

On the Dynamics of a Two-Strain Influenza Model with Isolation

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Abstract. Influenza has been responsible for human suffering and economic burden worldwide. Isolation is one of the most effective means to control the disease spread. In this work, we incorporate isolation into a two-strain model of influenza. We find that whether strains of influenza die out or coexist, or only one of them persists, it depends on the basic reproductive number of each influenza strain, cross-immunity between strains, and isolation rate. We propose criteria that may be useful for controlling influenza. Furthermore, we investigate how effective isolation is by considering the host's mean age at infection and the invasion rate of a novel strain. Our results suggest that isolation may help to extend the host's mean age at infection and reduce the invasion rate of a new strain. When there is a delay in isolation, we show that it may lead to more serious outbreaks as compared to no delay.

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1. Introduction

The emergence and reemergence of multi-strain infectious diseases driven by mutations has been known as a cause of death worldwide. Pathogen mutations are found commonly in many infectious diseases such as: 1) measles [1], 2) hepatitis B [2–4], 3) HIV [5], 4) West Nile virus [6], 5) pertussis [7, 8], 6) malaria [9], and 7) influenza [10, 11]. In this work, we are particularly interested in the dynamics of influenza. Influenza is an RNA virus which is separated into three types A, B, and C. Influenza A is the most common one in human and animal populations. On the influenza surface, there are two important proteins, hemagglutinin (HA) and neuraminidase (NA), that change significantly over time.

Two mechanisms of influenza viruses, shift and drift processes, allow them to escape the recognition of the host immune system. Antigenic shift generates a new subtype by drastically changing protein molecules (HA and NA) on a viral surface, while antigenic drift continually changes the protein molecules by point mutations to generate a new strain. In host, cross-immunity plays an important role against the escape mutant [12, 13]. Cross-immunity is high between similar strains and very low when they are genetically different, two strains from different subtypes for instance [14, 15]. Cross-immunity may act in different ways such as reducing susceptibility when hosts get infected with one strain and become

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less susceptible to other related strains, reducing transmissibility during subsequent infections with similar strains from previous infection, and polarizing immunity when only some individuals acquire total immunity to related strains from previous infection while others gain no immunity.

Mathematical models of multi-strain diseases have fruitfully been used to study the dynamics of the pathogens in a host population [16–29]. By considering the models relating to cross-immunity, they can be separated into many types, for instance a moving frame in immunity spaces [30,31], a season-to-season drift [25,26], a history-based framework [18], and a status-based framework [21,22]. This work is based on the latter type, where susceptible individuals are categorized by their current immune status instead of their immune memory.

Controlling diseases is an important means for public health to reduce the cost arising from the spread of the diseases. Several control strategies are available for influenza such as isolation, vaccination, and the use of treatments. Here, we only concentrate on isolation. Isolation is applied to infected individuals so as to prevent them from further contacts and subsequent transmissions to other individuals. It is primarily used for controlling the disease when it suddenly emerges or reemerges. A successful example is the isolation of those infected with SARS during 2003-2004. However, the disadvantages of this strategy are the difficulty of detecting infected individuals and the cost of isolation. Although many models for multiple-strain diseases have been fruitfully developed, models including isolation are very limited [32,33].

In this work, we study the dynamics of a host population when two strains of influenza are co-circulating. Inspired by the current use of isolation, we propose a new model to investigate how isolation may help to control influenza by considering threshold conditions, the host’s mean age at infection, the invasion rate of a new strain, and delay in isolation.

2. Model formulation

We here propose a model of isolation. The model is based on a status-based framework by [22]. The model assumes polarized susceptibility, i.e. each individual is either completely immune or completely susceptible to each strain of a disease. Immediately on infection with a strain of a disease, an individual is assumed to become immune to that strain with probability 1 and immune to related strains with reduced probabilities. For a disease with two co-circulating strains, each individual, whether infected or not, has one of four possible immune repertoires \emptyset , $\{1\}$, $\{2\}$, $\{1,2\}$. We assume that an individual with immune repertoire \emptyset has probability σ of acquiring immunity to strain 2 (as well as strain 1) on infection with strain 1, and the same probability σ of acquiring immunity to strain 1 on infection with strain 2. Following [22], we assume further that an individual with immune repertoire $\{1\}$ also has probability σ of acquiring immunity to strain 2 on contact with an individual infected with strain 1 even though infection with strain 1 is impossible, and similarly when an individual with immune repertoire $\{2\}$ comes into contact with an individual infected with strain 2. These assumptions allow us to write down a system of four equations for four classes of hosts: susceptible to strain 1, S_1 (whether with immune repertoire \emptyset or $\{2\}$ and whether or not infected with strain 2); infected with strain 1, I_1 ; susceptible to strain 2, S_2 ; and infected with strain 2, I_2 . Note that these classes are not mutually exclusive, and that some individuals do not belong to any of them. We assume that the a recovery rate from each strain is the same and denote it by ν_0 , but that each strain has a different rate of transmission denoted by β_1 and β_2 .

