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On the role of cross-immunity and vaccines on the survival of less fit flu-strains

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Abstract

A pathogen's route to survival involves various mechanisms including its ability to invade (host's susceptibility) and its reproductive success within an invaded host (''infectiousness''). The immunological history of an individual often plays an important role in reducing host susceptibility or it helps the host mount a faster immunological response de facto reducing infectiousness. The cross-immunity generated by prior infections to influenza A strains from the same subtype provide a significant example. The results of this paper are based on the analytical study of a two-strain epidemic model that incorporates host isolation (during primary infection) and cross-immunity to study the role of invasion mediated cross-immunity in a population where a precursor related strain (within the same subtype, i.e. H3N2, H1N1) has already become established. An uncertainty and sensitivity analysis is carried out on the ability of the invading strain to survive for given cross-immunity levels. Our findings indicate that it is possible to support coexistence even in the case when invading strains are ''unfit'', that is, when the basic reproduction number of the invading strain is less than one. However, such scenarios are possible only in the presence of isolation. That is, appropriate increments in isolation rates and weak cross-immunity can facilitate the survival of less fit strains. The development of ''flu'' vaccines that *minimally* enhance herd cross-immunity levels may, by increasing genotype diversity, help facilitate the generation and survival of novel strains.

Keywords: Influenza; Cross-immunity; Isolation; Invasion reproduction number; Coexistence; Sub-threshold coexistence; Uncertainty and sensitivity analysis

1. Introduction

The cocirculation of several pathogens (''strains'') during a particular flu season is a well known phenomenon that has been documented for several decades (Fig. 2 in Thacker, 1986). Pathogens' coexistence as a function of their ''relatedness'' or ''affinity'' continues to challenge the scientific community (Earn et al., 2002; Ferguson et al., 2003; Gog and Grenfell, 2002; Gomes and Medley, 1999; Gupta et al., 1998; Plotkin et al., 2002; Smith et al., 2004). Theoretical work grounded on explicit host–pathogen systems has shown that pathogens' diversity (coexistence) can be facilitated by a history of prior strain-specific infections (Andreasen et al., 1997; Gupta et al., 1998), the selection of antigenically distinct strains (Dietz, 1979; Earn et al., 2002; Gupta et al., 1998; May and Anderson, 1983), or by cross-immunity (Boni et al., 2004; Castillo-Chavez et al., 1988, 1989; Nuño et al., 2005). So, ''What characterizes a successful invader''? (May et al., 2001).

In this paper we carry out an uncertainty and sensitivity analysis within the context of a two-strain influenza host–parasite system that combines isolation and cross-immunity to quantify the ability of a pathogen to invade and coexist with a resident strain. Cross-immunity gives a relative measure of reduced susceptibility in a host following prior exposure to a related flu strain. We focus on the role of cross-immunity (at low levels) as a mechanism that can facilitate invasion and coexistence, and in the process increase phenotypic diversity (Earn

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et al., 2002). The discussion is carried out within the context of a population exposed to two competing strains (interference competition characterized by cross-immunity levels) of the same subtype of influenza type A. Disease invasion in a "virgin" population facing two competing strains is determined by the overall basic reproduction number, $\Re_0$, where $\Re_0 \equiv \max\{\Re_1, \Re_2\}$. The quantities $\Re_1$ and $\Re_2$ denote the basic reproduction numbers of Strains 1 and 2, respectively, in a non-competitive environment. This dimensionless ratio gives the average number of secondary infections generated by a "typical" infectious individual in a population of susceptibles at a demographic steady state. Here, it is assumed that $\Re_0 > 1$. That is, invasion by either one or both strains is possible. The cross-immunity coefficient ($0 \leqslant \sigma_{12} \leqslant 1$) measures the average reduced susceptibility to Strain 2 gained by a host after recovery from Strain 1. The focus is on quantifying whether or not a novel Strain 2 can successfully invade an established Strain 1 in the presence of cross-immunity (σ_{12}). The strain-specific invasion reproduction number $\Re_2^1(\sigma_{12})$ is defined as the average number of secondary infections generated by Strain 2 in a population where Strain 1 is at an endemic level. Hence, σ_{12} equal to zero corresponds to total cross-immunity (Strain-2 cannot invade) while σ_{12} equal to one corresponds to no cross-immunity.

Prior epidemiological studies that measure σ_{12} have been conducted (Couch and Kasel, 1983; Glezen and Couch, 1978; Taber et al., 1981). These studies are carried out by evaluating the impact (percentage of the population infected) on invading strains on populations with some degree of immunological memory (cross-immunity). These studies provide rough estimates of cross-immunity (σ_{12}) values which have been incorporated in models for the transmission dynamics of influenza (Castillo-Chavez et al., 1988, 1989; Nuño et al., 2005). Typically, we would expect a successful invasion by Strain 2 for cross-immunity values (σ_{12}) that guarantee that $\Re_2^1(\sigma_{12}) > 1$ with $\Re_2 > 1$. However, Nuño et al. (2005) showed that successful invasion (and coexistence) is also possible for some values of σ_{12} when $\Re_2 < 1$. That is, cross-immunity may facilitate the survival of less fit strains as long as the immune system has a limited ability to recognize the invading strain (weak cross-immunity). Here we compute the distribution of $\Re_2^1(\sigma_{12})$ as a function of the variability of parameters, including σ_{12}. We evaluate the possibility of a successful invasion (including sub-threshold coexistence) in the presence of uncertainty. The relation of these results to the possibility of invasion by highly "fit" (highest rate of reproduction within a host) strains as a function of low levels of herd cross-immunity are discussed (Galvani, 2003; Gandon et al., 2001; May and Anderson, 1983). These results may add useful insights into the potential impact of vaccines as promoters of invasions by novel strains since "flu vaccines" may possibly generate low levels of herd cross-immunity, reduce transmission and susceptibility (Ambrosch and Fedson, 1999; Boni et al., 2004; CDC, 2003; Gandon et al., 2001; Smith et al., 1999).

In the next section, we describe the influenza model, define the invasion reproduction number $\Re_2^1(\sigma_{12})$, and outline the approach used in our uncertainty analysis.

