delay and sustained oscillations can be observed [10]. Furthermore, it is shown that removing the delay posed by the cross-immunity and introducing n interacting strains continues to support the sustained oscillations. In the later models sustained oscillations appear to be supported by the delay introduced due to cross-immunity and multiple co-circulating strains correspondingly regardless of a strain definition.

In our model, we allow strain interactions that are realistic to the shared levels of cross-immunity. Some of our strain definitions can be extended for n-interacting strains. However, for choices of multiple strain interactions as in [10] an n-strain model may be inappropriate if strains interact as in definitions 1 and 3. The observed sustained oscillations as a result of strong cross-immunity may only be realistic if the strains satisfy definition 2.

The aim of this paper is to explore the role of cross-immunity and quarantine periods according to the proposed influenza strain definitions. Previous approaches have modeled the effects on cross-immunity and mechanisms such as age-structure, multiple strain interactions and seasonal effects attempting to understand the origin of the frequently observed sustained oscillations, but have not provided precise strain definitions. In our approach, clear assumptions on strain definitions are given to elucidate the role of cross-immunity. We trust that realistic conclusions can be made if precise strain assumptions are set forward. In particular, appropriate levels of cross-immunity should be explored based merely on the empirical evidence as proposed in the studies [3, 22].

In our two-strain model we explore stability conditions for the disease-free state as well as the endemic states. To gain intuition about the stability of our system in the absence of strains, we compute the two reproductive numbers $R_1, R_2$ of the strains. For stability in the presence of both strains, we find that there are two boundary equilibria $E_1$ and $E_2$ such that $E_1$ has only strain 1 and in $E_2$ has only strain 2. Due to the complexity of our system, we do not establish analytically the presence of coexistence equilibria but from the simulations it appears that there are such. In agreement with the results in [11], we suspect that there might be up to four coexistence equilibria. If $R_1$ and $R_2$ are below one then the disease-free equilibrium is locally stable. We have not been able to establish global stability of the disease-free equilibrium. We suspect that might be due to the presence of subthreshold coexistence equilibria and backward bifurcation. We establish that $E_1$ (respectively $E_2$) is locally stable under additional conditions and may lose stability which leads to oscillations. We give an explicit formula for the period of these oscillations and the threshold value of the bifurcation parameter $\alpha_c$.

The model developed in this paper explores quarantine as a possible mechanism leading to the sustained oscillations. We extend the approach of previous studies by proposing three strain definitions
and therefore realistic levels of cross-immunity for analyzing the system of equations. Our numerical simulations suggest that oscillations occur for strong ($\sigma = 0.01$) and intermediate ($\sigma = 0.4$) cross-immunity for realistic periods of quarantine (3, 15 days). For strong cross-immunity the epidemics disappears from the population for long intervals of time (up to 20 years) and is present for intervals of about 10 years as shown in [9]. In the case of intermediate cross-immunity, sustained oscillations exhibit close peaks of periods between 5 and 10 years; this mechanism is similar to the "exploitation competition" dynamics observed in previous studies where the presence of cross-immunity influences the potential of survival of the strains introduced into the population [3]. We also observe that the amplitude of the oscillations increase as the period of isolation increase for moderate isolation periods ($\frac{1}{\alpha} \in (3, 15) \text{ days}$), and moderate cross-immunity($\sigma = 0.01$).

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