Because of similar symptoms and the difficulty of clinically distinguishing a viral strain, we assume that rate at which infected individuals are detected and removed to isolation (q_0) is the same for strain 1 and strain 2. Removing such individuals to isolation does not change their immune status and they return to the same S_i class after recovery, so (on the assumption that there are few individuals in isolation at any one time) the equations for S_1 and S_2 are unchanged. We assume that individuals leave the isolation class when they recover, hence, at rate ν_0 .

The model takes the following form:

$$\begin{aligned}
S'_1(t) &= \mu_0 N - \mu_0 S_1 - \beta_1 S_1 I_1 - \sigma \beta_2 S_1 I_2, \\
I'_1(t) &= \beta_1 S_1 I_1 - (\nu_0 + \mu_0 + q_0) I_1, \\
S'_2(t) &= \mu_0 N - \mu_0 S_2 - \beta_2 S_2 I_2 - \sigma \beta_1 S_2 I_1, \\
I'_2(t) &= \beta_2 S_2 I_2 - (\nu_0 + \mu_0 + q_0) I_2, \\
Q'(t) &= q_0 (I_1 + I_2) - \nu_0 Q.
\end{aligned} \tag{2.1}$$

Note that this model can be derived from the status-based model presented by [21] and simplified by the assumptions in [22]. We consider the status-based model with isolation for two strains of influenza as follows:

$$\begin{aligned}
\dot{S}_\phi &= \mu N - \mu S_\phi - C(\phi, \{1\}, 1) A_1 S_\phi - C(\phi, \{1, 2\}, 1) A_1 S_\phi - \\
&\quad C(\phi, \{2\}, 2) A_2 S_\phi - C(\phi, \{1, 2\}, 2) A_2 S_\phi, \\
\dot{S}_{\{1\}} &= C(\phi, \{1\}, 1) A_1 S_\phi - C(\{1\}, \{1, 2\}, 2) A_2 S_{\{1\}} - \\
&\quad C(\{1\}, \{1, 2\}, 1) A_1 S_{\{1\}} - \mu S_{\{1\}}, \\
\dot{S}_{\{2\}} &= C(\phi, \{2\}, 2) A_2 S_\phi - C(\{2\}, \{1, 2\}, 1) A_1 S_{\{2\}} - \\
&\quad C(\{2\}, \{1, 2\}, 2) A_2 S_{\{2\}} - \mu S_{\{2\}}, \\
\dot{S}_{\{1,2\}} &= C(\phi, \{1, 2\}, 1) A_1 S_\phi + C(\phi, \{1, 2\}, 2) A_2 S_\phi + \\
&\quad C(\{1\}, \{1, 2\}, 2) A_2 S_{\{1\}} + C(\{2\}, \{1, 2\}, 1) A_1 S_{\{2\}} - \mu S_{\{1,2\}}, \\
\dot{I}_1 &= \Lambda_1 (S_\phi + S_{\{2\}}) - (\mu + \nu_1 + q_1) I_1, \\
\dot{I}_2 &= \Lambda_2 (S_\phi + S_{\{1\}}) - (\mu + \nu_2 + q_2) I_2, \\
\dot{Q}_1 &= q_1 I_1 - \kappa_1 Q_1, \\
\dot{Q}_2 &= q_2 I_2 - \kappa_2 Q_2,
\end{aligned} \tag{2.2}$$

where $\mathcal{J} \subseteq \{1, 2\}$, $A_i = \beta_i I_i$, $S_{\mathcal{J}}$ represents the number of hosts that are completely immune to the strains in the set \mathcal{J} , I_i the number of infectious individuals to strain i , Q_i the number of isolated individuals, previously infected with strain i , and $C(\mathcal{L}, \mathcal{J}, i)$ the probability that hosts recover to a state \mathcal{J} , having started in state \mathcal{L} and been infected by strain i . A flow diagram is shown in Figure 2 and other parameters can be found in Table 1.

In this model, we assume that rates at which individuals infected with strain 1 and strain 2 are detected and removed to isolation are q_1 and q_2 , respectively. We assume that isolated individuals are removed at rate κ_1 for strain 1 and κ_2 for strain 2, whenever they recover [34]. Note that removing individuals to isolation does not change their immune status, so they return to the same S_i class after recovery (see Figure 2). For simplicity, we now assume that rates of detecting individuals infected with strain 1 and 2 are equivalent ($q_1 = q_2 = q_0$). Also, individuals have the same rate of recovery from both strains ($\nu_1 = \nu_2 = \nu_0$) and rate of removing individuals from isolation equals rate of recovery ($\kappa_1 = \kappa_2 = \nu_0$).