2. Methods

The two-strain influenza model (Fig. 1, Nuño et al., 2005) incorporates host isolation during primary infection and competition (interference) through cross-immunity. The population is divided into 10 epidemiological classes. For instance, susceptible individuals (S) may become infected with Strain 1 (I_1) at the rate β_1 (primary infection); following infection with Strain 1, individuals are isolated (Q_1) at the rate δ_1 or moved directly into the recovered class (R_1) at the rate γ_1; upon recovery from Strain 1, individuals may become infected (secondary infection) with Strain 2 (V_2) at a reduced rate $\sigma_{12}\beta_2$; following a secondary infection, Strain-2 infected individuals recover at the rate γ_2 (W); the per capita mortality rate is denoted by μ. Although influenza infection involves a short latent period (1.9 days, CDC, 2006), for simplicity we do not include a latency class in the model (Dushoff et al., 2004). The cross-immunity parameter σ_{12} is a rough measure of the relative susceptibility to Strain 2 (secondary infection) generated by the immune system of an individual previously infected with Strain 1 (primary infection).

We assume that secondary infections result from minor variants of the original invader (primary infection) and therefore, result in clinically milder infections (i.e. isolation does not take place during secondary infection). However, this "somewhat" arbitrary assumption could be easily

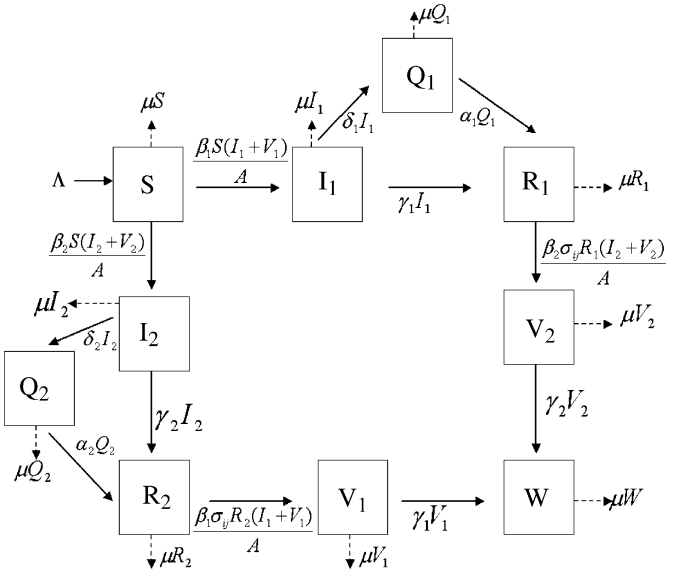

Fig. 1. Flow chart of the state progression of individuals in a population exposed to two influenza strains. Fully susceptible individuals (S) can become infected (primary infection) with Strain 1 (I_1) or Strain 2 (I_2). Infected individuals with Strain 1 (Strain 2) may become isolated Q_1 (Q_2) or recovered R_1 (R_2). Recovered individuals become infected (secondary infection) with Strain 1 (V_1) or Strain 2 (V_2). Infected individuals recover from both strains into class W.

removed but the algebra becomes harder. We suspect that the inclusion of additional isolation classes does not affect the qualitative results of this paper but may have potentially important quantitative differences. A detailed description of the host–pathogen interactions in this two-strain framework is provided in the Appendix (Fig. 1).

Pathogen's invasion is governed by $\Re_0 \equiv \max\{\Re_1, \Re_2\}$. The basic reproduction number of Strain 1 ($\Re_1$) is given by $\beta_1/(\mu+\gamma_1+\delta_1)$ where β_1 is the mean transmission rate of Strain 1 and $(\mu+\gamma_1+\delta_1)^{-1}$ is the mean infectious period of an individual infected with Strain 1. Invasion is only possible when $\Re_0 > 1$. The invasion reproduction number $\Re_2^1$, measures the ability of Strain 2 to invade a Strain 1 endemic population. Values of $\Re_2^1$ exceeding one (conditional on the first strain becoming established, that is, on $\Re_1 > 1$) guarantee the invasion of Strain 1 by Strain 2 (as well as their coexistence). For the epidemic model described above, we will show that in a realistic parameter space coexistence is possible under sub-threshold conditions, that is, when $\Re_2 < 1$ (Nuño et al., 2005). For the remaining of the paper, we study the case in which Strain 1 is assumed to be at the endemic equilibrium (E_1) while a "typical" Strain-2 infected individual is introduced. Moreover, considering that flu strain replacement occurs every 2–5 years (Plotkin et al., 2002) and the demographic time scale of our model (see Appendix) is in the order of decades, then our assumption of a constant total population is valid. Hence, we assume that $N(0) = \Lambda/\mu$, that is , $N(t) \equiv \Lambda/\mu$ for all time t (Castillo-Chavez and Thieme, 1995).

Here, we find that Strain 2 invades (and coexists with Strain 1 at equilibrium) if the number of secondary infections produced by Strain 2 exceeds one, that is, if $\Re_2^1 > 1$. The invasion reproduction number of Strain 2 given that Strain 1 is established is denoted by

$$\Re_2^1 = \frac{\beta_2}{\mu+\gamma_2+\delta_2}\frac{\tilde{S}_1}{\tilde{A}} + \sigma_{12}\frac{\beta_2}{\mu+\gamma_2}\frac{\tilde{R}_1}{\tilde{A}}, \tag{1}$$

where

$$\frac{\tilde{S}_1}{\tilde{A}} = \frac{1}{\Re_1}, \quad \frac{\tilde{R}_1}{\tilde{A}} = (\gamma_1(\mu+\alpha_1)+\alpha_1\delta_1)\phi_1,$$

$$\phi_1 = \frac{(1-1/\Re_1)}{(\mu+\gamma_1)(\mu+\alpha_1)+\alpha_1\delta_1}, \quad \tilde{A} = \frac{1}{\mu(1+\mu\delta_1\phi_1)}. \tag{2}$$

The proportion $\tilde{S}_1/\tilde{A}$ denotes the fully susceptible proportion of the population, and $\tilde{R}_1/\tilde{A}$ denotes the partially protected ("cross-immune") susceptible population to a Strain-2 infected individual. $\Re_2^1$ is given by the additive contribution of the "naive" and "cross-immune" reproduction numbers where $\Re_2^{\text{naive}} \equiv [\beta_2/(\mu+\gamma_2+\delta_2)][\tilde{S}_1/\tilde{A}]$ gives the number of secondary cases that Strain 2 infected individuals generate in the susceptible fraction $\tilde{S}_1/\tilde{A}$ (primary infection) and $\Re_2^{\text{cross-immune}} \equiv [\sigma_{12}\beta_2/(\mu+\gamma_2)][\tilde{R}_1/\tilde{A}]$ describes the number of secondary cases generated by Strain-2 infected individuals among the partially immune proportion, $\tilde{R}_1/\tilde{A}$. A direct analysis of Eq. (1) shows that the likelihood that Strain 2 invades a population endemic with Strain 1 ($\Re_2^1 > 1$) is reduced for antigenically similar strains ($\sigma_{12} \downarrow 0$) and enhanced for strains that differ significantly ($\sigma_{12} \uparrow 1$). A similar argument can be provided for the invasion of Strain 1 given that Strain 2 has become established.

