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ScienceDirect
Theoretical Population Biology 71 (2007) 20–29
Theoretical Population Biology
www.elsevier.com/locate/tpb

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

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Received 2 February 2006
Available online 11 July 2006

**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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doi:10.1016/j.tpb.2006.07.002

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 ($\sigma_{12}$). 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, $\sigma_{12}$ equal to zero corresponds to total cross-immunity (Strain-2 cannot invade) while $\sigma_{12}$ equal to one corresponds to no cross-immunity.

Prior epidemiological studies that measure $\sigma_{12}$ 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 ($\sigma_{12}$) 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 ($\sigma_{12}$) 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 $\sigma_{12}$ 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 $\sigma_{12}$. 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 $\beta_1$ (primary infection); following infection with Strain 1, individuals are isolated ($Q_1$) at the rate $\delta_1$ or moved directly into the recovered class ($R_1$) at the rate $\gamma_1$; 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 $\gamma_2$ ($W$); the per capita mortality rate is denoted by $\mu$. 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 $\sigma_{12}$ 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

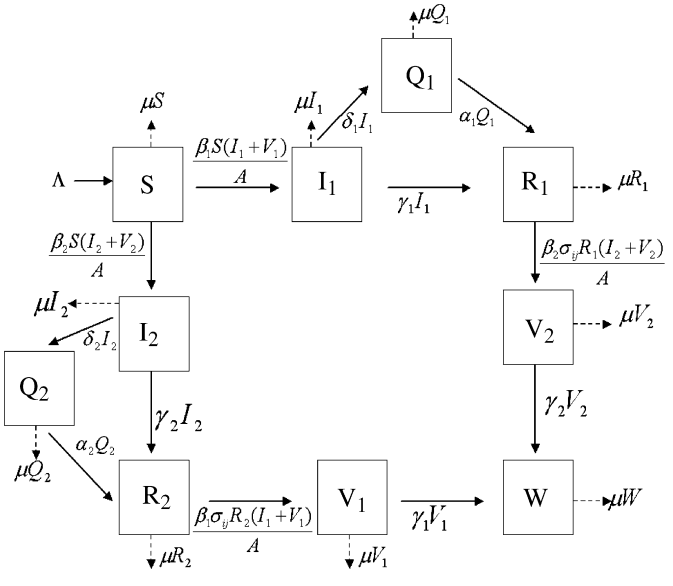


Fig. 1. Flow chart of the state progression of individuals in a population exposed to two influenza strains. Fully susceptible individuals ($S$) can become infected (primary infection) with Strain 1 ($I_1$) or Strain 2 ($I_2$). Infected individuals with Strain 1 (Strain 2) may become isolated $Q_1$ ($Q_2$) 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 $W$.