The polarized immunity is assumed which means that cross-immunity acts to render some hosts totally immune while other hosts gain nothing from infections. Also, the reduced-transmission of cross-immunity is assumed. By assuming that cross-immunity is conferred by exposure even if immunity prevents the full disease from developing, this allows all hosts to have the same chance of gaining immunity to a strain whatever their current immune status is. The system (2.2) can be reduced such that only one variable is needed to explain the host with respect to each strain. Since $S_{\{1,2\}}$ does not appear in other equations, it can be omitted from the system. We introduce a new variable Q as the total number of isolated individuals previously infected with both strains of influenza, $Q = Q_1 + Q_2$. Let $S_1 = S_\phi + S_{\{2\}}$ and $S_2 = S_\phi + S_{\{1\}}$. Hence, by the fact that $\sum_{\mathcal{J}} C(\mathcal{K}, \mathcal{J}, i) = 1$:

$$\dot{S}_1 = \mu N - \mu S_1 - A_1 S_1 - C(\phi, \{1, 2\}, 2) A_2 S_\phi - C(\{2\}, \{1, 2\}, 2) A_2 S_{\{2\}}$$

Define $C(\phi, \{1, 2\}, 2) = C(\{2\}, \{1, 2\}, 2) = \sigma_{12}$, which is the chance that an infection by strain 2 gives immunity to strain 1. Hence,

$$\dot{S}_1 = \mu N - \mu S_1 - A_1 S_1 - \sigma_{12} A_2 S_1.$$

The equations for S_2 can be obtained in the similar way. We further assume that $\sigma_{12} = \sigma_{21}$, for simplicity. Therefore, the system (2.2) becomes the system (2.1)

3. Analysis

We normalise the system (2.1) by introducing the new variables and parameters as follows:

$$s_1 = \frac{S_1}{N}, \quad i_1 = \frac{I_1}{N}, \quad s_2 = \frac{S_2}{N}, \quad i_2 = \frac{I_2}{N}, \quad q = \frac{Q}{N},$$

$$T = (\mu_0 + \nu_0 + q_0)t, \quad \mu = \frac{\mu_0}{\mu_0 + \nu_0 + q_0}, \quad \theta = \frac{q_0}{\mu_0 + \nu_0 + q_0}, \quad \nu = \frac{\nu_0}{\mu_0 + \nu_0 + q_0},$$

and the basic reproductive numbers for strain 1 and strain 2 in both interventions are

$$R_{1q} = \frac{\beta_1 N}{\mu_0 + \nu_0 + q_0} \quad \text{and} \quad R_{2q} = \frac{\beta_2 N}{\mu_0 + \nu_0 + q_0}.$$

Note that, for strain i , a single infectious individual introduced to an entirely susceptible population makes $\beta_i N$ contacts in unit time with susceptible individuals during its infectious period, which is $1/(\mu_0 + \nu_0 + q_0)$. We also remark here that R_{1q} and R_{2q} can be written in terms of $R_1(\beta_1 N/(\mu_0 + \nu_0))$ and $R_2(\beta_2 N/(\mu_0 + \nu_0))$, the basic reproductive numbers of strain 1 and 2 when isolation is absent as

$$R_{1q} = (1 - \theta)R_1 \quad \text{and} \quad R_{2q} = (1 - \theta)R_2.$$

The model is now in the following form:

$$\begin{aligned} s_1'(T) &= \mu(1 - s_1) - R_{1q}s_1i_1 - \sigma R_{2q}s_1i_2, \\ i_1'(T) &= R_{1q}s_1i_1 - i_1, \\ s_2'(T) &= \mu(1 - s_2) - R_{2q}s_2i_2 - \sigma R_{1q}s_2i_1, \\ i_2'(T) &= R_{2q}s_2i_2 - i_2, \\ q'(T) &= \theta(i_1 + i_2) - \nu q. \end{aligned} \tag{3.1}$$

3.1. Steady states

By setting the right-hand sides of the system (3.1), we have four steady states:

1. The disease-free steady state

$$P_q^0 = (s_{1q}^0, i_{1q}^0, s_{2q}^0, i_{2q}^0, q_q^0) = (1, 0, 1, 0, 0).$$

2. The single-strain steady state of strain 1

$$P_q^1 = (s_{1q}^1, i_{1q}^1, s_{2q}^1, i_{2q}^1, q_q^1) = \left(\frac{1}{R_{1q}}, \frac{\mu}{R_{1q}}(R_{1q} - 1), \frac{1}{1 + \sigma(R_{1q} - 1)}, 0, \frac{\theta\mu}{\nu R_{1q}}(R_{1q} - 1) \right)$$

which is positive if and only if

$$R_{1q} > 1. \tag{3.2}$$

3. The single-strain steady state of strain 2

$$P_q^2 = (s_{1q}^2, i_{1q}^2, s_{2q}^2, i_{2q}^2, q_q^2) = \left(\frac{1}{1 + \sigma(R_{2q} - 1)}, 0, \frac{1}{R_{2q}}, \frac{\mu}{R_{2q}}(R_{2q} - 1), \frac{\theta\mu}{\nu R_{2q}}(R_{2q} - 1) \right)$$

which is positive if and only if

$$R_{2q} > 1. \tag{3.3}$$

4. The coexistent steady state

$$P_q^* = (s_{1q}^*, i_{1q}^*, s_{2q}^*, i_{2q}^*, q_q^*)$$

where

$$s_{1q}^* = \frac{1}{R_{1q}}, \quad i_{1q}^* = \frac{\mu}{(1 - \sigma^2)R_{1q}} [(R_{1q} - 1) - \sigma(R_{2q} - 1)],$$

$$s_{2q}^* = \frac{1}{R_{2q}}, \quad i_{2q}^* = \frac{\mu}{(1-\sigma^2)R_{2q}} [(R_{2q}-1) - \sigma(R_{1q}-1)],$$