An *uncertainty* analysis on $\Re_2^1$ quantifies its variability generated from the uncertainty of the "input" parameters ($\beta_1, \beta_2, \delta_1, \delta_2, \gamma_1, \gamma_2, \alpha_1, \mu, \sigma_{12}$) while a *sensitivity* analysis of $\Re_2^1$ evaluates the relative impact on $\Re_2^1$ to changes in the same parameters (Blower and Dowlatabadi, 1994; Chowell et al., 2004). The invasion reproduction number $\Re_2^1$ as noted before, is a threshold that determines whether or not Strain 2 is capable of invading Strain 1. We observe that $\Re_2^1$ is a function of $\tilde{S}_1/\tilde{A}$ and $\tilde{R}_1/\tilde{A}$. Hence, the critical proportion of susceptibles needed to support an outbreak by Strain 2 may only be attained through appropriately balanced "efforts" by both strains (interference competition mediated by cross-immunity).

Since the analysis requires the explicit expressions for $\Re_2^1$, we replace

$$\frac{\tilde{S}_1}{\tilde{A}} = \frac{\mu+\gamma_1+\delta_1}{\beta_1} \quad \text{and} \quad \frac{\tilde{R}_1}{\tilde{A}} = (\gamma_1(\mu+\alpha_1)+\alpha_1\delta_1)\phi_1,$$

in our expression for $\Re_2^1$. Therefore,

$$\Re_2^1 = \left(\frac{\beta_2}{\mu+\gamma_2+\delta_2}\right)\left(\frac{\mu+\gamma_1+\delta_1}{\beta_1}\right) + \sigma_{12}\frac{\beta_2}{\mu+\gamma_2}(\gamma_1(\mu+\alpha_1)+\alpha_1\delta_1)\phi_1, \tag{3}$$

$$\phi_1 = \frac{(1-(\mu+\gamma_1+\beta_1)/\beta_1)}{(\mu+\gamma_1)(\mu+\alpha_1)+\alpha_1\delta_1},$$

where σ_{12} denotes the cross-immunity conferred by Strain 1 to invasion by Strain 2. Expression (3) involves nine parameters whose distributions are chosen using known information on flu epidemiology and US demographics (Table 1). Here, we assume a life expectancy of 70 years ($\mu \approx 4 \times 10^{-5}$ days^{-1}). The rate at which each infective gives rise to a new infection (β_i) is sampled from an exponential distribution to account for heterogeneity in transmission rates. The mean values chosen for β_i (0.7, 0.6, $i = 1, 2$) are chosen to support known reproduction numbers of regular influenza epidemics in the mean range 1.2–1.5 (Chowell et al. (2006); Flahault et al., 1988; Longini et al., 1982). The average duration of infectiousness for flu may vary according to the population at risk (CDC, 2006). For instance, healthy individuals are likely to clear the infection faster than immuno-compromised ones. In order to allow for variability in the recovery period and considering that a range of values (lower, peak, upper) are typically known, we sample recovery rates (γ_i, $i = 1, 2$) from asymmetric triangular distributions (Blower and Dowlatabadi, 1994). The corresponding distributions with peak of 7 days (3, 7, 10) for $1/\gamma_1$ and 8 days (5, 7, 12) for

Table 1
Parameter definitions and values used for the uncertainty and sensitivity analyses

Parameter	Definition	Range	Baseline	Reference
$\Re_2^1$	Invasion reproduction number of strain 2	0–15	1.5[a], 5[b]	Nuño et al. (2005)
$\Re_i$	Basic reproduction number of strain i	1.2–1.5	1.4[c],1.5[d]	Chowell et al. (2006), Flahault et al. (1988)
σ_{12}	Cross-immunity	0–1	0.3	Castillo-Chavez et al. (1988), Castillo-Chavez et al. (1989)
Λ, μ	Per capita birth and death rate	0–1 (days^{-1})	0.00004	Couch and Kasel (1983), CDC (2006)
β_i	Transmission rate	0.6–0.7 (days^{-1})	0.6[c], 0.7[d]	Couch et al. (1986), Elveback et al. (1976), Fox et al. (1982)
α_1	Recovery rate for isolated individuals	4–6 (days^{-1})	6[c] (days)	Couch and Kasel (1983), CDC (2006)
δ_i	Isolationrate	2–4 (days^{-1})	3[c], 3.5[d] (days)	Couch and Kasel (1983), CDC (2006)
γ_i	Recovery rate	5–8 (days^{-1})	7[c], 9[d] (days)	Couch and Kasel (1983), CDC (2006)

[a]With 50% probability.
[b]With 10% probability.
[c]Strain 1 parameter.
[d]Strain 2 parameter.

$1/\gamma_2$ are generated through Monte Carlo sampling (Blower and Dowlatabadi, 1994; Chowell et al., 2004). We assume that infected individuals isolate themselves from primary infection at a uniformly distributed rate with mean 3 (interval: 1–5) and 3.5 (interval: 2–5) days following infection from Strains 1 ($1/\delta_1$) and 2 ($1/\delta_2$), respectively (Blower and Dowlatabadi, 1994; CDC, 2006). Similarly, infectives who recover ($1/\alpha_1$) while in isolation do so at a uniformly distributed rate with a mean of 6 days (interval: 2–10) (Blower and Dowlatabadi, 1994; CDC, 2006). The cross-protection (σ_{12}) acquired from an infection with Strain 1 against Strain 2 takes values on the interval $(0, 1)$ (Castillo-Chavez et al., 1988, 1989). Values of σ_{12} near zero indicate strong levels of cross-immunity while values closer to one suggest little-to-none protection against the invading strain. Since the dynamics considered here involve strains within a particular subtype, we assume strong to mildly weak levels of cross-immunity (Castillo-Chavez et al., 1988, 1989). Moreover, we assume that minor variants (antigenic drift) of the original strain continue to provide high levels of protection. We assume a Gaussian distribution for cross-immunity where $1/\hat{\sigma}\sqrt{2\pi}$ describes the peak amplitude, $\hat{\mu}$ (mean) and $\hat{\sigma}$ (standard deviation) denote the centroid and width related to the peak (respectively) in the exponent $e^{-((x-\hat{\mu})/\hat{\sigma}\sqrt{2})^2}$. The analytical and numerical results in Nuño et al. (2005) showed that the model dynamics were highly sensitive to cross-immunity (σ_{12}). Therefore, we sample σ_{12} from a Gaussian distribution with high concentration around the distribution mean (small variance). The use of a Gaussian distribution for cross-immunity was previously discussed by Gog and Grenfell (2002).