and

$$q_q^* = \frac{\theta\mu}{(1-\sigma^2)\nu R_{1q}R_{2q}} [R_{2q}(R_{1q}-1) + R_{1q}(R_{2q}-1) - \sigma [R_{1q}(R_{1q}-1) + R_{2q}(R_{2q}-1)]],$$

which is positive if and only if both of the following conditions hold

$$(R_{1q}-1) - \sigma(R_{2q}-1) > 0 \quad (3.4)$$

and

$$(R_{2q}-1) - \sigma(R_{1q}-1) > 0. \quad (3.5)$$

Note that from these two conditions, q_q^* is consequently positive. Also note that the steady states when there is no isolation can be found by setting θ equaling to zero and they are parallel to the steady states here.

3.2. Stability analysis

Theorem 3.1. *Stability conditions for each steady state are as follows:*

1. *The disease-free steady state is stable if and only if $R_{1q} < 1$ and $R_{2q} < 1$, or $\theta > 1 - \frac{1}{R_1}$ and $\theta > 1 - \frac{1}{R_2}$.*
2. *The single-strain steady state of strain 1 is stable if and only if $R_{1q} > 1$ and $R_{2q} - 1 - \sigma(R_{1q} - 1) < 0$, or $\theta < 1 - \frac{1}{R_1}$ and $(R_2 - 1) - \sigma(R_1 - 1) < (R_2 - \sigma R_1)\theta$.*
3. *The single-strain steady state of strain 2 is stable if and only if $R_{2q} > 1$ and $R_{1q} - 1 - \sigma(R_{2q} - 1) < 0$, or $\theta < 1 - \frac{1}{R_2}$ and $(R_1 - 1) - \sigma(R_2 - 1) < (R_1 - \sigma R_2)\theta$.*
4. *The coexistent steady state is stable if and only if $R_{2q} - 1 - \sigma(R_{1q} - 1) > 0$ and $R_{1q} - 1 - \sigma(R_{2q} - 1) > 0$, or $(R_2 - 1) - \sigma(R_1 - 1) > (R_2 - \sigma R_1)\theta$ and $(R_1 - 1) - \sigma(R_2 - 1) > (R_1 - \sigma R_2)\theta$.*

Proof. The stability conditions can be derived by considering the Jacobian matrix of the system (3.1) and using the Routh-Hurwitz criteria. Each steady state is stable if and only if all eigenvalues of the Jacobian matrix at the steady state have negative real parts. In case we cannot determine the eigenvalues of the Jacobian matrix explicitly, we consider whether the coefficients of the characteristic equation satisfy the Routh-Hurwitz criteria [35]. If the characteristic polynomial is of order 4,

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0,$$

the steady state is stable if and only if

$$a_1 > 0, a_3 > 0, a_4 > 0, \text{ and } a_1a_2a_3 > a_3^2 + a_1^2a_4.$$

Since Q does not appear in other differential equations in (3.1), it can be omitted from the system. The Jacobian matrix of the system (3.1) is

$$J = \begin{bmatrix} -\mu - R_{1q}i_1 - \sigma R_{2q}i_2 & -R_{1q}s_1 & 0 & -\sigma R_{2q}s_1 \\ R_{1q}i_1 & R_{1q}s_1 - 1 & 0 & 0 \\ 0 & -\sigma R_{1q}s_2 & -\mu - R_{2q}i_2 - \sigma R_{1q}i_1 & -R_{2q}s_2 \\ 0 & 0 & R_{2q}i_2 & R_{2q}s_2 - 1 \end{bmatrix}. \quad (3.6)$$

At the disease-free steady state, four eigenvalues of the Jacobian matrix are

$$-\mu, -\mu, R_{1q} - 1, R_{2q} - 1.$$

All eigenvalues are negative if $R_{1q} < 1$ and $R_{2q} < 1$. Whenever $R_{1q} > 1$ or $R_{2q} > 1$, the steady state becomes unstable. Hence, the disease-free steady state is stable if and only if

$$R_{1q} < 1 \text{ and } R_{2q} < 1.$$

At the single-strain steady state of strain 1, the eigenvalues of the Jacobian matrix are

$$-\mu - \sigma R_{1q} i_{1q}^1, \frac{-(\mu + R_{1q} i_{1q}^1) \pm \sqrt{(\mu + R_{1q} i_{1q}^1)^2 + 4R_{1q}^2 s_{1q}^1 i_{1q}^1}}{2}, \text{ and } R_{2q} S_{2q}^1 - 1.$$

We see that all of these eigenvalues are negative if $R_{1q} > 1$ and $(R_{2q} - 1) - \sigma(R_{1q} - 1) < 0$. Since the steady state is unstable if at least $(R_{2q} - 1) - \sigma(R_{1q} - 1) > 0$, the single-strain steady state of strain 1 is stable if and only if

$$R_{1q} > 1 \text{ and } (R_{2q} - 1) - \sigma(R_{1q} - 1) < 0.$$

At the single-strain steady state of strain 2, the stability conditions can be found in the similar way.

At the coexistent steady state, we use the Routh-Hurwitz criteria to derive stability conditions. We consider the characteristic equation of the Jacobian matrix as follows:

$$\lambda^4 + a_1 \lambda^3 + a_2 \lambda^2 + a_3 \lambda + a_4,$$

where

$$\begin{aligned} a_1 &= (\mu + R_{1q} i_{1q}^* + \sigma R_{2q} i_{2q}^*) + (\mu + R_{2q} i_{2q}^* + \sigma R_{1q} i_{1q}^*), \\ a_2 &= (\mu + R_{1q} i_{1q}^* + \sigma R_{2q} i_{2q}^*)(\mu + R_{2q} i_{2q}^* + \sigma R_{1q} i_{1q}^*) + (R_{1q}^2 s_{1q}^* i_{1q}^* + R_{2q}^2 s_{2q}^* i_{2q}^*), \\ a_3 &= R_{1q}^2 s_{1q}^* i_{1q}^* (\mu + R_{2q} i_{2q}^* + \sigma R_{1q} i_{1q}^*) + R_{2q}^2 s_{2q}^* i_{2q}^* (\mu + R_{1q} i_{1q}^* + \sigma R_{2q} i_{2q}^*) \\ a_4 &= (1 - \sigma^2) R_{1q}^2 R_{2q}^2 s_{1q}^* i_{1q}^* s_{2q}^* i_{2q}^*. \end{aligned}$$

Obviously, $a_1 > 0, a_3 > 0$, and $a_4 > 0$, when $i_{1q}^* > 0$ and $i_{2q}^* > 0$. After comparing and canceling similar terms of $a_1 a_2 a_3$ and $a_3^2 + a_1^2 a_4$, we have two terms left to be compared:

$$\text{LHS: } (R_{1q}^2 s_{1q}^* i_{1q}^* - R_{2q}^2 s_{2q}^* i_{2q}^*)^2 (\mu + R_{1q} i_{1q}^* + \sigma R_{2q} i_{2q}^*) (\mu + R_{2q} i_{2q}^* + \sigma R_{1q} i_{1q}^*) \text{ from } a_1 a_2 a_3,$$

and

$$\text{RHS: } -2\sigma^2 R_{1q}^2 R_{2q}^2 s_{1q}^* i_{1q}^* s_{2q}^* i_{2q}^* (\mu + R_{1q} i_{1q}^* + \sigma R_{2q} i_{2q}^*) (\mu + R_{2q} i_{2q}^* + \sigma R_{1q} i_{1q}^*) \text{ from } a_3^2 + a_1^2 a_4.$$

Whenever i_{1q}^* and i_{2q}^* are both positive, the LHS term is positive while the RHS term is negative. Hence,

$$a_1 a_2 a_3 > a_3^2 + a_1^2 a_4.$$

In case i_{1q}^* and i_{2q}^* have different signs, $a_4 < 0$. When i_{1q}^* and i_{2q}^* are negative, $a_3 < 0$ if $(\mu + R_{1q} i_{1q}^* + \sigma R_{2q} i_{2q}^*)$ and $(\mu + R_{2q} i_{2q}^* + \sigma R_{1q} i_{1q}^*)$ are positive; $a_1 < 0$ if both of them are negative; and $a_1 a_2 a_3 < a_3^2 + a_1^2 a_4$ if they have different signs. Consequently, either i_{1q}^* or i_{2q}^* is negative, the coexistent steady state is unstable. Therefore, the coexistent steady state is stable if and only if $i_{1q}^* > 0$ and $i_{2q}^* > 0$, or

$$R_{2q} - 1 - \sigma(R_{1q} - 1) > 0 \text{ and } R_{1q} - 1 - \sigma(R_{2q} - 1) > 0.$$

□

Relating to the stability conditions in Theorem 3.1, Figure 2 shows the competition between two strains of influenza as functions of the basic reproductive numbers.

3.3. The mean age at infection

The mean age at infection or the mean time that a human remains susceptible is an important indicator of the disease prevalence [34]. Here, we study the mean age at infection of strain 1 by fixing the basic reproductive number of strain 2, varying the basic reproductive number of strain 1, and ignoring the small natural-death term in (2.1) when time is not rescaled. The mean age at infection of strain 2 can be studied in the similar way. We separate the mean age at infection into two cases:

1. in the absence of strain 2

2. in the presence of strain 2

Proposition 3.2. *Assume that $R_{1q} > 1$ and $R_{2q} > 1$.*

1. *The mean age at infection to strain 1 is absent when strain 2 persists ($R_{1q} < \sigma(R_{2q} - 1) + 1$).*
2. *The mean age at infection to strain 1 is*

$$A_{2q} = \frac{1}{\beta_1 i_{1q}^* N} = \frac{(1 - \sigma^2)}{\mu_0 [(R_{1q} - 1) - \sigma(R_{2q} - 1)]}, \quad (3.7)$$

when both strains exist or $\sigma(R_{2q} - 1) + 1 < R_{1q} < (R_{2q} - 1)/\sigma + 1$.