2.1. Uncertainty analysis of $\Re_2^1$

For the uncertainty analysis of $\Re_2^1$ we generate 10 Monte Carlo samples of 10^5 repetitions from the parameter distributions described above. Since we want to evaluate the possibility that Strain 2 invades the region where Strain 1 is established, parameter sampling is restricted to the case where $\Re_1 > 1$. Using the input vectors generated from these distributions, we assess the variability (mean and variance) of $\Re_2^1$ due to the uncertainty of the input parameters. We estimate the probability of coexistence (that is, $P[\Re_2^1 > 1]$) for the 10 samples and study the variability in $\Re_2^1$ resulting from the contributions of $\Re_2^{\text{naive}}$ and $\Re_2^{\text{cross-immune}}$. We calculate and illustrate the contribution of each of these quantities in support of strain coexistence (Table 2, Fig. 2).

Table 2
Statistics for $\Re_2^1$, $\Re_2^{\text{naive}}$ and $\Re_2^{\text{cross-immune}}$ for 10 Monte Carlo samples of size of 10^5

Sample	Mean	Variance	$P[\Re_2^{\text{naive}} > 1]$, $P[\Re_2^{\text{cross-immune}} > 1]$
1	1.42, 0.75, 0.69	2.21, 0.79, 0.81	0.25, 0.22
2	1.42, 0.78, 0.68	2.20, 0.96, 0.73	0.25, 0.22
3	1.45, 0.74, 0.68	2.29, 0.82, 0.77	0.24, 0.22
4	1.44, 0.75, 0.69	2.28, 0.78, 0.78	0.25, 0.23
5	1.44, 0.75, 0.68	2.17, 0.81, 0.74	0.25, 0.22
6	1.43, 0.77, 0.68	2.11, 0.91, 0.81	0.25, 0.22
7	1.42, 0.75, 0.68	2.15, 0.90, 0.77	0.24, 0.21
8	1.43, 0.77, 0.67	2.16, 0.87, 0.73	0.25, 0.22
9	1.44, 0.75, 0.68	2.29, 0.79, 0.72	0.24, 0.22
10	1.43, 0.73, 0.67	2.16, 0.78, 0.73	0.24, 0.21

Parameter distributions are illustrated in Figs. 2 and 3. The contribution of $\Re_2^{\text{naive}}$ and $\Re_2^{\text{cross-immune}}$ to coexistence ($\Re_2^1 > 1$) are quantified for cross-immunity with 0.3 mean. The rest of the parameter values are provided in Table 1.

2.2. Sensitivity analysis of $\Re_2^1$

We investigate the sensitivity of $\Re_2^1$ due to the uncertainty of the input parameters by assessing the partial rank correlation coefficients (PRCCs) between $\Re_2^1$ and each of the parameters. The PRCCs describe the correlation between two variables (e.g. $\Re_2^1$ and any parameter) while

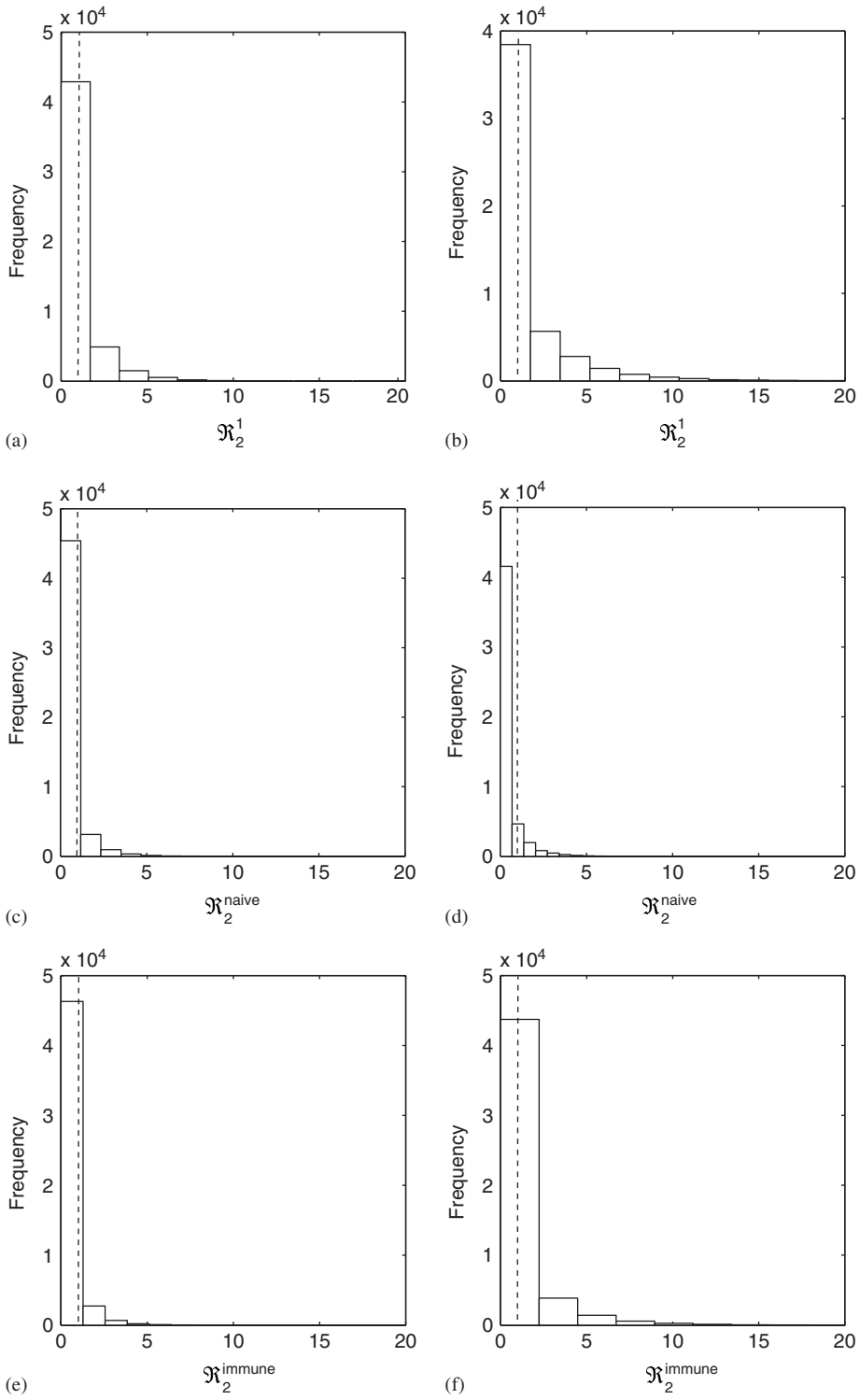

Fig. 2. Frequency distributions for contributions of $\Re_2^1$, $\Re_2^{naive}$ and $\Re_2^{cross\text{-}immune}$ sampling σ_{12} from a normal distribution with mean 0.3 (a),(c),(e) and 0.8 (b),(d),(f). The dash lines in each subplot are used to illustrate the frequency of $\Re_2^1$, $\Re_2^{naive}$ and $\Re_2^{cross\text{-}immune}$ on either side of 1.