3. *The mean age at infection to strain 1 is*

$$A_{1q} = \frac{1}{\beta_1 i_{1q}^1 N} = \frac{1}{\mu_0 (R_{1q} - 1)}, \quad (3.8)$$

when strain 1 outcompetes strain 2 or $R_{1q} > (R_{2q} - 1)/\sigma + 1$.

Proof. This follows the stability conditions and the definition of the mean age at infection. \square

3.4. Rate of invasion of the novel strain

In this section instead of assuming that we have two strains of influenza co-circulating in the host population to study the long-term dynamics, we consider the situation that strain 1 is endemic first while strain 2 is absent in order to examine the invasion rate of strain 2 to invade a resident strain (strain 1).

Proposition 3.3. *Assume that individuals are at the single-strain steady state of strain 1. The invasion rate of strain 2 is*

$$k_q = \frac{(R_{2q} - 1) - \sigma(R_{1q} - 1)}{(1 + \sigma(R_{1q} - 1))}. \quad (3.9)$$

Proof. In the presence of isolation, the invasion dynamics of strain 2 at the beginning of invasion can be approximated by linearisation about the resident-strain steady state. Because $i_2'(t) = R_{2q}s_2i_2 - i_2$,

$$i_2(t) = C_2 e^{(R_{2q}s_2 - 1)t} = C_2 e^{k_q t}$$

where C_2 is a positive constant. Hence, $k_q = R_{2q}s_2^1 - 1$. \square

4. Numerical Studies

We choose to show the numerical results when $R_1 > R_2$. Parameter values can be found in Table 1. If $R_1 = 3.5$, $R_2 = 3$, and $\sigma = 0.75$, both strains coexist when $\theta < 0.3333$; only strain 1 persists when $0.3333 < \theta < 0.7143$; and both strains die out when $\theta > 0.7143$. Figure 3(a) shows the numerical result when $\theta = 0.2$, so we have the coexistence of the strains. In Figure 3(b), $\theta = 0.5$, strain 2 is driven out by strain 1. In Figure 3(c), we have $\theta = 0.85$, so both strains die out from the host population.

In addition, we assume that the delay in isolation occurs for one month. Instead of starting the isolation at the beginning ($t = 0$), we introduce it one month later and compare it with the situation that the delay does not occur. We run the simulation with $\theta = 0$ until one month and then continue running it but with $\theta = 0.5$ after that and compare it with the result that we run the simulation with $\theta = 0.5$ constantly from the beginning. The sample case that we further study here is from the previous result (see Figure 3(b)) where strain 1 is endemic and when $R_1 = 3.5$, $R_2 = 3$, and $\sigma = 0.75$. The simulations were run until $t = 5000$ in years but we only choose to show the results in some time intervals that the difference between the models are distinguished because the models are synchronized when time becomes very large. By starting with the same number of infectious individuals, we simulate the model in the situation that we

have the delay in isolation to compare it with the situation that we start isolation at the beginning of the disease (see Figure 4). In Figure 4(a), we show the number of infectious individuals to strain 1 at the beginning of the disease. We can see that with the delay in isolation a high jump appears (or an outbreak) while the model without the delay produces the lower jumps. The high jumps continually appears but with the lower height when time increases (see Figure 4(b)) and finally the number of infectious diseases in both cases tends to $i_{1q}^1 N$ or I_1 . For strain 2, it dies out quickly in the absence of isolation delay while it leads to one outbreak (a high jump) and then dies out in the presence of isolation delay (see Figure 4(c)). From the result, we conclude that the delay in isolation leads to serious outbreaks.

By fixing the basic reproductive ratio of strain 2, $R_{2q} = 3$, and $\sigma = 0.8$, Figure 5(a) shows that the host's mean age of infection is A_{2q} in (3.7) when $2.6 < R_{1q} < 3.5$ or A_{1q} in (3.8) when $R_{1q} > 3.5$. In Figure 5(b), isolation extends the host's mean age of infection comparing with the system without intervention. Hence, isolation helps to increase the host's mean age of infection to the strain.

We consider the invasion rate of strain 2 by fixing $R_1 = 3$, $\sigma = 0.8$, and $q_0 = 365.3$. Figure 6 shows the comparison of the invasion rate between with and without isolation. The results suggest that isolation helps to reduce the invasion rate of a new strain.

5. Conclusion and discussion

In this work, we introduce an isolation model for two co-circulating strains of influenza. The model is based on a status-based framework by [22] that individuals are categorized according to their immune status.

Based on this study, whether both strains of influenza die out or coexist, or only one strain of them persists, it depends on the basic reproductive number of each strain of influenza, cross-immunity between strains, and isolation rate (see Table 2). When isolation is delayed, our results suggest that the delay leads to higher jumps of the number of infectious individuals which represent more serious outbreaks than when there is no delay in isolation. Hence, launching isolation as soon as possible may help to control influenza effectively.

We study the mean age of infection to strain 1 when strain 2 is either absent or present. We show that the host's mean age of infection to strain 1 is extended (so hosts are unlikely to get infected) by isolation. By assuming that strain 1 is endemic in the host population, we study the invasion rate of a new strain. The model predicts that isolation helps to reduce the invasion rate of a new strain.

All in all, we hope that this study may help to understand the strain dynamics of influenza when a control strategy like isolation is applied.