controlling for the remaining parameters in the model (Conover, 1980). A value of PRCC close to zero suggests weak correlation between two variables, whereas, strong correlations are given by absolute values close to 1. This analysis helped identified the parameters that are most effective in reducing the magnitude of $\Re_2^1$.

3. Results

3.1. Uncertainty results for $\Re_2^1$

Table 2 shows strong similarities between the mean values for the 10 estimates of the mean, variance, and

corresponding $\Re_2^1$, $\Re_2^{\text{naive}}$ and $\Re_2^{\text{cross-immune}}$ distributions using a distribution for σ_{12} with mean 0.3 and variance 0.05. It also shows that the average mean values for the contributions ($\Re_2^{\text{naive}}$ and $\Re_2^{\text{cross-immune}}$) are higher for $\Re_2^{\text{naive}}$ (0.75) than $\Re_2^{\text{cross-immune}}$ (0.68) (see Fig. 2(c)–(f)). Furthermore, Table 2 shows that for the $\Re_2^1$ distribution exceeding one, $\Re_2^{\text{cross-immune}}$ (25%) contributes (slightly) more than $\Re_2^{\text{naive}}$ (22%).

We investigate the empirical distributions of $\Re_2^1$ and the probabilities that Strain 2 may invade a population previously exposed to Strain 1 for scenarios that may include high-transmission seasons (high reproduction number). Table 3 provides the probabilities of reproduction numbers comparable to those of flu epidemics. Even though this study focuses on strain competitive dynamics as mediated through cross-immunity, we consider the hypothetical scenario of antigenically distinct strains. We consider the possibility that strains are considerably different as may be expected during high-transmission seasons (i.e. no significant cross-immunity available, $\sigma \approx 1$). We show that the possibility of high-transmission seasons may occur 14% ($2<\Re_2^1<3$, Mills et al., 2004) of the time for weakly coupled strains ($\sigma = 0.8$). Our findings suggest that an invading strain is almost equally likely (approximately 14%, Table 3) to become established for reproduction numbers that differ significantly ($2<\Re_2^1<3$ and $\Re_2^1>5$).

We illustrate the frequency distribution for $\Re_2^1$ as well as for the contribution of $\Re_2^{\text{naive}}$ and $\Re_2^{\text{cross-immune}}$ to assess the likelihood of coexistence for two cross-immunity distributions with different means ($\sigma_{12} = 0.3$ and 0.8). In order to distinguish these distributions in the regime that supports coexistence ($\Re_2^1>1$), we plot $\Re_2^1$ at the threshold value 1 (dashed-line). Fig. 2 shows that a frequency of $\Re_2^1$ higher than one is increased significantly when cross-immunity between the established and newly invading strain is reduced (from 0.3 to 0.8). We compare the densities in Fig. 2 for two σ_{12}-distributions and find that $\Re_2^1$ exceeds one 49% of the time (Fig. 2(c), $\sigma_{12} = 0.3$) while 65% of the values of $\Re_2^1$ exceed one under weaker cross-immunity (Fig. 2(d), $\sigma_{12} = 0.8$). We also compare the frequency distributions of $\Re_2^{\text{naive}}$ and $\Re_2^{\text{cross-immune}}$ and show that their contribution to coexistence is comparable (25%) for $\sigma_{12} = 0.3$ (Fig. 2(c), (e)). However, the contribution of $\Re_2^{\text{cross-immune}}$ to coexistence increases from 22% ($\sigma_{12} = 0.3$, Fig. 2(e)) to 50% ($\sigma_{12} = 0.8$, Fig. 2(f)) as cross-immunity is reduced ($\sigma_{12} \uparrow 1$).

A further assessment of $\Re_2^1$ is illustrated in Fig. 3. Cumulative distributions for the frequency of $\Re_2^1$ show that a 50th-percentile of $\Re_2^1$ (intermediate σ_{12}) is below 1 (top panel, Fig. 3). However, increasing the mean of σ_{12} to 0.8 gives a 50th-percentile above 1 (bottom panel, Fig. 3). That is, reducing cross-immunity ($\sigma_{12} \uparrow 1$) enhances coexistence. We calculate the probability of multiple and sub-threshold coexistence for two cross-immunity mean levels. Fig. 4 illustrates an example in which cross-immunity supports coexistence ($\Re_2^1>1, \Re_2>1$) 48% of the time with sub-threshold ($\Re_2^1>1, \Re_2<1$) occurring 2% of the time. As we reduce cross-immunity ($\sigma_{12} = 0.8$), the likelihood of coexistence, that is $P[\Re_2^1>1, \Re_2>1]$ increases to 49% with a significant increment in the likelihood of sub-threshold coexistence $P[\Re_2^1>1, \Re_2<1]$ ranging from 2% to 17% (see Figs. 4 and 5). The results of Figs. 4 and 5 are summarized in Fig. 6 where it can be clearly observed that decreasing cross-immunity increases the likelihood of both coexistence and subcoexistence significantly. In particular, the increased likelihood of sub-threshold coexistence for waning cross-immunity levels is evident.