Appendix

TABLE 1. Lists of parameters

Parameter	Description	Value	References
μ_0	birth or death rate	1/70	(estimated)
ν_0	recovery rate	365/7	[22]
β_i	transmission rate of strain i	$R_0(\mu_0 + \nu_0)/N$	
σ	cross-immunity coefficient (induced by infection)	0.75-0.8	[22]
q_0	rate of removing infectious individuals to isolation	365/3 (or varies)	(estimated)
R_0	the basic reproductive number	3 (or varies)	[31]
N	the total size of population	10000000	(estimated)
S_i	the number of susceptible individuals to strain i		
I_i	the number of individuals infected with strain i		
Q	the total number of isolated individuals		

TABLE 2. Steady state chart for the isolation model.

Basic reproductive numbers	P_q^0	P_q^1	P_q^2	P_q^*
$R_{1q}, R_{2q} < 1$	stable	undefined	undefined	undefined
$R_{1q} > 1,$ $R_{2q} < 1 + \sigma(R_{1q} - 1)$	unstable	stable	unstable or undefined	undefined
$R_{2q} > 1,$ $R_{1q} < 1 + \sigma(R_{2q} - 1)$	unstable	unstable or undefined	stable	undefined
$R_{1q} > 1 + \sigma(R_{2q} - 1),$ $R_{2q} > 1 + \sigma(R_{1q} - 1)$	unstable	unstable	unstable	stable

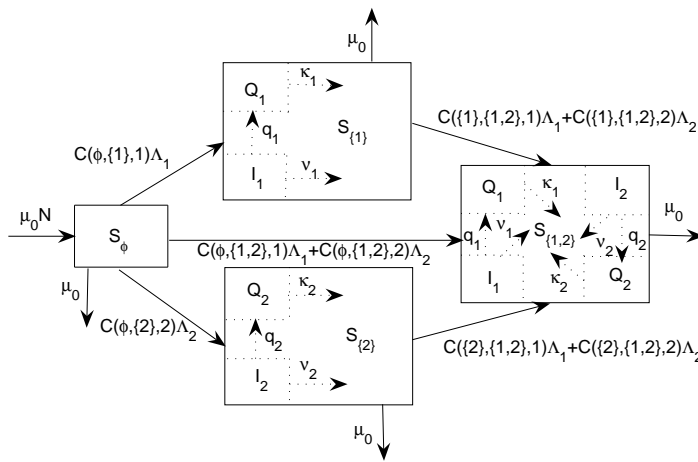


FIGURE 1. A flow diagram for the status-based model with isolation.

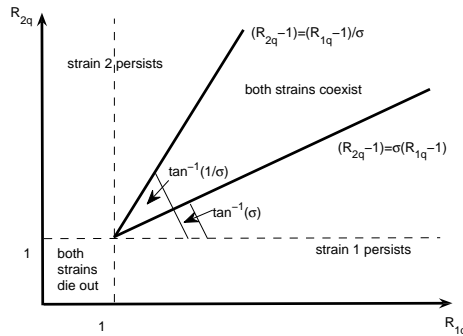


FIGURE 2. The competition between two strains of influenza as functions of the basic reproductive numbers when isolation is present.

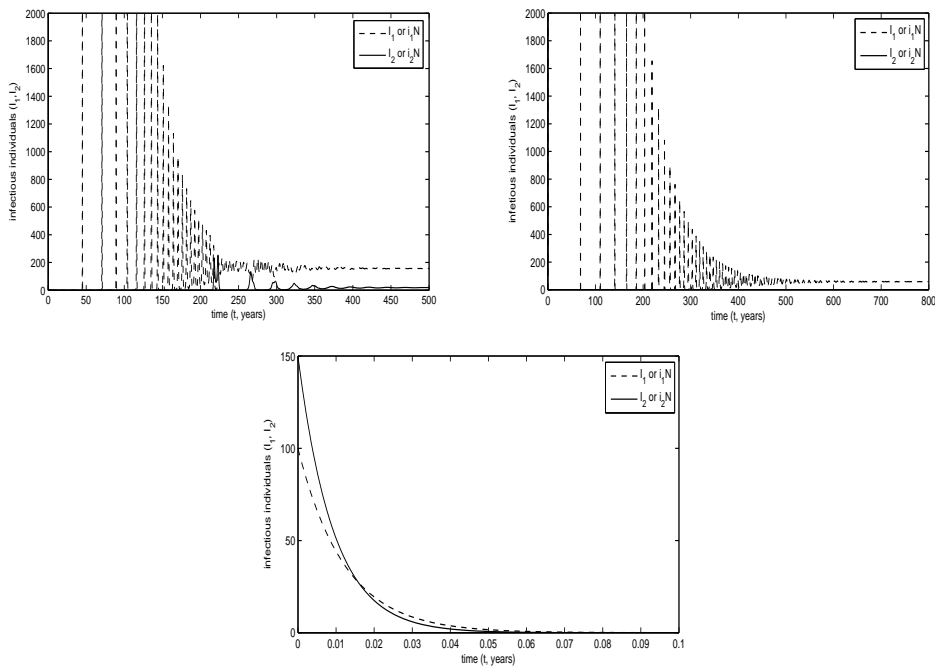


FIGURE 3. Numerical results when isolation is launched; (a) Coexistence of two strains occurs (b) Only strain 1 is endemic (c) Both strains go extinct.