Quantitatively speaking, coexistence occurs for low levels of cross-immunity. That is, there exists a σ^* such that for $\sigma>\sigma^*$ coexistence is the outcome while if $\sigma<\sigma^*$ then the outcome is competitive exclusion. Specifically, we know (Nuño et al., 2005)

$$\sigma^* = \frac{1}{(1+\delta_2/(\mu+\gamma_2))(1-\mu(\mu+\alpha_1)/((\mu+\gamma_1)(\mu+\alpha_1)+\alpha_1\delta_1))}. \tag{4}$$

If $\delta_2 = 0$, then we have $\sigma^*>1$, a value out of the acceptable range (no coexistence). In order to have $\sigma^*<1$, the

Table 3
Mean values of the 10 estimates for the mean, variance and corresponding probability for $\Re_2^1$, given that $\Re_1>1$ for cross-immunity with mean 0.8

	Mean	Variance	$P[\Re_2^1<1]$	$P[1<\Re_2^1<2]$	$P[2<\Re_2^1<3]$	$P[3<\Re_2^1<4]$	$P[4<\Re_2^1<5]$	$P[\Re_2^1>5]$
1	2.58	7.84	0.34	0.22	0.14	0.10	0.06	0.14
2	2.55	7.65	0.34	0.22	0.14	0.10	0.06	0.14
3	2.56	7.74	0.34	0.22	0.14	0.09	0.06	0.14
4	2.58	7.97	0.34	0.22	0.14	0.09	0.06	0.14
5	2.59	7.56	0.34	0.22	0.14	0.09	0.06	0.15
6	2.59	7.79	0.34	0.21	0.15	0.10	0.06	0.14
7	2.57	7.60	0.34	0.21	0.14	0.09	0.06	0.14
8	2.59	7.70	0.34	0.21	0.14	0.09	0.06	0.15
9	2.57	7.66	0.34	0.22	0.14	0.10	0.06	0.14
10	2.55	7.53	0.34	0.22	0.14	0.10	0.06	0.14

The rest of the parameter values are provided in Table 1.

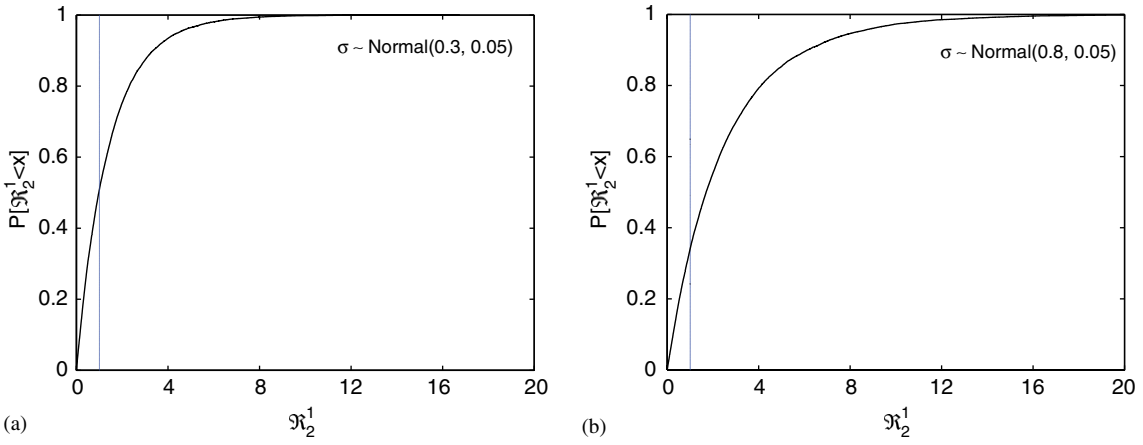

Fig. 3. Cumulative distribution functions of $\Re_2^1$ for two separate cross-immunity regimes ($\sigma_{12} = 0.3, 0.8$) using a Monte Carlo sample of 10^5.

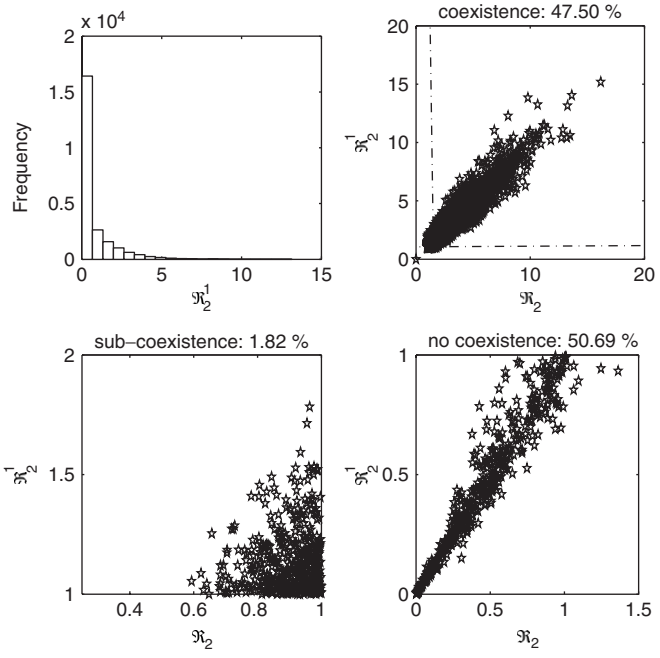

Fig. 4. Summarized statistics for $\Re_2^1$ for intermediate cross-immunity levels ($\sigma_{12} = 0.3$). Upper panels illustrate the frequency distribution of $\Re_2^1$ (left panel) and probability of coexistence (right panel). Bottom panels provide the probabilities of sub-threshold coexistence (left panel) and no coexistence (right panel). Dashed-lines illustrate the threshold value $\Re_2^1 = 1$ (upper-right panel). Parameters used in these calculations are provided in Table 1.

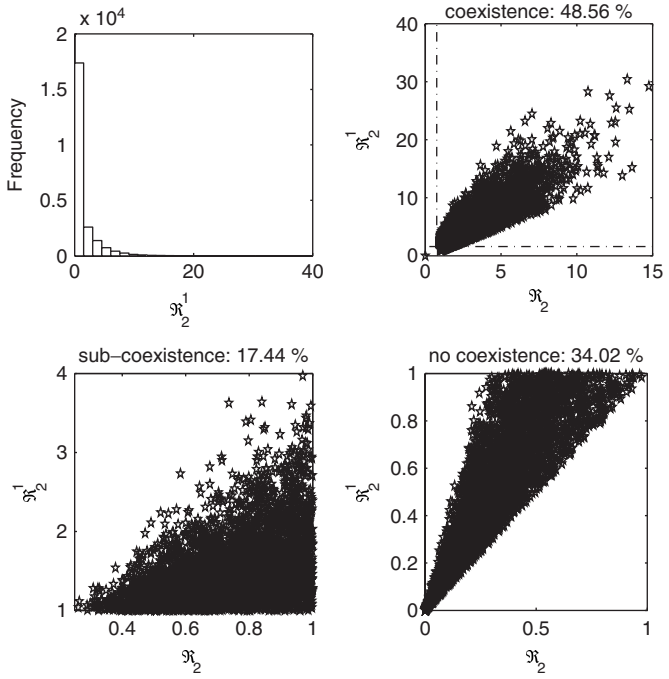

Fig. 5. Summarized statistics for $\Re_2^1$ for weak cross-immunity levels ($\sigma_{12} = 0.8$). Upper panels illustrate the frequency distribution (left panel) of $\Re_2^1$ and probability of coexistence (right panel). Lower panels provide the probabilities of sub-threshold coexistence (left panel) and no coexistence respectively (right panel). Dashed-lines illustrate the threshold value $\Re_2^1 = 1$ (upper-right panel). Parameters used in these calculations are provided in Table 1.