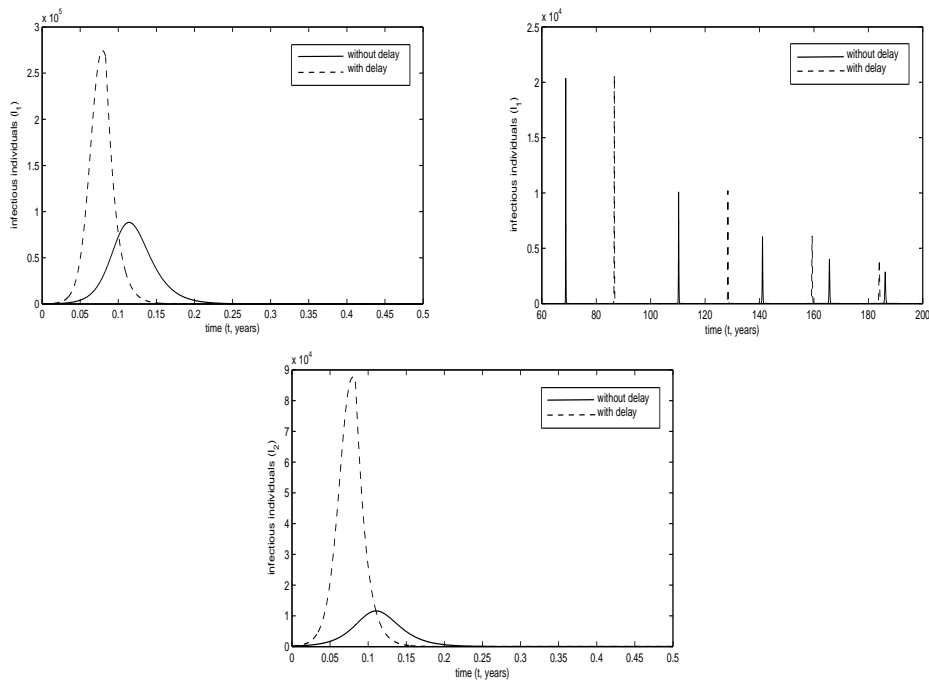


FIGURE 4. Numerical results when a delay in isolation occurs: (a) The dynamics of strain 1 at the onset of the disease: (b) The dynamics of strain 1 after the onset of the disease and when $t \in [60, 200]$ (c) The dynamics of strain 2

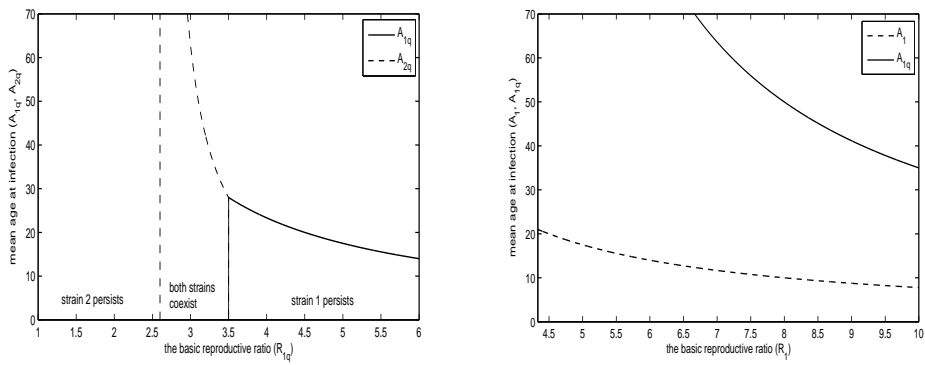


FIGURE 5. (a) The mean age of infection to strain 1 when $R_{2q} = 3$, $\sigma = 0.8$, and R_{1q} is varied. (b) The comparison of A_1 when isolation is absent and A_{1q} when isolation is present (solid and dashed trace, respectively).

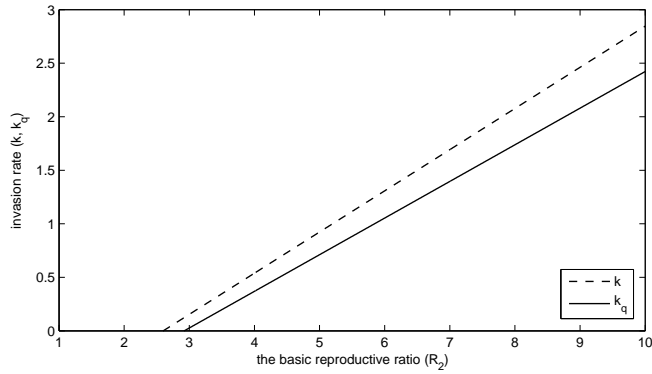


FIGURE 6. The invasion rate when isolation is present (dashed trace) and absent (solid trace) ($R_1 = 3$, $\sigma = 0.8$, $q_0 = 365/3$).

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