following inequality must be satisfied:

$$\delta_2 > \frac{\mu(\mu+\alpha_1)(\mu+\gamma_2)}{\gamma_1(\mu+\alpha_1)+\alpha_1\delta_1}, \tag{5}$$

or equivalently, for a given level of cross-immunity σ, there is a threshold isolation rate

$$\delta_2^* = \frac{\mu+\gamma_2}{\sigma}\left[\frac{(\mu+\gamma_1)(\mu+\alpha_1)+\alpha_1\delta_1}{\gamma_1(\mu+\alpha_1)+\alpha_1\delta_1} - \sigma\right]. \tag{6}$$

That is, if $\delta_2 > \delta_2^*$ then coexistence is the outcome. If we substitute the mean values of the distributions used in our uncertainty and sensitivity analysis in inequality (5), including the value of $1/\delta_1 = 3$ then we see that δ_2 exceeds δ_2^*. Consequently, coexistence under reasonable rates of isolation ($\delta_2 > 0.2511$) is possible.

3.2. *Sensitivity results for* $\Re_2^1$

The sensitivity of $\Re_2^1$ due to the uncertainty of the input parameters is addressed through the use of the PRCCs of

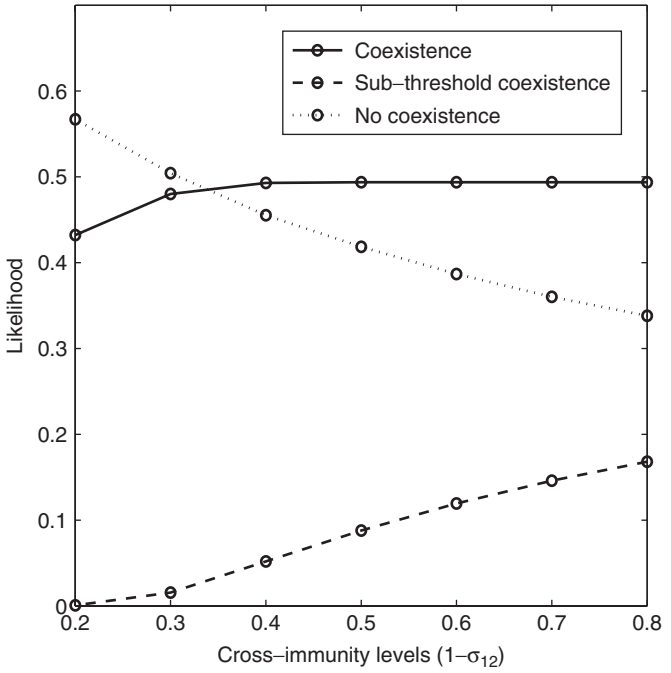

Fig. 6. Summarized statistics for $\mathfrak{R}_2^1$ for varying levels of cross-immunity. The likelihood of coexistence, sub-threshold coexistence and no coexistence are illustrated for varying levels of cross-immunity. Parameters used in these calculations are provided in Table 1 with the exception of σ_{12} (which varies between 0 and 1).

$\mathfrak{R}_2^1$ with each of the input parameters of the model. These coefficients measure the independent effect of each input variable on $\mathfrak{R}_2^1$ (assuming no correlation between the parameter values). We summarize the PRCCs between $\mathfrak{R}_2^1$, $\mathfrak{R}_2^{\text{naive}}$ and $\mathfrak{R}_2^{\text{cross-immune}}$ and each input parameter. Parameters are listed in decreasing order of their PRCCs for $\mathfrak{R}_2^1$, $\mathfrak{R}_2^{\text{naive}}$ and $\mathfrak{R}_2^{\text{cross-immune}}$. $\mathfrak{R}_2^1$: $\beta_2(0.97), \gamma_2(0.64), \delta_1(-0.39), \sigma_{12}(0.38), \delta_2(0.18), \gamma_1(-0.07), \beta_1(-0.04), \alpha_1(0.005)$; $\mathfrak{R}_2^{\text{naive}}$: $\beta_2(0.89), \delta_2(-0.37), \gamma_1(-0.32), \beta_1(-0.30), \gamma_2(-0.16), \delta_1(-0.05)$; $\mathfrak{R}_2^{\text{cross-immune}}$: $\beta_2(0.86), \gamma_2(-0.36), \gamma_1(0.31), \sigma_{12}(0.28), \beta_1(0.26), \delta_1(0.06), \alpha_1(-0.01), \delta_2(-0.003)$. These results show that β_2 and γ_2 are the most influential ($|\text{PRCC}|>0.5$) and significant ($p<0.05$) parameters in $\mathfrak{R}_2^1$. Increments in β_2 extend the magnitude of $\mathfrak{R}_2^1$ while increments in γ_2 reduce $\mathfrak{R}_2^1$. We address the sensitivity of $\mathfrak{R}_2^{\text{naive}}$ and $\mathfrak{R}_2^{\text{cross-immune}}$ to each parameter through the PRCCs. These results indicate that β_2 is the most influential parameter in $\mathfrak{R}_2^{\text{naive}}$. Finally, an assessment of the PRCCs corresponding to $\mathfrak{R}_2^{\text{cross-immune}}$ suggests that β_2 is the only influential parameter positively correlated with the invasion reproduction number of the partially immune population. A summary of the sensitivity results for $\mathfrak{R}_2^1$, $\mathfrak{R}_2^{\text{naive}}$ and $\mathfrak{R}_2^{\text{cross-immune}}$ indicates that β_2 is always the most influential parameter.

4. Discussion

Using a two-strain influenza model that incorporates partial cross-immunity and host isolation during primary infection, we studied the possibility that an emergent pathogen (strain) invades a population already infected by a "similar" intruder. The possibility of invasion is determined by the distribution of $\mathfrak{R}_2^1$ values generated from the distribution of model parameters.

Our uncertainty study shows that immunological interference between distinct (low cross-immunity) competing strains may enhance the possibility that an invading strain becomes established. As cross-immunity is reduced ($\sigma_{12}\uparrow 1$), coexistence turns out to be the most likely outcome. Moreover, whenever coexistence is possible, the possibility that it occurs in sub-threshold is significantly enhanced by decreasing cross-immunity (from 2% to 17% in the case presented here). In other words, decreasing cross-immunity increases the survival of less fit strains. However, cross-immunity is not solely responsible for these outcomes. Our results shows that appropriate isolation rates are required to support coexistence for cross-immunity regimes that are reasonable for flu (Eq. (6)).

We showed that a pathogen can invade a resident pathogen as long as it generates more than one infection (on the average) in a population characterized by two immunological distinct subpopulation proportions $\tilde{S}_1/\tilde{A}$ (naive) and $\tilde{R}_1/\tilde{A}$ (partially immune). Cross-immunity plays a significant role in determining which population is most likely to contribute to the success of an invading pathogen. $\mathfrak{R}_2^{\text{naive}}$ contributes most to a successful invasion when both strains are weakly coupled ($\sigma_{12}\uparrow 1$). The situation changes as cross-immunity increases ($\sigma_{12}\downarrow 0$). The sensitivity analysis of $\mathfrak{R}_2^1$ suggests that an outbreak may be prevented most efficiently by reducing transmission (β_2). Reducing the length of recovery period (γ_2) also helps.

Our results support and extend the findings of researchers who have used multi-strain models where competition is mediated by cross-immunity (Abu-Raddad and Ferguson, 2005; Bremermann and Thieme, 1989; Castillo-Chavez et al., 1988, 1989; Dietz, 1979; May et al., 2001). The possibility that a novel strain invades a population where a "similar" strain has become established may depend on the size of the "effective" susceptible population and other host–pathogen interactions (Boni et al., 2004; Ferguson et al., 1999; Galvani, 2003; Gandon et al., 2001; May et al., 2001; Porco and Blower, 2000). Here, the effective size of such population is enhanced by cross-immunity but only when cross-immunity is low, that is, when the strains are dissimilar (Castillo-Chavez et al., 1988, 1989; Dietz, 1979). If strains are antigenically similar, competition for susceptibles is likely to drive the weaker strain to extinction (Bremermann and Thieme, 1989; Galvani, 2003). Results on the possibility of sub-threshold coexistence in multiple pathogen (strains) models are fairly recent and their understanding requires further investigation (Martcheva and Thieme, 2003; Martcheva and Pilyugin, 2006; May et al., 2001). Theoretical models that allow for the possibility of super-infection (as observed in schistosomiasis) and coinfection have shown to support coexistence in sub-threshold as the work discussed here.

The work in this manuscript can be interpreted in terms of "flu" vaccines which tend to be developed on the basis of

cross-reactivity tests (in animal models) of likely incoming strains (Ambrosch and Fedson, 1999; Gandon et al., 2001; Smith et al., 1999). Moderate increases in cross-immunity ($\sigma_{12} \downarrow \zeta,\ \zeta \in (0,1)$) due to repeated vaccination or "flu" exposure may be unable to prevent the invasion of less fit strains (Lambert et al., 2005). Could vaccination policies facilitate a flu pandemic (Ferguson et al., 2005; Longini et al., 2005)?

The findings here have been discussed in terms of pathogens (flu strains) that cocirculate during influenza seasons, however, "competition exclusion" and coexistence dynamics have been observed among other pathogens (Altizer et al., 2003; Cleaveland et al., 2001; May and Anderson, 1983; Rabsch et al., 2000). More recently, Gomes et al. (2004) studied the impact of temporary and partial immunity in epidemic models (*S-I-S* and *S-I-R*) and analyzed the outcome of vaccination. Although these models allow for single-pathogen interactions, their findings emphasize the challenges of recurrent pathogens through the association of disease prevalence and vaccine failure (Gomes et al., 2004).

Host–pathogen interactions and the role of partially protecting vaccines have been discussed by Gandon et al. (2001). Using a classical *S-I-S* model that allowed for partial and full susceptibility, they showed that imperfect vaccines that reduce transmission or susceptibility selected for lower virulence ("induced host mortality"), while those reducing replication and/or toxicity selected for greater virulence. In the "low-virulence" outcome, persistence (from a pathogen's perspective) was a priority and a tradeoff between persistence (host survival) and "optimal" transmission became key in determining a pathogen's survival. Another example that illustrates the impact of vaccine in cocirculating pathogens is given by a recent study in Boni et al. (2004). They showed that vaccines aimed to decrease transmission rates also reduced the production of new flu strain variants, thereby, influencing the drift evolution and severity of flu in the population. Furthermore, invading pathogens with high-mutation potential were likely to become established in the population, while, low-mutation pathogens became excluded.

In summary, the theoretical work here shows that decreasing the levels of cross-immunity may allow for the survival of novel but less fit (not good invaders) strains. Whether or not these "unfit" strains are more lethal (at the individual level) and consequently, more likely to generate outbreaks with unusually high death rates is a question of further research.

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Appendix

The description of the model equations can be derived from Fig. 1. The host isolation plays a significant role in the dynamics of disease transmission since a proportion of infected individuals are removed from the population through self-isolation. This assumption replaces the standard disease incidence term $\beta_i S(I_i + V_i)/N$ by the quarantine-adjusted incidence $\beta_i S(I_i + V_i)/(N - Q)$ where N is the total population size. This enhances the force of infection since the probability that a given contact ("effective contact") leads to transmission of a primary infection increases from $(I_i + V_i)/N$ to $(I_i + V_i)/(N - Q)$. The model becomes:

$$\frac{dS}{dt} = \Lambda - \sum_{i=1}^{2} \beta_i S \frac{(I_i + V_i)}{A} - \mu S,$$

$$\frac{dI_i}{dt} = \beta_i S \frac{(I_i + V_i)}{A} - (\mu + \gamma_i + \delta_i) I_i,$$

$$\frac{dQ_i}{dt} = \delta_i I_i - (\mu + \alpha_i) Q_i,$$

$$\frac{dR_i}{dt} = \gamma_i I_i + \alpha_i Q_i - \beta_j \sigma_{ij} R_i \frac{(I_j + V_j)}{A} - \mu R_i, \quad j \neq i,$$

$$\frac{dV_i}{dt} = \beta_i \sigma_{ji} R_j \frac{(I_i + V_i)}{A} - (\mu + \gamma_i) V_i, \quad j \neq i,$$

$$\frac{dW}{dt} = \sum_{i=1}^{2} \gamma_i V_i - \mu W,$$

$$A = S + W + \sum_{i=1}^{2} (I_i + V_i + R_i), \tag{7}$$

where A denotes the population of non-isolated hosts.

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